BEFORE THE CONTROLLER OF PATENTS
THE PATENT OFFICE BRANCH, MUMBAI

In the matter of:

Indian Patent 270765

Application no.: 1863/MUMNP/2009

Date of Patent: 10.03.2009

Date of Grant: 18.01.2016

And

In the matter of:

Application for Compulsory Licence under Section 92(1) read with Section 92(3) of The Patents Act, 1970

By:

BAJAJ HEALTHCARE LIMITED …Applicant

An Indian company having corporate office at:

602-606, Bhoomi Velocity Infotech Park,

Plot No. B-39, B-39A, B-39 A/1, Rd No.23,

Wagle Ind. Estate, Thane West, Thane

Maharashtra, 400604, India

The Applicant above-named respectfully submits as follows:

I. BACKGROUND TO THIS APPLICATION

1. In the interest of our nation India and to empower the central and state government's fight against deadly Coronavirus (COVID-19), this application is made to request the Hon'ble Controller to grant a compulsory license under section 92(1) read with Section 92(3) of the Patents Act, 1970 in relation to the Indian patent no. 270765 for manufacture and supply of Baricitinib API and formulation in the treatment of COVID-19 in India.

2. COVID-19, caused by a coronavirus called SARS-CoV-2 has crippled not only human lives but also the economies of almost all countries. This loss in the form of human deaths is unprecedented both globally and in India. Despite our best efforts, India records the second-highest number of reported confirmed cases of COVID-19 infection among all nations, and the number of associated deaths is over 3 lakh. Thus, it is a situation of "national emergency" and there is "extreme urgency" for scientifically competent individuals/companies to step in and support the government to save the precious lives of our countrymen on a priority basis.

3. The COVID-19 pandemic in India is part of the worldwide pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of COVID-19 in India was reported on 30 January 2020. India currently has the largest number of confirmed cases in Asia. As of May 2021, India has the second-highest number of reported confirmed cases of COVID-19 infection in the world (after the United States) and approximately 295,525 deaths as of 22 May 2021. The numbers are continuously increasing.

4. While few states like Maharashtra had already implemented the lockdown the first national lockdown has been announced in March 2020 for 21 days. Hon'ble Prime Minister of India Mr. Modi also added that if the spread is not controlled in the next 21 days, India "could go 21 years behind". By mid-May 2020, five cities accounted for around half of all reported cases in the country: Mumbai, Delhi, Ahmedabad, Chennai and Thane. On 10 June, 2020 India's recoveries exceeded active cases for the first time. Infection rates started to drop in September 2020 along with the number of new and active cases. A biggest one day spike was then observed with more than 90,000 cases reported in a day on 06th September 2020 on continued easing of containment measures to revive an economy that was heading towards its 40 years low figures. The cases begin to drop below 15,000 in January 2021. However, the spread had deepened its

roots all over India including the smallest villages of the countries. A second wave of COVID-19 soon hit the country bringing havoc.

5. A second wave that began in February 2021 was much larger than the first, with shortages of vaccines, hospital beds, oxygen cylinders and other medicines in parts of the country. By late April 2021, India led the world in new and active cases. On 30 April 2021, it became the first country to report over 400,000 new cases in a 24-hour. Then, India Situation Report-68 on Coronavirus Disease (COVID-19) published by WHO on 19.05.2021 reported the highest number of cases (4,14,188) on 7 May 2021.

6. Till this time the entire world is been struggling with finding suitable medicines and therapies against the COVID-19 infections and the severe medical complications developing in patients due to it. The oxygen level drop is generally seen to be a symptom of severity calling for the close monitoring of the patient with timely administration of necessary therapy, oxygen and medicines.

7. The medicine's availability is another major concern in this situation. As already mentioned, the countries across the globe are encouraging the firms, research institutes to find the drug/vaccine to help in mitigating the challenge of COVID-19.

   In India, the Central Drug Standard Control Organization (CDSCO) on 19.03.2020 had issued the notice concerning this matter. In an attempt to encourage the research and development of the drug for the treatment of COVID-19 it has declared that any application submitted to CDSCO shall be processed on high priority. It also declared to provide guidance of regulatory pathway and offered multiple assistances including the regulatory assistance for the drug under development for COVID-19, the priority in review and approval for the protocol for repurposing of existing drug for COVID-19 treatment, fast processing of the clinical trials permissions, fast approval of the drugs if they

are approved in any other country, toxicity, clinical and stability study data requirement waivers in certain cases, fast processing of the applications for manufacture or import of drug for test and analysis and further use BA/BE or clinical trial etc.

8. Amid a devastating second COVID-19 wave, India's high courts have stepped in to address the government's handling of the crisis. Multiple courts have issued orders in the face of a shortage of oxygen and vital medication. As countless patients have rushed to hospitals due to the deadly second coronavirus wave in India, the country's judiciary has taken serious cognizance of it. The issues most commonly brought before the courts include shortages of oxygen and other life-saving drugs. The state governments have directed the industrial oxygen to the hospitals. There is still a large demand for oxygen and the new plants are been built up for the production of oxygen. Therefore the continuous increase in the number of patients requiring oxygen can be imagined. Another major issue is the scarcity of medicines and their overpricing due to their shortage. Recently, the Hon'ble Supreme Court, Hon'ble Bombay High Court and Hon'ble Delhi High Court intervened to tackle overcharging by private hospitals and clinics, ensuring the supply of oxygen to hospitals, and the availability of the essential medicine.

9. Though the scientists, researchers, doctors, pharmaceutical firms are continuously working on the development of suitable treatments, the need and supply of the same is kept on increasing day by day even after a year and the disease has become more severe. Hon'ble Supreme court has mentioned in its order dated 30.04.2021 that COVID-19 falls under the definition of a disaster under Section 2(d) of The Disaster Management Act, 2005 (DMA) and the provisions of the DMA were invoked for the first time to deal with the present pandemic. Under Section 6(2)(i) of the DMA, the National Disaster Management Authority (NDMA) issued an order dated 24 March 2020 directing the Ministries, UOI, State/UTs and their authorities to take effective

measures to prevent the spread of COVID-19 in the country. Section 12 of the DMA empowers the NDMA to recommend guidelines for the minimum standard of relief to be provided to persons affected by the disaster.

Hon'ble Supreme Court took note of even this fact that when individuals often get their family member admitted in a hospital in one city, but have to travel to another city to look for oxygen or essential drugs and are denied their use because they are to be bought for an individual admitted in a different city. It also noted that medical oxygen is critical to the treatment of COVID affected patients. The entire available capacity of oxygen is being used for supply for industrial and medical use, which is in the form of Liquid Medical Oxygen.

10. There is a rampant increase in the number of patients in need of oxygen as recognized by the Hon'ble Supreme Court also. The drugs for reducing the external oxygen dependency of patients and/or enhancing their health more speedily are of extreme importance today.

11. The EMBO Molecular Medicine Journal reported that there was support in real time for the AI-predicted use of Baricitinib in Covid-19 treatment. The Journal reports that in a series of patients with bilateral COVID-19 pneumonia, Baricitinib treatment was associated with clinical and radiologic recovery, a rapid decline in SARS-CoV- 2 viral loads, inflammatory markers, and IL-6 levels. A copy of said EMBO Molecular Medicine Article is annexed herewith as **ANNEXURE 1**.

12. Baricitinib in combination with [Remdesivir] for the treatment of COVID-19, was granted USFDA Emergency Use Authorization on 19 November 2020.

13. The CDSCO/DCGI had already given permission for the manufacture and marketing of Baricitinib API and tablets considering the emergency situation and unmet medical need in light of the COVID-19 outbreak. One such permission granted to M/s Natco Pharma Ltd. for manufacture and marketing of Baricitinib API and 1 mg, 2mg and 4mg tablets for Emergency Use in Covid-

19 pandemic forms a part of public documents. Copies of such letters are annexed herewith as **ANNEXURE 2 Colly**.

14. Baricitinib is being prescribed as a stand alone or in combination with Remdesivir for treatment in Covid-19 patients. The prescribed dosage is one tablet per day for a maximum of 14 days.

15. There was an extreme urgency in filing this present application owing to the fearful situation due to the COVID-19 deaths crossed lakhs in numbers, the shortage of medicines and therapies, and the public health emergency situation. The situation in India has become worst and people are dying due to lack of access to life-saving drugs, high prices of medicines and unmet medical treatment.

II. ABOUT THE APPLICANT

16. The applicant, BAJAJ HEALTHCARE LTD is a Company registered under provisions of the Companies Act having Registered Office at 602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39 A/1, Rd No.23, Wagle Ind. Estate, Thane West Thane, Maharashtra, India 400604 (hereinafter referred to as the "Applicant"). It is a well-known company in the domestic as well as international pharmaceutical industry and is a largest manufacturer of certain pharmaceutical products in India and Asia and also a regular exporter of pharmaceutical products. It is in the manufacturing and distribution of API's (More than 40 Api's) and formulation (more than 150 finished products) business and is located mainly in Maharashtra and Gujrat in India. The products emanating from the applicant are known for their superior and high quality and have acquired substantial reputation and goodwill in Indian and global market. Its products and brands are highly trusted by healthcare professionals and patients.

17. **Brief introduction of Applicant's Manufacturing facilities of API and Formulation units: -**

Founded in 1993, Bajaj Healthcare Ltd is engaged in manufacturing a large range of Active pharmaceutical ingredients, intermediates, nutraceuticals and finished formulations. With Headquarters in Mumbai, Bajaj Healthcare Ltd. has several manufacturing facilities located in Maharashtra and Gujarat.

It has world class facilities, capability and resources to manufacture and distribute APIs and formulations as well. It adheres to all guidelines and follows cGMP and cGLP practices in the manufacturing and testing of pharmaceutical products. It strictly maintains the quality checks in all its operations and maintains the best quality for all the pharmaceutical products it manufactures.

It has the API unit situated in Savli Vadodara which is an EU GMP certified, Korean FDA approved and WHO-GMP certified facility. Further, in addition to its formulation unit it has 18 state-of-the-art manufacturing blocks where Intermediates, APIs and nutraceuticals are produced. The company is equipped with highly competent scientific and management human resources.

Its formulation unit is located at Manjusar - Gujarat which is designed to meet the regulatory market requirements. It is WHO-GMP & ISO 9001:2015 Certified & along with the approval of MOH- Sri Lanka, Malawi and Lesotho.

Few of the products offered by the Applicant in Indian and foreign markets that are very much useful in COVID-19:

18. Applicant has a strong R&D backup team that aggressively works on the development of new therapies.

Applicant is the leading manufacturers of Formulation in solid dosage forms (Tablets, Capsules & Sachets). It is the largest manufacturer of Vitamin C, in India. In this ongoing global pandemic of COVID-19 situation Vitamin C plays a vital role and stands out for having immune modulatory functions. Vitamin C is been prescribed regularly to almost all COVID-19 patients irrespective of the severity of the disease. Applicant produce and supply in the

market various dosage forms like Vitamin C plain Tablets 500mg, Vitamin C Chewable Tablets 100mg/500mg.

19. Applicant is one of the Largest Manufacturer of ASCORBYL PALMITATE in India with RSPO certification. It is used as a source of Vitamin C and also used as an antioxidant food additive.

20. Applicant holds the CEP certificate for Chlorhexidine Digluconate solution EP and is the world's largest manufacturer of Chlorhexidine Digluconate Solution. It is used to treat gingivitis (swelling, redness, bleeding gums). It is also an antiseptic and the most widely used disinfectant. It is of great importance in the current COVID-19 pandemic.

21. Applicant had successfully developed the Active pharmaceutical ingredient (API) and the formulation for FAVIJAJ® with the help of its R&D team, ensuring self-sufficiency with regards to long-term manufacturing and supply of the said Product. It holds respective product permissions granted by the drug control authorities to supply the drug substance and drug products in the domestic as well as export market. FAVIJAJ comprising Favipiravir tablets in different dosage forms 200mg/400mg/800mg are used for the treatment of patients with mild to moderate COVID-19 disease. Looking into the current emergency requirements applicant has decided to sell the product in the Indian market and the same was launched on 04th May 2021. Also, during emergency requirements applicant has offered FABIDAC comprising 200mg/800mg strengths Favipiravir tablets for COVID-19 treatment to Zydus Healthcare Ltd on P2P [Product to product] basis.

22. Applicant's IVEJAJ tablets comprising Ivermectin 3mg/6mg/12mg were used for the treatment of patients with mild to moderate COVID-19 disease. Looking into the current emergency requirements applicant is going to sell the product in the Indian market and the same was launched on 6th May 2021. Also, during emergency requirements applicant has offered IVERTREAT and IVELOC

tablets 12mg for COVID-19 treatment to Zydus Healthcare Ltd on P2P [Product to product] basis.

Other lifesaving drugs manufactured and supplied by the applicant:

23. Applicant is the market leader in API manufacturing which is supplied to all major Pharma MNC's in the Domestic and International Market.

24. Applicant also manufacture and supply new complex speciality molecules such as: -

Sr. No.	Name of the API	Uses	Supplied to Countries
1	Fosfomycin Tromethamine USP	It is used in the treatment of bladder infections (such as acute cystitis or lower urinary tract infections) in women. This antibiotic treats only bacterial infections.	Latin America
2	Fosfomycin Trometamol BP/EP	It is used in the treatment of bladder infections (such as acute cystitis or lower urinary tract infections) in women. This antibiotic treats only bacterial infections.	Latin America
3	Ticagrelor IH/IP	Indicated for the prevention of atherothrombotic events in adult patients	Domestic
4	Diosmin BP/EP/USP/IH	It is used for treating various disorders of blood vessels including hemorrhoids, varicose veins, poor circulation in the legs (venous stasis), and bleeding (hemorrhage) in the eye or gums.	Domestic
5	Ascorbic Acid IP/BP/EP/USP	It is used to prevent or treat low levels of vitamin C in people who do not get enough of the vitamin from their diets which results in a condition called scurvy.	Pakistan, Bangladesh, Singapore & Australia
6	Chlorhexidine Gluconate Solution IP/BP/EP/USP	It is used to treat gingivitis (swelling, redness, bleeding gums)	Worldwide [Specifically Europe market]

7	ASCORBYL PALMITATE	It is used as a source of Vitamin C and also used as an antioxidant food additive.	South Africa, USA, Malaysia and Brazil

25. It has submitted the CEP application to EDQM for Sitagliptin Phosphate Monohydrate EP. It is one of the very important an antidiabetic drugs.

26. Applicant is also in the business of supplying the best quality Formulation products to other reputed pharmaceutical companies which provides us an upper hand over other contract manufacturers. Below is an exemplary list of some important products offered by the applicant:

Sr. No.	Name of the Customer	Product Name	Supplied
1	M/s. Glaxo SmithKline Pharmaceuticals Ltd.	Celin 500 Tablets	Domestic market
		Celin Chewable Tablets	
2	M/s. USV Pvt. Ltd.	Ecosprin Tablet 75 mg	Domestic market
		Ecosprin Tablet 150 mg	
		Mashyne Tablet 1000	
3	M/s. Koye Pharmaceuticals Pvt. Ltd.	Celin 500 Tablets	Domestic market
		Celin Chewable Tablets	
		Septran Tablets	
4	M/s. Intas Pharmaceuticals Ltd.	Thalap Tablets 250mg/400mg/500mg	Domestic market
5	M/s. TTK Healthcare Ltd.	Ossopan MCM Tablets	Domestic market
		Ossopan MCM Forte Tablets	
		Hemobest XT Tablets	
		Truferin XT Tablets	
		Erafos Sachet	
6	M/s. Medley Pharmaceuticals Ltd.	Ticagold Tablets 90 mg	Domestic market
7	M/s. Zydus Healthcare Ltd.	Fabi Dac Tablets 200 mg/800mg	Domestic market
		Ivertreat and Iveloc Tablets 12 mg	

27. Solely for the purpose of justification of its capabilities in manufacture and supply of the drug products in the market and to other pharmaceutical players, the applicant provides below the exemplary list of some of its renowned and valued customers with whom the applicant has developed a smooth and trustworthy relationship for the supply of drug products:
    - Glaxo SmithKline Pharmaceuticals Ltd.
    - USV Pvt. Ltd.
    - Koye Pharmaceuticals Pvt. Ltd.
    - Intas Pharmaceuticals Ltd.
    - TTK Healthcare Ltd.
    - Alvita Pharma Pvt. Ltd.
    - SRS Pharmaceuticals Pvt. Ltd.
    - BDR Pharmaceuticals Internationals Pvt. Ltd.
    - Medley Pharmaceuticals Ltd.
    - Wallace Pharmaceuticals Ltd.

28. The history, infrastructure and capabilities of the applicant are available at the official website of the applicant at http://www.bajajhealth.com/. The annual reports for the financial year 2010-2011 and onwards are also available to download at said website. For quick reference, the latest Annual Financial Report for the year 2019-2020 is annexed herewith as **ANNEXURE 3.**

29. Moving along with our wide range of products; **Bajaj Healthcare Limited** is prioritizing actions in its supply chain to deliver more products that are in high demand, to sustain against this pandemic situation.

III. BARICITINIB IN COVID-19 TREATMENT

30. Baricitinib, is a drug for the treatment of rheumatoid arthritis (RA) in adults whose disease was not well controlled using RA medications called tumor necrosis factor (TNF) antagonists. It acts as an inhibitor of Janus kinase (JAK),

blocking the subtypes JAK1 and JAK2. The drug is approved for use in the European Union and the United States and in India for this indication.

31. Baricitinib is an orally available small molecule inhibitor of Janus kinases that is used to treat moderate-to-severe rheumatoid arthritis and more recently was given emergency use authorization for severe COVID-19. Baricitinib is a selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor. Janus kinases belong to the tyrosine protein kinase family and play an important role in the proinflammatory pathway signalling that is frequently over-activated in autoimmune disorders such as rheumatoid arthritis. By blocking the actions of JAK1/2, Baricitinib disrupts the activation of downstream signalling molecules and proinflammatory mediators.

32. In the EU, Baricitinib was approved in February of 2017 as a second-line orally administered treatment for moderate to severely active rheumatoid arthritis in adults, either as a monotherapy or when combined with Methotrexate. It is marketed under the trade name Olumiant. In May 2018, Baricitinib was approved for use in India for the treatment of moderate to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modification anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with Methotrexate. A copy of the Olumiant leaflet is annexed herewith as **ANNEXURE 4**.

33. The International Journal "The Lancet" had reported that "Baricitinib as a potential treatment for 2019-nCoV acute respiratory disease". It shows Baricitinib, which is predicted to reduce the ability of the virus to infect lung cells. Given the scale and rapid spread of the 2019 novel coronavirus (2019-nCoV) acute respiratory disease, there is an immediate need for medicines that can help before a vaccine can be produced. A copy of this article is annexed herewith as **ANNEXURE 5.**

34. Another article published on 27 April 2020 which shows that, Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis and it is suggested that this drug could be of use in countering SARS-CoV-2 infections. A copy of this article is annexed herewith as **ANNEXURE 6.**

35. The combination of Baricitinib, an anti-inflammatory drug, and Remdesivir, an antiviral, reduced time to recovery for people hospitalized with COVID-19, according to clinical trial results published on March 4, 2021 in vol. 384 no. 9 of the New England Journal of Medicine. The study was supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. A copy of this literature reference is annexed herewith as **ANNEXURE 7**.

36. The research study authored by Heinz-Josef Lenz et al. published by Oxford University Press for the Infectious Diseases Society of America, in Clinical Infectious Diseases, Volume 72, Issue 7, dated 1 April 2021, Pages 1247–1250 states that the use of Baricitinib in COVID-19 treatment. The abstract published states *"Hyperinflammation is associated with increased mortality in coronavirus disease 2019 (COVID-19). In this retrospective, the uncontrolled patient cohort with moderate -severe COVID19, treatment with Baricitinib plus hydroxychloroquine was associated with recovery in 11 of 15 patients. Baricitinib for the treatment of COVID-19 should be further investigated in randomized, controlled clinical trials."* A copy of this article is annexed herewith as **ANNEXURE 8.**

37. Another study was reported in Reumatología Clínica, Vol. 17. Núm. 6. Páges 307-370 (Junio - Julio 2021) and authored by José Rosas et al. mentioned the Experience With the Use of Baricitinib and Tocilizumab Monotherapy or Combined, in Patients With Interstitial Pneumonia Secondary to Coronavirus COVID19. The study conclusion in human patients revealed that the treatment with Baricitinib and Tocilizumab did not cause serious side effects. They could

be considered early in patients with NI secondary to COVID19 and impaired PaO2/PaFi. This study report was made online available on 28 November 2020 as reported at https://www.sciencedirect.com/science/article/pii/S1699258X20302710?via%3Dihub

Also, a copy of this study report is annexed herewith as **ANNEXURE 9.**

38. In yet another study article authored by Hasan et al. and published by BMC Infectious Diseases (2021) 21:427 and available at, https://doi.org/10.1186/s12879-021-06119-2 since 07 May 2021 find the conclusion that the daily high dose of Baricitinib in severe COVID-19 results in early stabilization of the respiratory functions, declined requirements of critical care supports, reduced rehospitalization with mortality rate compared to its daily usual dose. This study was conducted on 238 adult patients with severe COVID-19 pneumonia. 8 mg and 4 mg of Baricitinib were given orally to 122 patients in the high dose (HD) group and 116 patients in the usual dose (UD) group, respectively daily for 14 days, and clinical outcomes were compared among the groups. A copy of this study report is annexed herewith as **ANNEXURE 10.**

BARICITINIB REGULATORY APPROVAL FOR COVID-19 TREATMENT

39. Baricitinib in combination with [Remdesivir] for the treatment of COVID-19, was granted USFDA Emergency Use Authorization on 19 November 2020. A copy of said approval is annexed herewith as **ANNEXURE 11**.

40. The U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the drug Baricitinib, in combination with Remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and paediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane

oxygenation (ECMO). In a clinical trial of hospitalized patients with COVID-19, Baricitinib, in combination with Remdesivir, was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received a placebo with Remdesivir. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated. A copy of this USFDA Communication is annexed herewith as **ANNEXURE 11**.

41. The CDSCO/DCGI had already given permission for the manufacture and marketing of Baricitinib API and tablets considering the emergency situation and unmet medical need in light of the COVID-19 outbreak. One such permission granted to M/s Natco Pharma Ltd. for manufacture and marketing of Baricitinib API and 1 mg, 2mg and 4mg tablets for Emergency Use in Covid-19 pandemic forms a part of public documents. Copies of such letters are annexed herewith as **ANNEXURE 2 Colly.**

42. https://www.newindianexpress.com/states/karnataka/2021/may/12/karnataka-adds-new-medicinesto-covid-treatment-protocol-2301517.html, on 12.05.2021 reported that as the intense second Covid-19 wave continues to ravage the state, the Karnataka Government added new medicines to the treatment protocol. It includes the Baricitinib tablets of 1mg, 2mg and 4mg strength which are approved by the Central Drugs Standard Control Organisation for emergency use. A copy of said news article is annexed herewith as **ANNEXURE 12**.

IV. BARICITINIB PATENT IN INDIA

43. The search in the Indian Patent Office database IPAIRS revealed that the Baricitinib API is claimed in a patent no. 270765 (Titled "AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS") in India and the patentee is INCYTE HOLDINGS CORPORATION. The patentee's address as mentioned in the E-register page of IPAIRS was found to be at 1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States of America while the

address for service in India was mentioned to be at its Patent Agent's address at K & S PARTNERS, INTELLECTUAL PROPERTY ATTORNEYS, B1-601, 6TH FLOOR, MARATHON NEXTGEN INNOVA, OPPOSITE PENINSULA CORPORATE PARK, OFF G.K. MARG, LOWER PAREL, MUMBAI-400013, INDIA.

44. As per the records displayed at the Indian Patent office Website IPAIRS it was granted on 18/01/2016 and it is valid till 10/03/2029 subject to the payment of renewal fees to the patent office. Currently the renewal fees are shown to be paid till 10/03/2022.

45. Usually a Form 16 is filed for making application for registration of title/interest in a patent or share in it or registration of any document purporting the to affect the proprietorship of the patent. There appears to be filed one such a Form 16 on 18/06/2019 with the License, Development and Commercialization Agreement dated 18/12/2009 between the INCYTE CORPORATION (the grantee of patent) and Eli Lilly & Company. The E-register of Patent Office mention about the same but the copy of said documents is not published on Patentee's request of keeping the terms of the license secure (secrete). Eli Lilly in the working statements in the format of Form 27 filed for calendar year 2018 and 2019 reported to sell the 2 MG and 4Mg tablets in the Indian market under the Brand name OLUMIANT. The copy of said E-Register page of the Indian patent office website IPAIRS is annexed herewith as **ANNEXURE 13** and the copy of said patent as granted and available at the Indian patent office website IPAIRS is annexed herewith as **ANNEXURE 14**.

46. Working statements (in the Form 27 format) in this patent have been filed since 2018 for the years from 2017. The copy of said working statements (in the Form 27 format) obtained from the Indian patent office website IPAIRS is annexed herewith as **ANNEXURE 15 Colly**.

* For the year 2017 the patentee on 07.02.2018 submitted that Claimed invention is in development (clinical or pre-clinical) and cannot be sold until regulatory approval is obtained.

* For the year 2018 the working statement dated 11.02.2019 appears to be filed by the **patentee** and following sell in INR is been reported therein:

Product Description	Received Qty	Invoice Value
OLUMIANT TAB 2 MG	1,627	5,255,698
OLUMIANT TAB 4 MG	5,763	18,616,219
OLUMIANT TAB 4 MG samples	995	3,214,149

Surprisingly in answer to the question of whether the public requirement has been met partly/adequately/to the fullest extent at a reasonable price, it was mentioned "***While we (Eli Lilly) cannot know for sure, Eli Lilly believes that the public requirement is being adequately met at a market appropriate price***." It is pertinent to note that the license agreement between INCYTE CORPORATION and Eli Lilly & Company was recorded with the Patent Office on 18.06.2019 and this working statement was filed before the recording of such an agreement vide Form 16. **Ultimately, without debating on the sales figures and the information in a said working statement the applicant states here that who exactly filed the working statement for the year 2018 is unclear.** However, if one believes that the same was filed commonly by the patentee and Eli Lilly then it is crystal clear that none of them was surely knowing the facts about whether the public requirement was being adequately met at a reasonable price.

It was clearly mentioned in the said statement that the product was not manufactured in India and imported from Spain.

* For the year 2019 there were two working statement dated 13.03.2020 and 01.01.2021 appears to be filed by the patentee and the licensee respectively. Following sales figures in INR were mentioned in both the working statements:

Product Description	Received Qty	Invoice Value
OLUMIANT TAB 2 MG	263	849,569
OLUMIANT TAB 4 MG	7997	25,832,709
OLUMIANT TAB 4 MG samples	810	2,616,543

While the 13.03.2020 working statement mentioned that Registration Certificate and Import License granted by DCGI for Olumiant on 05-Sep-2018, the 01.01.2021 working statement (filed by Eli Lilly) mentioned "*We have already been granted exclusive license to develop and commercialize the patented technology.*"

In answer to the question of whether public requirement has been met partly/adequately/to the fullest extent at reasonable price, both statements mentioned to the best of their (filers) knowledge, the public requirement has been met adequately to the fullest extent at a reasonable price.

In both these statements also it was clearly mentioned that the product was not manufactured in India and imported from Spain.

* For the year 2020-2021 the working statement was filed on 05.05.2021 by the licensee. Following was mentioned in said the working statement:

Baricitinib has been approved for the treatment of Rheumatoid arthritis. Recently, on 3rd May 2021, the Licensee (Lilly) was granted a restricted emergency use for baricitinib (2 mg and 4 mg) in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) by the Drug Regulatory Authorities. Lilly is working with local Indian pharmaceutical companies to execute royalty-free voluntary licensing

agreements to accelerate the manufacturing and distribution of the medicine in India during the pandemic and ensure continuous and sufficient supply of baricitinib. In the meantime, Lilly has decided to donate baricitinib to the Indian Government through Direct Relief to make the same readily available for free. As an initial donation Lilly is making immediately available 400,000 baricitinib tablets to the Indian government for eligible hospitalized COVID-19 patients in India.

V. APPLICABILITY OF SECTION 92 IN THIS CASE

V(I). CIRCUMSTANCES OF NATIONAL EMERGENCY

47. The National Disaster Management Authority had declared the COVID-19 as a pandemic which is still in subsistence. The Drug Controller General of India/CDSCO had also issued a notification dated 19.03.2020 having the following statements,

X-11026/07/2020-PRO
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Public Relation Office)

FDA Bhawan, Kotla Roac
New Delhi-110002
Date: 19/3/2020

NOTICE

Novel Corona-virus Disease (COVID-19) has spread over 118 countries with now more than 191,127 cases and 7807 people have lost their lives as on 18.03.2020. World Health Organization (WHO) has declared it as pandemic. At present there is no current evidence from randomized clinical trials to recommend any specific treatment for suspected or confirmed patients with COVID-19.

In order to encourage research & development of drug or vaccine for prevention or treatment of COVID-19, any application submitted to CDSCO will be processed on high priority. CDSCO will also provide guidance on regulatory pathway on such matter.

The details are as under -

1. Any firm having a Drug/Vaccine under development for COVID-19 can directly approach DCG(I) through Public Relations Office for seeking guidance for regulatory pathway.
2. Any firm or research institute having protocol for repurposing of existing drugs/vaccines for treatment of COVID-19 will also be given priority for review and approval.
3. Applications for Clinical Trial permission and applications to import or manufacture Drug/Vaccine for sale and distribution would be processed on priority though expedited review/accelerated approval.
4. Any firm having Drug/Vaccine already approved for COVID-19 in any other country can directly approach DCG(I) through Public Relations Office regarding expedited review/accelerated approval for marketing in India.
5. Data requirement for animal toxicity study, clinical study, stability study etc. may be abbreviated, deferred, or waived on case to case basis depending upon the type of vaccine, nature of drug, plant from which the drug is extracted & its experience in case of Phyto-pharmaceuticals.
6. Applications to manufacture or import Drug/Vaccine for test, analysis and further use BA/BE or Clinical Trial may be processed within 7 days.
7. In case of emergency, Import license (Form 10) would be granted without Registration Certificate (Form 41) subject to approval of Central Government.

This order recognized COVID-19 as a pandemic and in order to mitigate the health problems of COVID-19 affected patients, it is attempting to encourage the research and development of the drug for the treatment of COVID-19. As explained hereinbefore, it has declared that any application submitted to CDSCO shall be processed on high priority. It also declared to provide guidance of regulatory pathway and offered multiple assistances including the regulatory assistance for the drug under development for COVID-19. This order is for any drug which can be useful in COVID-19. It signifies the intensity of the disease and the extreme national public health emergency situation arisen due to it. A copy of this notification is annexed herewith as **ANNEXURE 16.**

48. Hon'ble Delhi High Court in Rakesh Malhotra v. GNCTD dated 20.04.2021 stated in its order that

27. ***There are a number of other drugs which are being used for treatment Covid-19 patients, such as*** *Tocilizumab, Favipiravir, Ivermectin, Dexamathasone, Methylprednisolone, Dalteparin, Enoxaparin, HCQ and* ***Baricitinib. As per news reports, there are shortages of some, if not all, of the aforesaid drugs. Looking to the emergent situation****, we direct the Central*

Government to immediately reach out to the manufacturers/ patent holders/ licensees so as to forthwith ramp up the production capacities of the above, and all such other medications, as are essential for treatment of Covid positive patients. We may take note of the fact that the Patents Act provides for Compulsory Licenses under Section 84, and Special Provision for Compulsory Licenses or Notifications by the Central Government, under Section 92. Section 100 provides the power of the Central Government to use inventions for purposes of the Government.

28. Looking to the present day situation, there can be no doubt that a case is made out for exercise of its power by the Central Government/ Controller under the aforesaid provisions of law. At the same time, the interests of the Patent holders/ licensees should be kept in mind, since it on account of their investments, inventions and hard work that such like medicines are made available to the public at large. The best course would be encourage the existing manufacturers to ramp up their production on a war footing. They should also be encouraged to grant voluntary licenses to other entities to manufacture the requisite drugs. However, if such efforts do not fructify soon enough, the Government/ Controller should not hesitate to invoke their jurisdiction and powers under the aforesaid provisions of the Patents Act, since the lives of thousands of people are being lost each day in the country due to COVID. The lives of the people take priority over everything else. Even if such like powers are exercised, the patent holders/ manufacturers can be adequately compensated by fixation of fair license fee.

The copy of said order is annexed herewith as **ANNEXURE 17**.

49. Further, Hon'ble Supreme Court of India in its order dated 30.04.2021 in Suo Motu Writ Petition (C) 3/2021 mentioned:

43 In India, the patent regime is governed by the Patents Act, 1970[22], Section 92 of which envisages the grant of a compulsory license, inter alia, in circumstances of national emergency and extreme urgency. Once a declaration of national emergency is made, and the relevant patents notified,

any person interested in manufacturing the drug can make an application to the Controller General of Patents who can then issue a compulsory license. The patentee would be paid a reasonable royalty as fixed by the Controller General of Patents. *Further, under Section 100 of the Patents Act, the Central Government can authorize certain companies to use any patents for the "purpose of the government". Indian companies can begin manufacturing the drugs while negotiating the royalties with the patentees. If the Central Government or its authorized company is not able to reach an agreement with the patentee, the High Court has to fix the reasonable royalty that is to be paid to the patentee. Another alternative is for the Central Government to acquire the patents under Section 102 from the patentees. If the Central Government and the patentee is not able to reach a consensus on the price of the patents, it is up to the High Court to fix the royalty. Additionally, under Section 66 of the Patents Act, the Central Government is also entitled to revoke a patent in the public interest.*

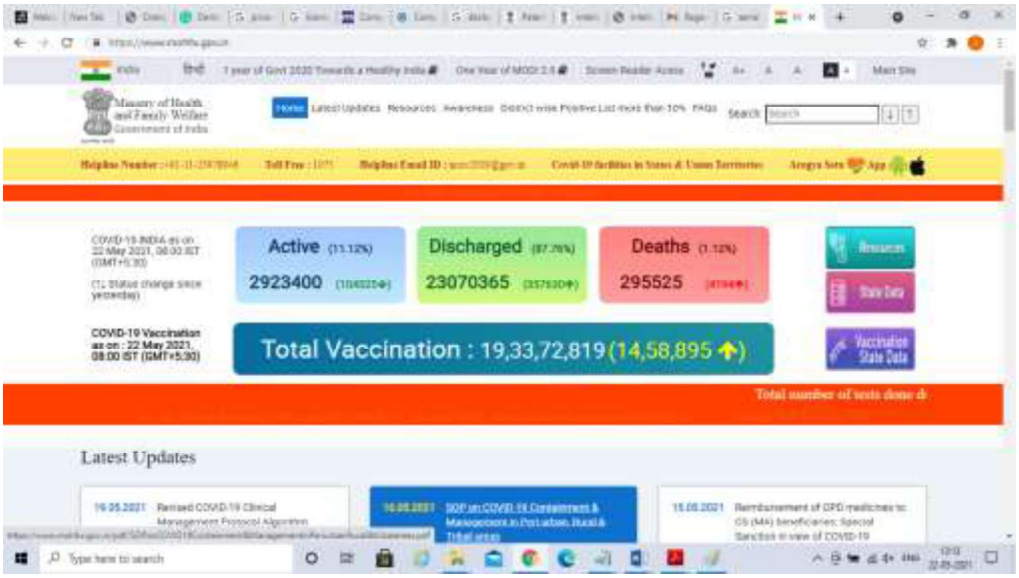
50. Hon'ble Supreme Court took note of even this fact that when individuals often get their family member admitted in a hospital in one city, but have to travel to another city to look for oxygen or essential drugs and are denied their use because they are to be bought for an individual admitted in a different city. It also noted that medical oxygen is critical to treatment of COVID affected patients. The entire available capacity of oxygen is being used for supply for medical use, which is in the form of Liquid Medical Oxygen. The Baricitinib being useful in such cases for early improvements in oxygen demanding patients health, it is very much important and essential drug in this emergency situation.

    The copy of said order is annexed herewith as **ANNEXURE 18**.

51. The Ministry of Health and Family Welfare produces the COVID-19 patient's data on daily basis on their official website https://www.mohfw.gov.in/.

Latest data available on 22/05/2021 on said website, shows the total Covid -19 active patients (29, 23,400 patients), discharged (2,30,70,365) and deaths (2,95,525) patient data in India

Following screenshot of the website https://www.mohfw.gov.in/ shows the latest number of covid-19 patient status present in India on 22/05/2021.



Adding the unreported cases to the above data the number of patients are going to be more than the numbers reported above. The deaths are also drastically increasing day by day.

52. The India Situation Report-68 on Coronavirus Disease (COVID-19) published by WHO on 19.05.2021 reports the highest number of cases (4, 14, 188) on 7 May 2021. It states the 2, 52, 28, 996 confirmed cases as on 19.05.2021 which account for 18,008 cases per million. Notably, it has reported 22, 36, 479 cases in the last 7 days. With this latest update, the cases per month can be estimated to be on an average 89.5 lakhs to 1.12 crores. Said report is attached herewith as **ANNEXURE 19**.

53. India is facing a huge shortage of essential medicines, equipment and medical oxygen as Covid-19 ravages the country. Several countries, including the US, UK, Canada, other EU and Gulf countries, have come out in support, however,

patients continue to die due to a shortage of essential medicines and medical oxygen across majorly-hit cities like Delhi and Mumbai. There are several news reports which throw light on the current pandemic situation in India.

54. Principal Scientific Adviser to the Government of India, K. VijayRaghavan warned on 05.05.2021 that the third wave of Covid is inevitable given the amount of virus circulating in India. Addressing the Union Health Ministry press conference, he said: *"Third phase is inevitable given the amount of virus circulating. But it is difficult to predict the timeline. We should prepare for the new (third) wave."* He also stated the need to take the strong measures for the country to altogether avert the third wave. Various news reports covered this in their news articles:
https://www.nationalheraldindia.com/health/third-wave-of-covid-19-inevitable-warns-govts-scientific-advisor
https://www.financialexpress.com/lifestyle/health/coronavirus-in-india-is-coronavirus-3rd-wave-100-inevitable/2255542/

55. On 19.03.2020, the CDSCO, which operates under the direction and control of the Ministry of Health & Family Welfare, Government of India, already declared that in the light of the prevailing Covid-19 pandemic, any drug approved anywhere in the world for Emergency Use Authorisation would be entitled to the same status i.e. Emergency Use Authorisation through a Special Regulatory Pathway in India. It is pertinent to mention here that Baricitinib in combination with [Remdesivir] for the treatment of COVID-19, was granted USFDA Emergency Use Authorization on 19 November 2020. The permission recognized its use in patients requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

56. The CDSCO/DCGI had already given permission for the manufacture and marketing of Baricitinib API and tablets considering the emergency situation and unmet medical need in light of the COVID-19 outbreak. One such

permission granted to M/s Natco Pharma Ltd. for manufacture and marketing of Baricitinib API and 1 mg, 2mg and 4mg tablets for Emergency Use in Covid-19 pandemic forms a part of public documents.

57. This signifies that there are circumstances of national emergency and considering the warning of the unavoidable third wave of COVID in India by the principal scientific adviser to the government of India, K. Vijayraghavan the situation has become alarming. The urgent steps need to be taken for availability of the essential medicines in the treatment of COVID-19.

V (II). NON FULFILMENT OF THE PUBLIC REQUIREMENTS

58. The working statements filed by the patentee/Eli Lilly admits that the Baricitinib tablets were never manufactured in India and the supply in India was exclusively through import from Spain. The quantity imported in years 2018 and 2019 is only 8385 and 9070 tablets respectively. Looking at the currently prescribed 14 days course of tablets for a patient, this would hardly be sufficient for the 600 to 650 people. For 2020-2021 the Eli Lilly has announced free donation of 4 lakh tablets it would not be sufficient looking at the numbers mentioned hereinbefore on the basis of valid reasons that include the WHO Situation report. Though there are some news in media that the Eli Lilly has signed agreements with some Indian drug manufacturers, their supply through local manufacturing or otherwise, the cost, the availability of products post these agreements have not been disclosed. There is no certainty on the local manufacturing, launch and adequate supply of the drug products in the Indian market.

59. The confusion about the need, the adequate supply and the affordability of Baricitinib tablets in the Indian market is apparent from the working statement filed for the year 2018. It is believed to be filed jointly by the patentee and Eli Lilly and on a bare perusal of the same it is crystal clear that none of them was surely knowing the facts about whether the public requirement was being

adequately met at a reasonable price. This is already been discussed at length hereinbefore. Therefore the patentee and Eli Lilly's approach towards the supply of Baricitinib tablets in the Indian market at the earliest and the sufficiency, affordability of the same to the Indian patients through the so-called licensing deals is unreliable and may lead to worsening of the health crisis. Thus, there is extreme urgency to mitigate the scarcity of Baricitinib tablets in the market and the genuine drug manufacturers capable to provide the Baricitinib tablets at affordable prices shall be allowed to do so. This is very important in the view of current public health crisis as well as the warning of the inevitability of the COVID third wave.

60. Secondly, the price of the Baricitinib tablets imported by patentee/Eli Lilly is another major issue. It has affected the availability as well as the affordability of the drug to Indian patients. The calculations on the basis of disclosures for the years 2018 and 2019 show that the average cost of the Baricitinib tablet is INR.3230/-. The Baricitinib tablet course for COVID-19 treatment is prescribed for at least 14 days. The total course would cost Rs. 45,220/- per patient. Therefore, not affordable to the Indian general public as it is not even a monthly family income of the majority of people in India. **The affordability issue due to high cost is another reason behind unmet need of Indian patents population.**

61. The India Situation Report-68 on Coronavirus Disease (COVID-19) published by WHO on 19.05.2021 report the 2,52,28,996 confirmed cases as on 19.05.2021. Notably, it has reported 22, 36, 479 cases in the last 7 days. With this latest update, the cases per month can be estimated to be on an average 89.5 lakhs to 1.12 crores. There are warnings that will be followed by a third and more dangerous wave. Considering the 25% of the population requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) the number comes out to be approximately 26 lakhs. Further, the Baricitinib is alone or in combination with other drugs is

found to be effective in COVID 19 at various stages including the abovementioned. **This eventually indicates the huge requirement of the Baricitinib therapies and the shortage of the drug in the market to cope with this huge requirement. It underlines the need for immediate preparedness with maximum doses of Baricitinib.** Said report is attached herewith as **ANNEXURE 19**.

62. The manufacturing and supply shortcomings of the Patentee/Eli Lilly, their ignorance about the ground realities in India shall not be allowed to affect the health of Indian patients and the mechanism for manufacture and supply to the grass root level at affordable cost is of utmost necessity in this public health emergency situation.

63. Hon'ble Supreme Court and Hon'ble Delhi High Court already took cognizance of the situation and passed orders relating to the availability of the essential medicines. Importantly Baricitinib is recognized to be useful in the treatment of Covid-19 patients. Further, the orders recommend the compulsory license issuance under sections 84, 92 and 100 of the Patents Act, 1970.

64. Thus, all the requirements, under section 92 for issuance of the Compulsory license are fulfilled in relation to Baricitinib and this is a fit case for the Learned Controller to exercise his discretionary powers and grant the compulsory license in relation to Patent no. 270765 for Baricitinib for the period that the Covid-19 pandemic continues to subsist in India.

V (III). SPECIFIC APPLICABILITY OF SECTION 92(3)

65. The applicant had already requested the voluntary license on to the Patentee INCYTE HOLDINGS CORPORATION through their Patent Agents in India and the copy was marked to ELI LILLY AND COMPANY through Mr. Steven P. Caltrider, believed to be Vice President and General Patent Counsel for ELI LILLY AND COMPANY. However, the sincere request was turned down by the Indian patent agents under the pretext

"As you may have heard, Lilly is offering continuous donations of baricitinib to the Indian government in big quantities to treat the eligible Covid-19 patients. Moreover, we have already announced the signature of 6 royalty-free voluntary licensing agreement to ensure baricitinib is available in the country for the Covid-19 patients in sufficient quantities and good quality. Couple of additional agreements are in the final phase of negotiations and may be announced soon. In the last few weeks, we have been inundated with many pharma companies who are also interested in the above purpose. We prioritized the negotiations with those companies who have reached out first and committed to ensure the licensed product will be available in the market as soon as possible. As you can understand, it will be challenging for Lilly to sign Voluntary Licensing Agreements with all companies who have requested for the same. Thus, we decided to stop at this stage responding to additional Voluntary licensing requests and will only make sure we conclude those that are already about to be executed."

On further request by applicant with assurance on making the high quality product available to the Indian patient population at affordable price and also showing the willingness to pay the royalty, following reply was received by the applicant:

"As indicated earlier, it is really challenging for Lilly to sign Voluntary Licensing Agreements with all the Indian companies who have requested for the same. Lilly has now executed 7 Voluntary licenses. At this stage, Lilly has decided to stop considering any additional Voluntary licensing requests. Lilly, at this stage, would like to ensure that licenses executed are concluded.

If the situation changes in the near future and in case the events would justify the issuance of additional licenses, we will reach out to you appropriately."

Thus, applicant finds no other option than to reach to the Office of the Controller General of Patents, Designs and Trade Marks (CGPDTM) vide this application under section 92 of the Patents Act, 1970. The detailed email communications and the letters exchanged are attached herewith as **ANNEXURE 20.**

66. All the attempts of applicant to get the voluntary license were futile. The patentee is not willing to consider the licensing request at this time and this may result in unnecessary delay in supply of the essential medicine in this emergency situation in India. As this being the situation is pertaining to the public health crisis relating to COVID-19 pandemic that is spread in entire India and over multiple countries and continents, the section 92(3) prescribing the non-applicability of procedure under section 87 for grant of this compulsory license is applicable here.

VI. APPLICANT'S CAPABILITY AND PREPAREDNESS FOR SUPPLY OF BARACITINIB IN INDIAN MARKET

67. Applicant is already manufacturing the essential and lifesaving drugs for COVID-19 treatment and has strong experience and expertise in manufacture and supply of the drug products.

68. The applicant has received the permission from the Central Licensing Authority/CDSCO to manufacture Test license of Baricitinib API and Baricitinib 1MG, 2Mg and 4MG Tablets for examination, test and analysis is enclosed as **ANNEXURE 21 Colly**. The applicant has applied for further permissions at regulatory authorities which are expected to be granted soon.

69. Applicant shall manufacture said Baricitinib batches through its own state of art manufacturing facilities located at Savli, Vadodara, Gujarat, India (For API) and at Manjusar, Vadodara, Gujarat, India (for formulation) in compliance with the regulatory norms.

70. Tentatively the Baricitinib API shall be available on commercial scale in first week of August of this year and the Baricitinib 1MG, 2MG and 4MG Tablets shall be available on commercial scale by mid of the August this year by the applicant. Applicant have distributor in all 4 zones [East, West, North and South] of India therefore the tablets can be supplied in each zone easily.

71. Applicant has an added advantage of his own API manufacturing capacity and said API can be readily consumed in the manufacture of tablets. Applicant states here that currently he is equipped with the resources and manufacturing capacity to monthly produce 1crore tablets of each strength (1MG, 2MG and 4MG). With this huge quantity, the applicant shall be able to fill the gap to a significant extent and the medicines shall be available to the public at large.

72. Without focusing on the profit margins, but concentrating on access at any cost following prices have been estimated by the applicant:

	Cost of Baricitinib 1mg tablet	**Cost of Baricitinib 2mg tablet**	**Cost of Baricitinib 4mg tablet**
	INR 14.00/- per tablet	**INR 18.00/- per tablet**	**INR 28.00/- per tablet**
Cost for 14 days therapy	**INR 196.00/-**	**INR 252.00/-**	**INR 392.00/-**

The above cost is excluding GST and any other taxes and any local variations etc. The applicant shall try his best to keep the variations minimum.

73. The applicant believes that the above cost shall bring this essential medicine within the purchasing power of all the Indian patients from all economic segments.

74. The applicant also focusing on supply preference to be given to patients in the economically weaker sections, government (both central and state government) welfare schemes and in remoter areas of the Country.

75. In deserving cases, the product may be made available free of cost to patients.

76. Considering the public health emergency the applicant filed this application on an urgent basis and reserves the right to file additional supporting documents and material as may be necessary in support of its case. The applicant also undertakes to file any additional information as may be required by the Learned Controller.

77. Given the circumstance of national emergency and huge requirement, the applicant request for the grant of Compulsory License so his country India does not suffer shortage of this essential medicine as it suffered for the supply of oxygen.

PRAYER

In the light of the above, the Applicant respectfully prays that the Learned Controller be pleased to exercise the duty mandated under Section 92(1) read with 92(3) of the Act and grant the Applicant the Compulsory Licence requested and on the following terms and conditions:

a. Permission to the applicant for manufacture and market Baricitinib as bulk API;
b. Permission to the applicant for manufacture and market 1 mg, 2 mg, and 4mg Baricitinib tablets subject to approval of DCGI/CDSCO;
c. Grant of compulsory license to manufacture the drug covered by the patent for Covid-19 indication only;
d. Payment of the royalty up to 7% of the net profits;
e. Grant of a compulsory license for the territory of India for the period till the prevailing pandemic situation continues;

f. Preference is to be given to patients in the economically weaker sections, government (both central and state government) welfare schemes and in remoter areas of the Country;
g. In deserving cases, the product will be made available free of cost to patients.

We specifically request that in case the Learned Controller is not satisfied with this application and decides to refuse or pass any adverse decision with respect to the application, we shall be given a hearing before refusal or any such adverse decision. So that we will be able to represent and/or provide the justifications, evidences as the case may be to the satisfaction of the Learned Controller.

Most respectfully submitted
Dated this the 26th day of May 2021.

For and on behalf of
BAJAJ HEALTHCARE LIMITED
Signature: To be digitally signed by
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(Patent Agent Reg. No. IN/PA-1688)
OF INTELLECTUAL PLATFORM®
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ANNEXURE-1

Article

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

33

Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients

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Abstract

Baricitinib is an oral Janus kinase (JAK)1/JAK2 inhibitor approved for the treatment of rheumatoid arthritis (RA) that was independently predicted, using artificial intelligence (AI) algorithms, to be useful for COVID-19 infection via proposed anti-cytokine effects and as an inhibitor of host cell viral propagation. We evaluated the *in vitro* pharmacology of baricitinib across relevant leukocyte subpopulations coupled to its in vivo pharmacokinetics and showed it inhibited signaling of cytokines implicated in COVID-19 infection. We validated the AI-predicted biochemical inhibitory effects of baricitinib on human numb-associated kinase (hNAK) members measuring nanomolar affinities for AAK1, BIKE, and GAK. Inhibition of NAKs led to reduced viral infectivity with baricitinib using human primary liver spheroids. These effects occurred at exposure levels seen clinically. In a case series of patients with bilateral COVID-19 pneumonia, baricitinib treatment was associated with clinical and radiologic recovery, a rapid decline in SARS-CoV-2 viral load, inflammatory markers, and IL-6 levels. Collectively, these data support further evaluation of the anti-cytokine and anti-viral activity of baricitinib and support its assessment in randomized trials in hospitalized COVID-19 patients.

Keywords anti-cytokine; anti-viral; baricitinib; case series; COVID-19

Subject Categories Microbiology, Virology & Host Pathogen Interaction; Pharmacology & Drug Discovery

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See also: **MB Schultz *et al*** (August 2020)

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently the biggest public health challenge to the biomedical community. Despite multiple public health measures, there remains an urgent need for pharmacologic therapies to treat infected patients, minimize mortality, and optimally decrease viral shedding and subsequent transmission. Artificial intelligence (AI) allows for rapid drug development (Schneider *et al*, 2020) including repurposing existing drugs. Algorithms were used to search for approved drugs capable of inhibiting both the inflammatory damage and infectivity associated with SARS-CoV-2 (Richardson *et al*, 2020a; Stebbing *et al*, 2020). Baricitinib, an oral inhibitor of Janus kinase (JAK)1 and JAK2 (Fridman *et al*, 2010) approved for the treatment of moderately-to-severely active rheumatoid arthritis (RA) in adults,

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‡These authors contributed equally to this work as senior authors
§Sacco Baricitinib Study Group members are listed in the Appendix

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was independently hypothesized to be a therapeutic option for COVID-19. It was considered among all molecules studied to have a unique role by virtue of its potential to both inhibit relevant cytokine signaling and have activity against the numb-associated kinases (NAKs), AAK1 and GAK (Richardson *et al*, 2020a; Stebbing *et al*, 2020), which stimulate AP-2-mediated host viral propagation (Inoue *et al*, 2007; Bekerman *et al*, 2017; Owczarek *et al*, 2018).

Infection by pathogenic coronaviruses (e.g., SARS and SARS-CoV-2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS; Huang *et al*, 2005, 2020; Cameron *et al*, 2007; Ruan *et al*, 2020; Siddiqi & Mehra, 2020; Zhou *et al*, 2020). In patients with moderate-to-severe forms of these diseases, anti-viral cytokine signaling is maintained at inappropriate levels (perhaps due to incomplete viral clearance) causing acute lung injury (Nicholls *et al*, 2003), persistent interferon (IFN) activity, and impaired T-cell and antibody responses (Cui *et al*, 2003; Huang *et al*, 2005; Shi *et al*, 2020). In the COVID-19 setting, ARDS is the leading cause of death and is associated with high levels of interleukin-6 (IL-6), which appears to be a predictor of mortality (Ruan *et al*, 2020). Therefore, treating hospitalized patients requires both improved viral clearance and restriction of the inflammatory response, with the potential to improve outcomes such as mortality and reduce admissions to intensive care units. The anti-inflammatory benefit of baricitinib has been previously demonstrated through a reduction in a range of JAK-STAT-dependent cytokines (Fridman *et al*, 2010; Shi *et al*, 2014; McInnes *et al*, 2019). Phase 3 clinical trials providing safety and efficacy data have been conducted or are ongoing for baricitinib treatment in patients with autoimmune diseases including RA, atopic dermatitis, systemic lupus erythematosus, alopecia areata, juvenile idiopathic arthritis, and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE). Now, we provide biochemical and cellular evidence confirming predictions focused on anti-cytokine signaling and potential anti-viral effects for baricitinib, along with a case series, supporting its potential utility in hospitalized COVID-19 patients.

Results

Anti-cytokine activity for baricitinib

The anti-cytokine and anti-inflammatory activity of baricitinib was evaluated with a focus on cytokines relevant to COVID-19 infection. We evaluated the *in vitro* pharmacology of baricitinib across relevant leukocyte subpopulations coupled to its *in vivo* pharmacokinetics to determine its effect on distinct cytokine pathways. Concentration–response curves combined with exposure data from baricitinib-treated healthy volunteers demonstrated that baricitinib affects cytokine-dependent phosphorylated STAT (pSTAT) inhibition to varying degrees (Fig 1A). Baricitinib inhibited signaling of cytokines implicated in COVID-19 infection, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF, with lower half-maximum inhibitory concentration (IC_{50}) values translating to a greater overall inhibition of cytokine-induced JAK/STAT signaling during the dosing interval (Fig 1A). Furthermore, baricitinib treatment resulted in a significant reduction ($P < 0.05$) from baseline in plasma IL-6 at week 12 in patients with active RA who had an inadequate response to methotrexate from a phase 2b (Tanaka *et al*, 2016), randomized, placebo-controlled, dose-ranging study (Fig 1B).

Anti-viral activity for baricitinib

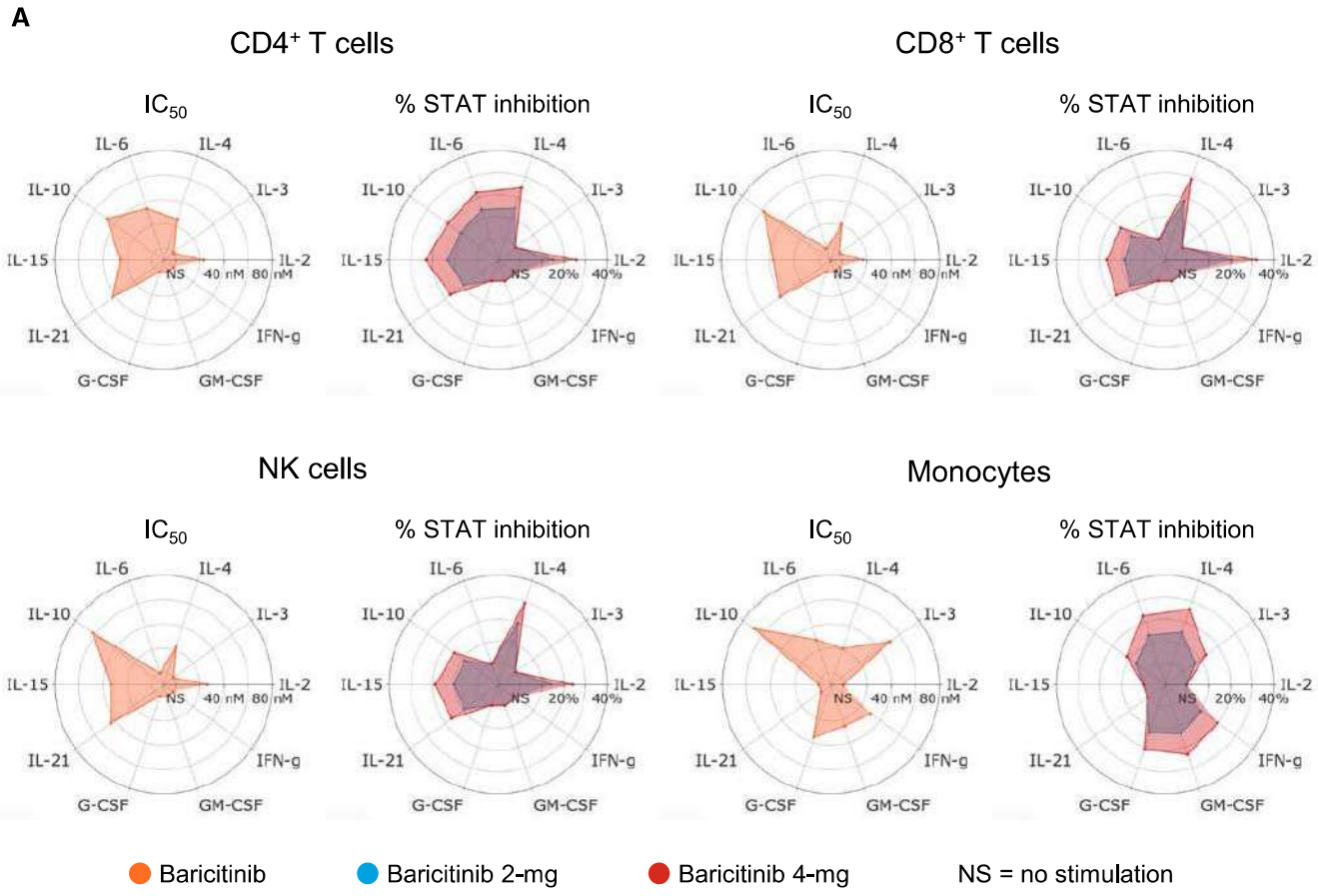
Next, we validated the proposed biochemical inhibitory activity of baricitinib on the NAK family members AAK1, BIKE, GAK, and STK16, some of which are hypothesized to facilitate viral propagation of coronavirus in epithelial cells (Bekerman *et al*, 2017; Owczarek *et al*, 2018; Richardson *et al*, 2020a). Baricitinib activity demonstrated affinity against AAK1 (8.2 nM), BIKE (20 nM), and GAK (120 nM; Fig 2A and B); these values are within the exposure range of the approved 2 mg (US, EU) and 4 mg (EU) once-daily doses of baricitinib for the treatment of RA (Shi *et al*, 2014). The pharmacokinetics of baricitinib show the unbound fraction of free bioavailable drug in RA patient sera as being 326 nM area under the curve (AUC) and 652 nM (AUC) for baricitinib 2 and 4 mg, respectively (data on file). We compared the relative binding affinities of different JAK inhibitors (JAKis) for these NAKs. Notably, among JAKis approved for the treatment of RA, baricitinib uniquely demonstrated high affinity for AAK1, BIKE, and GAK, whereas tofacitinib and upadacitinib did not demonstrate high affinity for these kinases (Fig 2B). The binding affinity of baricitinib for AAK1 and GAK is similar to the binding affinity of baricitinib for JAK1 (5.9 nM) and JAK2 (5.7 nM) (Fridman *et al*, 2010).

To extend these activities on NAKs, we evaluated the effect of baricitinib in reducing viral infectivity in 3D primary human liver spheroids (Bell *et al*, 2016) infected with purified SARS-CoV-2 and treated with baricitinib. Specifically, we used a 3D spheroid model of primary human liver cells in which hepatocytes retain their transcriptomic, proteomic, and metabolomic phenotype and functionality for multiple weeks (Bell *et al*, 2016, 2017; Vorrink *et al*, 2017), including expression of AAK1 and GAK (Fig 2C). The overlay of the viral antigen spike (as detected with 1A9 antibody) with the ACE-2 protein as detected by immunofluorescence, after 5 days of SARS-CoV-2 infection in these spheroids, provides a visual confirmation of virus infectivity in this system (Fig 2C). SARS-CoV-2 was able to infect human primary liver spheroids in this experimental paradigm, as demonstrated by a day post-infection (dpi) dependent increase in viral RNA (Fig 2D and E). Baricitinib did not result in liver cell injury up to concentrations approximately eightfold higher than the clinically observed AUC values at 4 mg (AUC = 652 nM; Fig 2F). Importantly, pretreatment of spheroids with physiologically relevant concentrations of baricitinib (400 and 800 nM) significantly ($P < 0.05$) reduced viral load by 30–40%, corroborating the proposed inhibitory effects of baricitinib on AAK1 and GAK-mediated viral propagation (Fig 2G and H). These results suggest that host cells that express these NAKs may serve as a target for baricitinib-mediated reduction in viral propagation.

Clinical case series using baricitinib

Following the recent publications by Richardson *et al* (2020a) and Stebbing *et al* (2020), COVID-19 patients were treated with baricitinib in a pilot study in Milan, Italy. Four patients with bilateral COVID-19 pneumonia, who presented with varying degrees of disease severity (Table 1), were included in this pilot study; three individuals (Patients B, C, and D) were clinically unstable with

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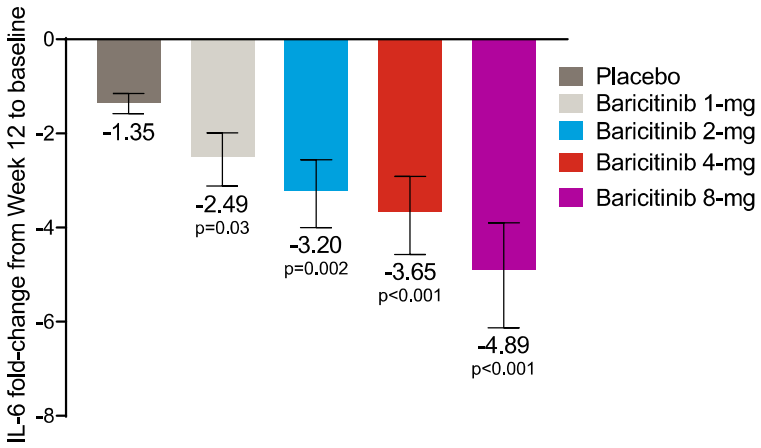


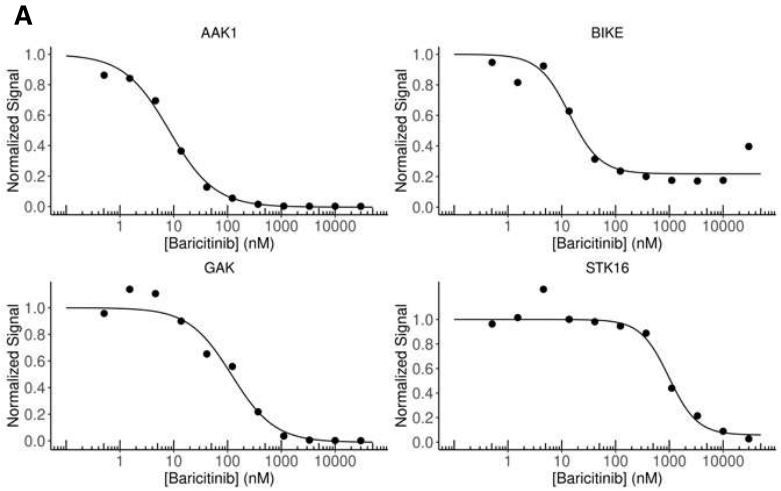
Figure 1. Anti-cytokine activity of baricitinib.

A IC_{50} values for baricitinib (orange) in cytokine-stimulated human $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and monocytes are shown for IL-2/pSTAT5, IL-4/pSTAT6, IL-3/pSTAT5, IL-6/pSTAT3, IL-10/pSTAT3, IL-15/pSTAT5, IL-21/pSTAT3, G-CSF/pSTAT3, GM-CSF/pSTAT5, and IFN-γ/pSTAT1. Average daily percent STAT inhibition was calculated using *in vitro* concentration–response curves and published human exposure data. Cytokine treatments that did not result in sufficient pSTAT stimulation are denoted as "NS" in the radar plots.

B Fold change ± standard error in baseline IL-6 plasma levels at week 12 from RA patients treated with placebo (n = 47), and baricitinib 1 mg (n = 23), 2 mg (n = 24), 4 mg (n = 23), and 8 mg (n = 23) in the phase 2b randomized, placebo-controlled study NCT01469013. P values are for comparisons of baricitinib 1, 2, 4, and 8 mg change from baseline compared with the placebo change from baseline. Treatment effects were estimated using a mixed-effects repeated-measures model (SAS Proc Mixed) using log_{10}-transformed IL-6 levels with an unstructured covariance matrix.

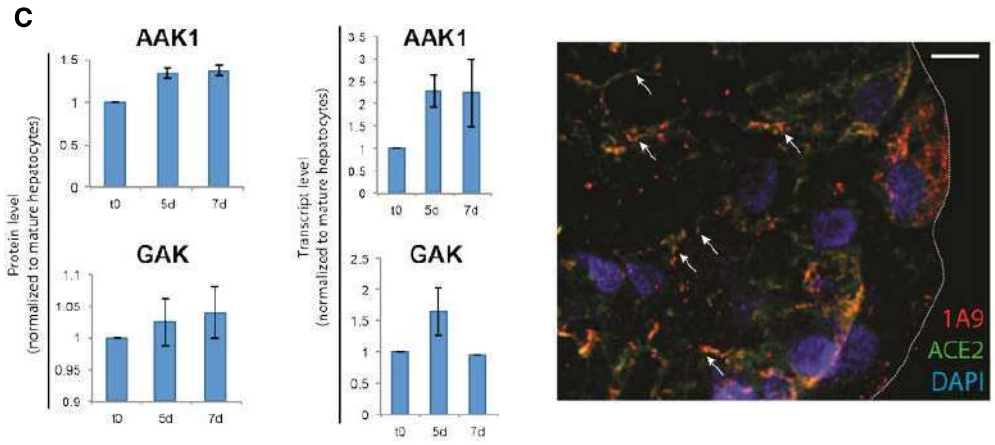
Data information: IC_{50}, half-maximum inhibitory concentration; NK, natural killer; pSTAT, phosphorylated signal transducer and activator of transcription.

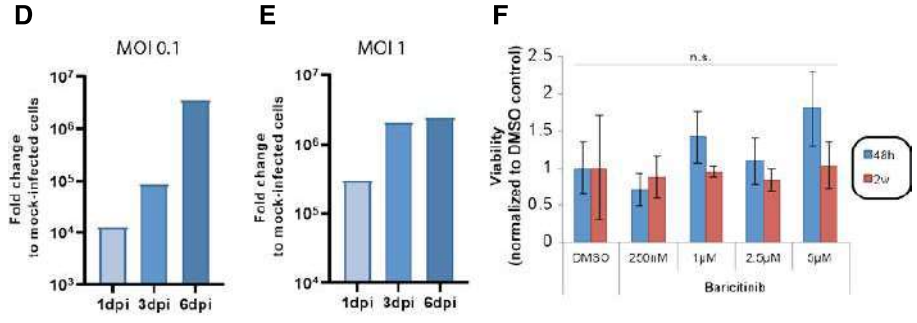
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B

Compound	AAK1 Kd (nM)	BIKE Kd (nM)	GAK Kd (nM)	STK16 Kd (nM)
Baricitinib	8.2	20	120	1100
Tofacitinib	7500	4900	18000	5000
Upadacitinib	9900	11000	2200	9300
AZD7762	2.9	13	1.4	1900
Sunitinib	35	6.5	35	300
Erlotinib	2000	280	21	>30000





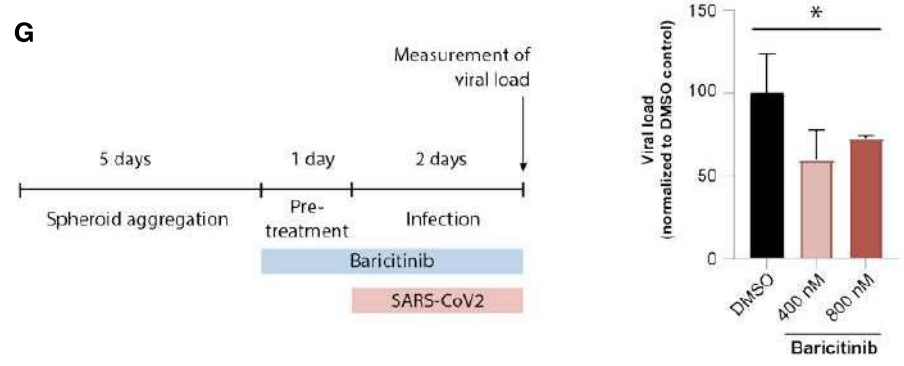


Figure 2.

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Figure 2. NAK-binding affinities of baricitinib and other comparators.

A, B Binding affinities in equilibrium affinity constant (Kd) are shown for baricitinib (A and B), tofacitinib, upadacitinib, AZD7762 (positive control), and broad-spectrum tyrosine kinase inhibitors sunitinib and erlotinib (B). Kd values were estimated from an 11-point concentration–response curve with fixed top parameters and a four-parameter logistic model ($n = 3$).

C Protein and mRNA expression of relevant numb-associated kinases in primary human liver organoids ($n = 3$) ($P < 0.05$). The immunofluorescence shows the juxtaposition of 1A9 (detecting spike protein from the SARS-CoV-2) in red and ACE2 in green along with the spheroid nuclei in blue as a DAPI stain ($n = 1$). Colocalization of spike and ACE2 is depicted with an arrow.

D, E Time course of days (one, three, and six days) post-infection (dpi) using liver spheroids and SARS-CoV-2 at 0.1 and 1.0 multiplicity of infection (MOI) ($n = 1$).

F Viability of spheroids was quantified by measuring intracellular ATP concentrations. Note that no significant (n.s.; Student's *t*-test) decrease in cell viability was observed for any concentration tested ($n = 10$).

G Schematic showing the timeline for the experiment shown in panel H.

H Viral load in infected (MOI 0.1) spheroids as measured by qPCR after treatment with 400 and 800 nM of baricitinib 48 h after infection (*$P < 0.05$; Student's *t*-test). Data are mean ± standard error of mean ($n = 3$).

Table 1. Clinical characteristics of patients in baricitinib COVID-19 case study.

	Patient A	Patient B	Patient C	Patient D
Age (years)	29	76	57	51
Gender	Female	Male	Male	Male
Coexisting conditions	None	AH, COPD, CAD	AH, COPD	Obesity
BMI	22	28	29	35
Medications	Combined oral contraception	Losartan, propranolol, omeprazole, aspirin, LMW heparin	Losartan, hydrochlorothiazide, inhaled beclomethasone	None
Smoking	No	Former	No	No
Data at presentation				
Symptoms	Fever, dry cough, and myalgias	Fever, dry cough	Fever, dry cough, dyspnea	Fever, dry cough, headache
Blood oxygen levels PaO2 (mmHg)	111	81	62	80
Alveolar oxygen gradient (KPa)	0	4.7	12.9	4.9
SpO2 (%)	98	97	94	91
RR/min	26	32	28	28
Baricitinib dose/days on treatment	4 mg for 10 days	2 mg for 10 days	4 mg for 12 days	4 mg for 10 days
Antibiotic therapy	None	Ceftriaxone, tazocin, fosfomycin	Ceftriaxone, azithromycin	None

Study note: According to the eligibility criteria, Patient A tested negative for pregnancy and all four patients tested negative for HIV-1/2, and tuberculosis using QuantiFERON-TB Gold Plus. AH, arterial hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RR, respiratory rate.

moderate-to-severe disease. All four patients were admitted to the ward from the emergency department in March 2020. As shown in Table 1, Patient A was a female nurse, aged 29. Patient B, a 76-year-old male, had significant co-morbidities (a former smoker, arterial hypertension (AH), chronic obstructive pulmonary disease [COPD], coronary artery disease (CAD), and had undergone an aortic aneurysm Endurant II graft repair on February 25, 2020). Patient C, a 57-year-old male, had co-morbidities including AH and COPD (non-smoker); he suddenly deteriorated a few hours following hospitalization, and was placed on continuous positive airway pressure at the time baricitinib was initiated. Patient D, a 51-year-old male, had a high body mass index (BMI) of 35. All four patients had detectable plasma IL-6 levels (Fig 3A) with markedly raised inflammatory markers (C-reactive protein [CRP]), as would be expected in patients with COVID-19 pneumonia.

As shown in Fig 3A, all four patients showed improvement with baricitinib treatment in signs and symptoms such as cough, fever, and reduction in plasma IL-6 levels, along with a reduction in the SARS-CoV-2 RNA viral load, as detected by the real-time reverse transcriptase–polymerase chain reaction (RT–PCR) signal from the nasopharyngeal carriage. Stringent criteria were used for RNA detection of SARS-CoV-2 in nasopharyngeal carriage and peripheral blood. Real-time RT–PCR was performed on three distinct viral gene targets (Corman *et al*, 2020; Appendix Table S1), using the most sensitive target (N gene) and a cutoff using Ct values > 40 for the analyses illustrated in Fig 3A, in contrast to others, for example in the hydroxychloroquine study (Ct values ≥ 35; Gautret *et al*, 2020). Only two of the patients (Patients A and C) had detectable viral RNA in their peripheral blood (Fig 3A and Appendix Table S1).

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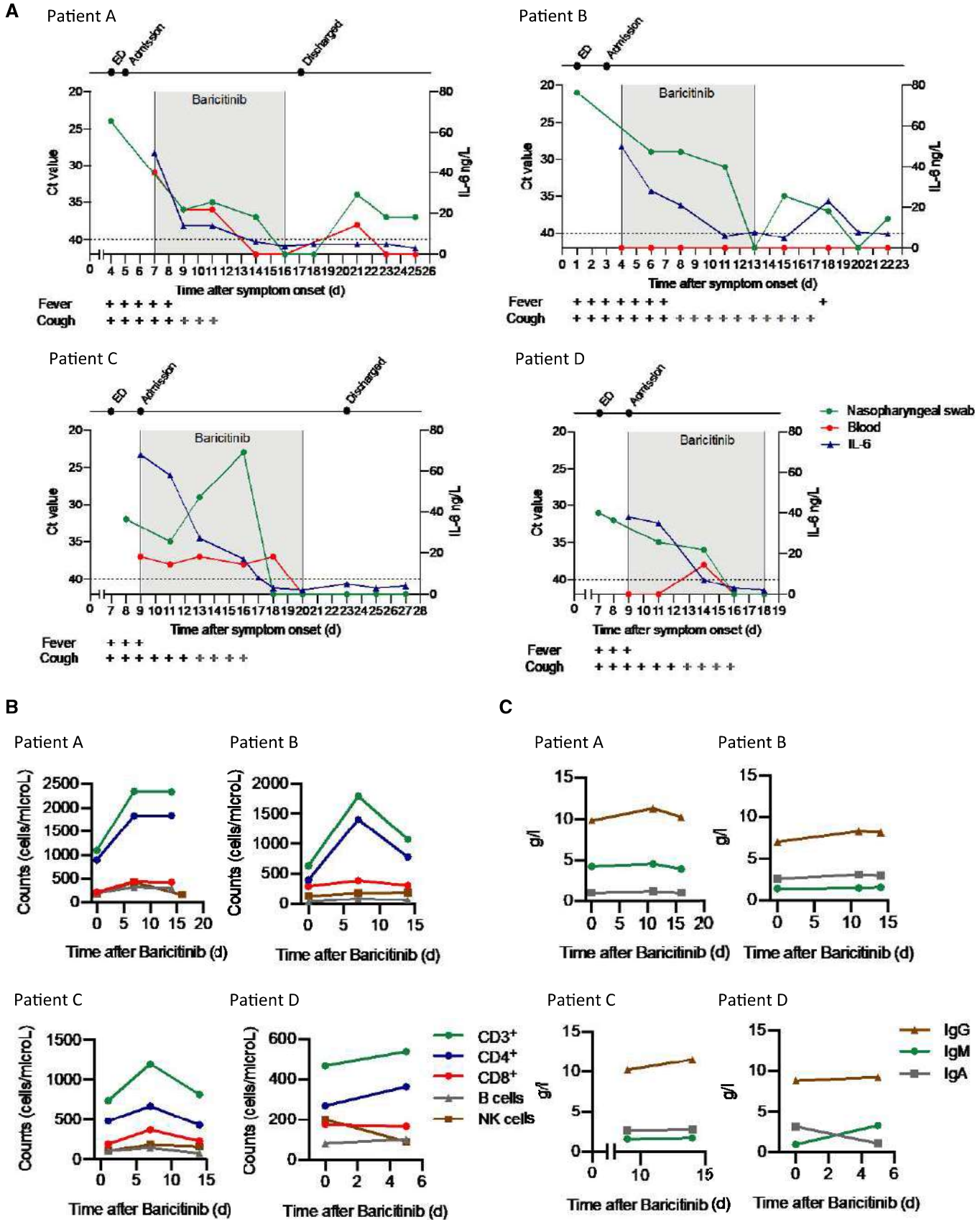


Figure 3.

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Figure 3. Viral detection and immunological features of four COVID-19 patients treated with baricitinib.

A Detection of SARS-CoV-2 in nasopharyngeal swabs and peripheral blood using the GeneFinder™ COVID-19 Plus RealAmp Kit assay (ELITechGroup S.p.A., Turin, Italy). Three viral target genes, RdRp, N, and E, together with the housekeeping gene GAPDH, were simultaneously amplified. Here, the most sensitive target gene, N, is shown. Samples with Ct values > 40 were defined as negative. A dashed horizontal line indicates the cutoff. IL-6 values are shown in the same graph. Time of baricitinib treatment is highlighted (Patients A, B, and D for 10 days, Patient C for 12 days) with total time of evaluation on the x-axis. Fever and cough symptoms are indicated. The bars in gray indicate that cough has improved but has not resolved.

B Levels of $CD3^+$, $CD4^+$, $CD8^+$, B cells ($CD19^+$), and NK cells ($CD3^-$, $CD16^+$, $CD56^+$) were determined using the AQUIOS CL Flow *Cytometry* System (Beckman Coulter).

C Total serum IgG, IgA, and IgM levels are shown for all patients.

Data information: Ct, cycle threshold; E, envelope membrane; ED, emergency department; N, nucleocapsid protein; NK, natural killer; RdRp, RNA-dependent RNA polymerase.

There were nominal changes in lymphocyte counts throughout the course of treatment with baricitinib in all four patients (Fig 3B). In addition, changes in IgG and IgM (Fig 3C) suggest adequate levels consistent with the confirmed sero-conversion for 3/4 of the patients after initiation of baricitinib (Fig 4). Most importantly, all four patients achieved sero-conversion as evidenced by the presence of neutralizing antibodies against the S1 and S2 spike proteins of SARS-CoV-2 after baricitinib exposure (Fig 4). Neutrophil and total white blood cell counts tracked with improvement in disease severity (Fig 5A). In addition, all four patients demonstrated improvement in their CRP, ferritin, and D-dimer levels (Fig 5A). Notably, Patient C, who had the lowest PaO_2 at baseline, showed radiographic improvement in lymphocytic infiltrates when comparing the computer tomography scan from day 1 to day 19 (Fig 5C). Overall, a total of 10 days of dosing for Patients A, B, and D and 12 days for Patient C, with baricitinib 4 mg once-daily orally in Patients A, C, and D, and 2 mg in Patient B (in accordance with the label guidelines for treatment of RA), was sufficient to document in all patients improved lung function, resolution of their illness, and reductions in viral load, plasma IL-6, ferritin, and CRP levels. Baricitinib treatment was associated with a rapid and consistent improvement in clinical, radiologic, virologic, inflammatory, and cytokine measures

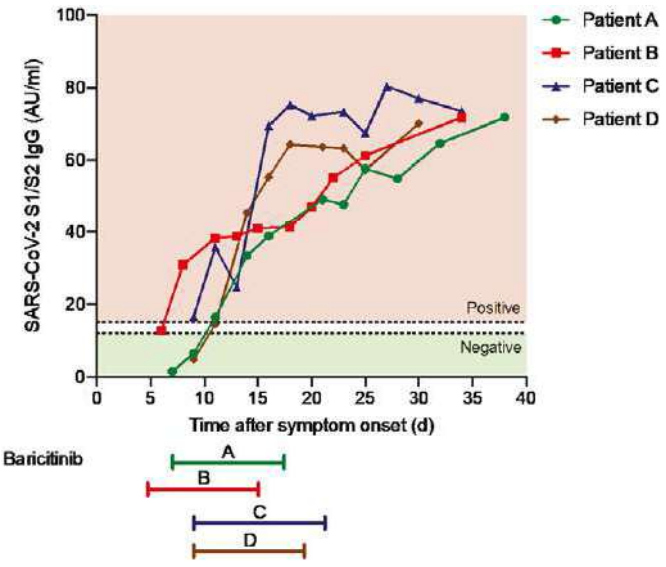


Figure 4. Sero-conversion of patients during baricitinib treatment.

Detection of IgG antibodies against the S1/S2 antigens of SARS-CoV-2. Time of baricitinib treatment is indicated for all patients (Patients A, B, and D for 10 days, Patient C for 12 days).

in this diverse group of patients, including 3 (Patients B, C, and D) who were deemed to be moderately-to-severely unwell and at high risk of deteriorating rapidly (i.e., those apart from the 29-year-old nurse). Transient increases in liver aminotransferases were observed in all four patients, with no changes in other liver enzymes or bilirubin (Fig 5B); however, these liver enzyme elevations improved within 72 h without interrupting baricitinib treatment, suggesting that these elevations may not be causally related to baricitinib treatment, but may be reflective of disease severity (Fig 5B). In general, these data demonstrate that treatment with baricitinib in these four patients with bilateral COVID-19 pneumonia was well-tolerated. Collectively, this limited case series provides preliminary evidence that baricitinib treatment may lower inflammatory burden and may result in a reduction in disease severity in COVID-19 patients.

Discussion

The pharmaceutical interventions for the treatment of COVID-19 patients proposed to date include testing anti-viral mechanisms, either in combination or alone, along with anti-malarials and immunomodulators (Siddiqi & Mehra, 2020). One such potential pharmacological approach is the use of immunomodulators in the subset of patients who develop a cytokine storm associated with pulmonary involvement including ARDS that leads to a rapid deterioration of the co-morbid conditions in such patients (Appendix Fig S1; Huang *et al*, 2020; Siddiqi & Mehra, 2020; Zhou *et al*, 2020). In this report, we demonstrate that baricitinib is an inhibitor of cytokines implicated in intensive care unit-bound COVID-19 patients, which have been collated from several reports, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF (Huang *et al*, 2020; Ruan *et al*, 2020; Zhou *et al*, 2020). Elevated IL-6 and hyperferritinemia were predictors of death in COVID-19 patients in China (Ruan *et al*, 2020; Zhou *et al*, 2020). The relevance of IL-6 in COVID-19-associated ARDS was recently shown in an open-label study where blockade with tocilizumab, an IL-6R antibody, resulted in a rapid recovery of peripheral oxygen saturation and recovery from febrile signs and symptoms (Xu *et al*, 2020). Baricitinib has been previously shown to inhibit IL-6-induced MCP-1 production from human peripheral blood mononuclear cells (Fridman *et al*, 2010). In addition to a marked and rapid reduction in levels of human serum CRP in adult RA patients previously described (Tanaka *et al*, 2016), baricitinib treatment also reduced the mean change from baseline of plasma IL-6 in adult RA patients. The anti-inflammatory effects of baricitinib have also been demonstrated by the reduction in serum levels of IFN-γ, IP-10, GM-CSF, and MCP-1 in pediatric patients with steroid-dependent chronic inflammation,

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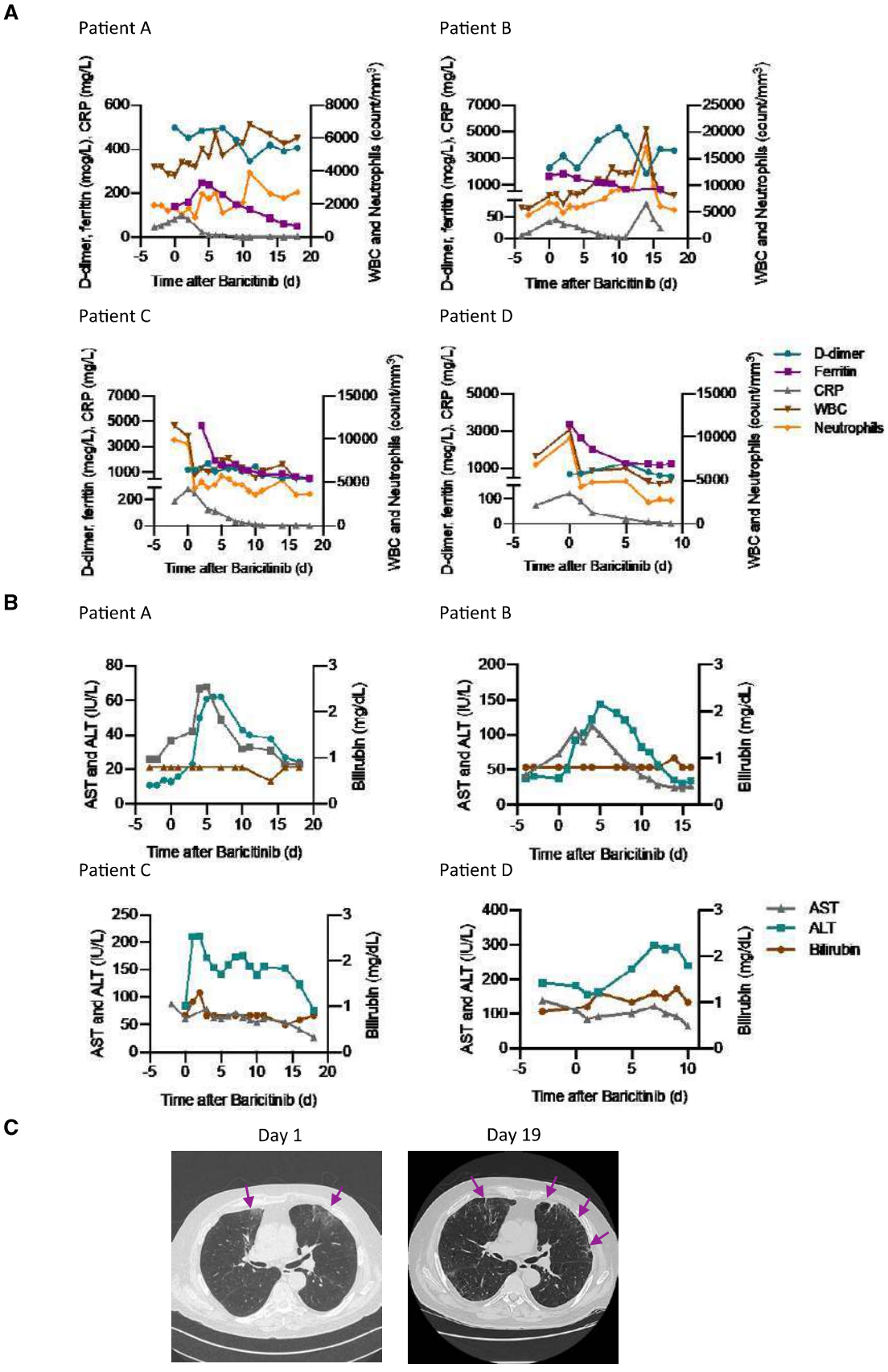


Figure 5.

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Figure 5. Standard laboratory and radiologic features of the four COVID-19 cases treated with baricitinib.

A Levels of D-dimer, CRP, ferritin, white blood cells, and neutrophils are shown for all patients.

B Levels of aspartate aminotransferase, alanine aminotransferase, and bilirubin are shown for all patients.

C Chest CT scan for Patient C on day 1 and day 19 from symptom onset showing clinical improvement over time. Day 1 CT scan shows ground-glass opacity (arrows) sub-pleurally in the lower lobes bilaterally (early stage one according to Pan *et al*, 2020). Day 19 CT scan shows that consolidation was gradually absorbed with evident residual fibrosis and emphysema bubbles (arrows) in the site of the early lesions (absorption stage 4 according to Pan *et al*, 2020).

Data information: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CT, computed tomography; WBC, white blood cells.

resulting in control of disease activity and the ability to wean or taper steroids (Sanchez *et al*, 2018).

Another pharmacologic strategy could include targeting members of the NAK family (AAK1, GAK, BIKE, and STK16) that activate the AP-2 scaffolding protein vital to viral entry and propagation (Bekerman *et al*, 2017; Owczarek *et al*, 2018). Previous reports demonstrated inhibiting such kinases was effective in reducing cellular infectivity for viruses that rely on the activity of AP-2 such as HCV, dengue, HIV, SARS, and Ebola (Chaudhuri *et al*, 2007; Neveu *et al*, 2015; Bekerman *et al*, 2017; Owczarek *et al*, 2018). While baricitinib demonstrated potent inhibition of several NAKs that phosphorylate the AP-2 adaptor and reduced viral infectivity in primary human liver spheroids, it is still unknown whether this inhibition inhibits SARS-CoV-2 propagation in COVID-19-infected patients.

The aforementioned four COVID-19 patients offer support to the mechanism of action of baricitinib as an anti-cytokine and a potential anti-viral agent. Reductions in inflammatory markers of COVID-19 diseases, such as IL-6, CRP, and ferritin, are consistent with expected anti-inflammatory activity. While the consistent reduction in viral RNA observed in all four patients (measured from their nasopharyngeal carriage) is suggestive of reduction in viral load, this could be a consequence of the natural ability in these patients to clear the virus. At the time of manuscript submission, a few weeks have elapsed since cessation of baricitinib. Active clinical, biochemical, and virologic surveillance of each patient to monitor any sequelae, including the possible appearance of an immune reconstitution inflammatory syndrome or molecular evidence of *de novo* SARS-CoV-2 replication in the respiratory tract or peripheral blood, clearly shows that all four patients were devoid of viral load and signs and symptoms of COVID-19.

Given many unknowns concerning this novel SARS-CoV-2 virus, it is necessary to consider safety concerns alongside potential efficacy. As an effective immunomodulatory agent used for the treatment of RA, baricitinib was associated with an increased risk of infections such as upper respiratory tract infections and herpes zoster (Eli Lilly and Company, 2019). Baricitinib treatment in RA patients has been associated with increased incidence of deep vein thrombosis (DVT), and it is recommended that appropriate prophylactic measures be considered with use of baricitinib in hospitalized patients with higher risk of DVT (Eli Lilly and Company, 2019). This is especially relevant given recent findings of thrombotic complications in COVID-19 patients (Klok *et al*, 2020). As baricitinib is an inhibitor of IFN-responsive genes (Sanchez *et al*, 2018), its potential impact on the subsequent development of protective humoral and cell-mediated anti-viral immunity needs to be assessed in the context of COVID-19 infection. Of relevance, RA patients on long-term baricitinib treatment achieved satisfactory humoral responses to pneumococcal conjugate (PCV-13) vaccination suggesting that humoral responses remain partially intact (Winthrop *et al*, 2019). Changes seen in lymphocyte subsets in this limited clinical case series suggest that baricitinib treatment does not reduce T-cell subsets ($CD3^+$ and $CD4^+$) or NK cells. It is too early to ascribe observed reductions in SARS-CoV-2 RNA loads in the nasopharyngeal carriage to a putative anti-viral activity of baricitinib, since the underlying T-cell subset levels were maintained in these treated patients. This is consistent with previous reports wherein various T-cell and B-cell subsets remained within normal reference ranges after initiation of baricitinib treatment in RA patients (Tanaka *et al*, 2018). It is, however, reassuring to underscore that after treatment with an immunomodulatory agent such as baricitinib, we could measure IgG anti-S1- and anti-S2-neutralizing antibodies. Most importantly, three out of four patients, while under baricitinib exposure, achieved sero-conversion, as evidenced by the appearance of IgG antibodies with neutralizing activity against SARS-CoV-2. Moreover, in all four patients, a progressive rise in the titer of these neutralizing antibodies was observed during follow-up. However, the frequency and time course of this occurrence would require prospective validation in randomized controlled trials (Ottoviani & Stebbing, 2020). Translational research from these studies will also help delineate the relative contributions of the humoral, cellular, and innate immune responses to SARS-CoV-2.

Baricitinib has a well-established safety profile in patients with RA over long-term treatment; in 10,127 patients-year of exposure and up to 6.9 years of duration, the incidence rate of serious infection was 2.8/100 patient-years and stable over time (Genovese *et al*, 2019). Furthermore, in 89 individuals treated with baricitinib in four separate single-center studies across northern Italy, no over-arching adverse safety signals have been observed with transient use (< 14 days) of baricitinib in COVID-19 patients (Francesco Menichetti, Fabio Lena, Fabrizio Cantini, and Pinuccia Omodeo, *personal communications*). Vigilance for detecting serious adverse events and appropriate management of potential complications is essential given the inhibition on IFN-responsive genes by baricitinib (Sanchez *et al*, 2018). Therefore, the impact of baricitinib on the subsequent development of protective humoral and cell-mediated anti-viral immunity in COVID-19 patients must be evaluated in randomized clinical trials (Ottoviani & Stebbing, 2020). Importantly, baricitinib is administered orally once a day and has a low cytochrome P_{450} inhibitory activity with a low drug–drug interaction risk; its short half-life (approximately 12 h in RA patients) and renal elimination as the main clearance mechanism make it fast to wash-out if necessary (Eli Lilly and Company, 2019).

Collectively, these data provide preliminary evidence that baricitinib could be tested as an effective intervention strategy to stem the cytokine storm and viral propagation seen in hospitalized COVID-19 patients. The finding that baricitinib is a potent AAK1/BIKE/GAK inhibitor that may reduce host cell infectivity, along with reaffirmation of its anti-cytokine profile, provides reasons to study this intervention in randomized clinical trials. We cannot over-interpret the

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findings from the case series described in this manuscript. Therefore, results from such randomized trials, notably the adaptive National Institute of Allergy and Infectious disease (ADAPTIVE COVID-19 ACCT2), will be central to define efficacy and safety of baricitinib and to manage effective clinical care as this outbreak continues to expand across the globe.

Materials and Methods

Leukocyte preparation and experimental design

Leukocyte preparation and experimental design were largely performed as previously described (McInnes *et al*, 2019). Whole blood samples from healthy donors ($N = 6$) were apheresed, and leukocyte-enriched fractions were transferred to the company Primity Bio (Fremont, CA, USA). Immediately following apheresis, approximately 600,000 cells were plated in 100 µl into 96-well plates and incubated with baricitinib using an 8-point dose range from 0.1 nM to 10,000 nM for 1 h prior to stimulation with cytokines for 15 min at 37°C. Baricitinib (Eli Lilly and Company) was prepared as 10 mM stocks in dimethyl sulfoxide. Cytokines were used at the following concentrations: IL-2 (4 ng/ml), IL-3 (12 ng/ml), IL-4 (350 pg/ml), IL-6 (1.5 ng/ml), IL-10 (12 ng/ml), IL-15 (850 pg/ml), IL-21 (200 pg/ml), IFN-γ (100 pg/ml), G-CSF (5 ng/ml), and GM-CSF (5 pg/ml). The choice of cytokine concentrations and incubation conditions was optimized in order to ensure consistent signaling in alternate cell types and pSTAT readouts. After stimulation, cells were fixed, permeabilized, and fluorescence-barcoded, and multicolor flow cytometry was performed as previously described to quantify STAT phosphorylation in gated leukocyte subpopulations (McInnes *et al*, 2019). For a given case (stimulation, cell type, and pSTAT combination), the IC_{50} was determined if there was a consistent response to the stimulus as described in the statistical analysis section. The primary pSTAT observed for each stimulus is reported. Leukocyte populations were defined as $CD20^+$ (B cells), $CD3^+CD4^+$ ($CD4^+$ T cells), $CD3^+CD4^-$ ($CD8^+$ T cells), and $CD3^-CD56^+$ (natural killer cells), and by forward and side scatter (monocytes). Whole blood samples from healthy volunteers were obtained under a protocol approved by the Institutional Review Board of Stanford University (reference numbers eProtocol #13942 and IRB Registration #5136). The IRB provided a Waiver of Consent because leukocyte-enriched fractions are by-products of the blood donation.

IL-6 changes in baricitinib-treated RA patients

Patient samples were obtained from the double-blind, randomized, placebo-controlled, phase 2b study NCT01469013. Patients had moderate-to-severe active adult-onset RA, despite stable methotrexate treatment. Patients ($N = 145$) were randomized (2:1:1:1:1) to placebo or once-daily oral 1, 2, 4, or 8 mg baricitinib for 12 weeks (Tanaka *et al*, 2016). Plasma IL-6 levels were analyzed using an enzyme immunoassay. Treatment effects were estimated using a mixed-effects repeated-measures model (SAS Proc Mixed) using log10-transformed IL-6 levels with an unstructured covariance matrix. NCT01469013 was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All investigation sites received approval from the appropriate authorized institutional review board or ethics committee. All patients provided written informed consent before the study-related procedures were undertaken.

Human NAK assays and viral infection

AAK1-, BIKE-, GAK-, and STK16-binding assays were performed with DNA-tagged recombinant human proteins derived from HEK-293 cells or *Escherichia coli*. AAK1 kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log phase and infected with T7 phage and incubated with shaking at 32°C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases (BIKE, GAK, and STK16) were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 min at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock; Thermo Scientific Pierce, 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1× binding buffer (20% SeaBlock, 0.17× PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 111× stocks in 100% DMSO. Equilibrium affinity constants (Kds) were determined using an 11-point threefold compound dilution series with three DMSO control points.

All compounds for Kd measurements were distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions were performed in polypropylene 384-well plates with a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 h, and the affinity beads were washed with wash buffer (1× PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1× PBS, 0.05% Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 min. The kinase concentration in the eluates was measured by qPCR.

SARS-CoV-2 infection of human liver spheroids

Protein levels of AAK1 and GAK were pulled out from tandem mass tag (tmt)-based proteomic datasets (Oliva-Vilarnau *et al*, In press) generated from total protein of 192 spheroids at the Clinical Proteomics Mass Spectrometry facility (Science for Life Laboratory, Stockholm, Sweden). Both proteins had a protein spectrum match (PSM) level of > 1 in all analyzed samples. The corresponding RNA expression values were obtained by bulk RNA sequencing (poly-A) of a minimum of 100 ng total RNA at the National Genomics Infrastructure (NGI) facility (Science for Life Laboratory, Stockholm, Sweden).

SARS-CoV-2 (GenBank accession number MT093571) was isolated from a nasopharyngeal sample of a patient in Sweden on Vero E6 cells. Cryopreserved PHH (BioIVT, USA) was thawed and seeded into 96-well ultra-low attachment plates (Corning) with 1,500 cells per well as previously described (Bell *et al*, 2016). Spheroids were pre-exposed to baricitinib for 24 h starting five days after cell seeding. At day 6 of culture, cells were exposed to SARS-CoV-2 at a multiplicity of infection of 0.1 in triplicate for 48 h. After 48 h, spheroids were

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washed with PBS, pooled (32 wells/condition), and lysed using TRIzolTM (Thermo Fisher). RNA was extracted using Direct-zol Mini Kit (Zymo Research), and relative level of viral RNA was determined by qRT–PCR as previously described (Monteil *et al*, 2020).

Immunofluorescence microscopy

Primary human hepatocyte spheroid cryo-sections were washed twice with PBS for 10 min at room temperature. Afterward, samples were blocked with PBTA buffer (5% BSA, 0.25% Triton X-100, 0.01% NaN_3 in PBS) for 2 h at room temperature prior to an overnight incubation at 4°C with the monoclonal primary antibody anti-1A9 (diluted in PBTA to a final concentration 5 µg/ml). Samples were washed 3 × 15 min with PBS at room temperature before incubation with the secondary antibody (donkey anti-mouse diluted in PBTA 1:500) for 2 h at room temperature. Subsequently, samples were washed 3 × 15 min with PBS at room temperature and mounted with DAPI Gold Antifade.

Clinical case series

Study design and participants

On the basis of the two reports of AI-derived discovery of baricitinib in COVID-19 (Richardson *et al*, 2020a; Stebbing *et al*, 2020), the Sacco Baricitinib Study Group and Imperial College developed a protocol to assess baricitinib in a small case series of patients, acknowledging potential risks of pulmonary infections (Favalli *et al*, 2020; Richardson *et al*, 2020b) based on its mechanism of action while leveraging the hypothesis for a potential therapeutic benefit in COVID-19. Herein, we describe the cases from the independent research conducted. Ethics and local Institutional Review Board approval was authorized on March 16, 2020 (number 14581/2020), which provided permission to treat three patients with bilateral COVID-19 pneumonia with baricitinib. Three patients (Patients A, B, and C) were immediately recruited that day, having been admitted to the wards from the emergency department. A supplementary approval was sought on March 25, 2020, and obtained to treat a fourth patient (Patient D) for validation purposes.

Inclusion criteria for compassionate use of an investigational oral medicine (albeit one that was approved in another indication) for patients with signs of severe illness at diagnosis or secondary clinical aggravation (respiratory symptoms or general signs) were based on World Health Organization (WHO) criteria for severe pneumonia caused by SARS-CoV-2 (WHO, 2020a).

Written informed consent was obtained from each patient, and 4 mg oral baricitinib was administered once-daily according to the label for treatment of RA with a 2 mg lower dose as per the label, for 10–12 days.

Criteria for patient discharge with recovery were from the European Centre for Disease Prevention and Control guidelines (ECDC, 2020). The open-access Clinical Characterization Protocol for Severe Emerging Infections of the International Severe Acute Respiratory and Emerging Infection Consortium (supported by WHO) has been updated and used in response to COVID-19 (Dunning *et al*, 2014).

Procedures

Clinical samples for SARS-CoV-2 diagnostic testing were obtained according to WHO guidelines (WHO, 2020b). For each patient, a sampling strategy was implemented in which nasopharyngeal and blood samples were obtained regularly from hospital admission, and subsequently once every two or three days until patient discharge. At the time of manuscript submission, these four patients continue to be monitored for COVID-19 disease. Upper respiratory samples were nasopharyngeal swabs, and blood samples were EDTA tubes adapted for RT–PCR. All samples were analyzed in the same center as the patients where procedures for RNA extraction, real-time RT–PCR (rRT–PCR), were undertaken.

Throat swabs and plasma for each patient were processed using the automated ELITe InGenius® system and the GeneFinderTM COVID-19 Plus RealAmp Kit assay (ELITechGroup, France). The reaction mix was manually prepared (according to the manufacturer's instruction) and loaded onto the system with other reagents, while RNA was extracted from 200 µl of sample and eluted in 100 µl; the final reaction volume consisted of 5 µl of RNA plus 15 µl of reagent mix. The RT–PCR setup according to the manufacturer's instructions was 50°C for 20 min, 95°C for five minutes plus 45 cycles at 95°C for 15 s, and 58°C for 60 s. Three target genes, RNA-dependent RNA polymerase (RdRP), nucleocapsid protein (N), and envelope membrane protein (E) were simultaneously amplified and tested. A cycle threshold value (Ct value) < 40 was defined as a positive test result, and a Ct value greater than 40 was defined as a negative outcome according to our criteria. The quality of nasopharyngeal swabs was checked using the CELL Control r-gene Kit (bioMérieux).

IL-6 levels were determined on the fully automated immunochemistry platform COBAS e601 (Roche Diagnostics) by the proprietary electrochemiluminescent immunoassay (ref. 05109442190, lot 43676101) using 30 µl of serum. SARS-CoV-2 serum IgG and serum IgM were qualitatively assessed using the immunochromatographic COVID-19 IgG/IgM Rapid Test, following instructions (PRIMA Lab SA, Balerna, Switzerland). Briefly, 10 µl of EDTA-anticoagulated plasma was loaded into the well of each cassette. 80 µl of buffer was subsequently added to the well. The presence of SARS-CoV-2 IgG and IgM was visually determined after an incubation of 10 min.

Immunoglobulin levels (IgG, IgA, IgM) were measured on the automated platform AU 480 (Beckman Coulter) by their respective proprietary immunoturbidimetric assays; complete blood cell count was performed on XN-9000 Automated Hematology System (Sysmex); coagulation tests including D-dimer levels were carried out on the fully automated hemostasis testing analyzer ACL 750 TOP (Werfen) using proprietary reagents; alanine aminotransferase and aspartate aminotransferase activity, CRP, and serum ferritin concentrations were determined on the fully automated platform for Clinical Chemistry and Immunoassay Alinity ci (Abbott Diagnostics) with the proprietary reagents. For measuring AST and ALT, the assays with the addition of pyridoxal-5-phosphate (P-5′-P) traceable to the reference measurement system, for CRP the high-sensitive immunoturbidimetric assay, and for ferritin levels the chemiluminescent microparticle immunoassay, were respectively used.

On the wards, standard laboratory and clinical management according to two treating physicians' discretions (MC and GC) were used. The chest CT shown was performed using a single inspiratory phase in one commercial multidetector CT scanner (General Electric Healthcare Revolution64) with a breath-holding protocol (tube

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Primer and probe sequences used for SARS-CoV-2 rRT–PCR

Assay	Oligonucleotide	Sequence
N	Forward primer (HKU-NF)	TAATCAGACAAGGAACTGATTA
N	Reverse primer (HKU-NR)	CGAAGGTGTGACTTCCATG
N	Probe (HKU-NP)	FAM-GCAAATTGTGCAATTTGCGG-TAMRA
E	Primer E_Sarbeco_F1	ACAGGTACGTTAATAGTTAATAGC GT
E	Primer E_Sarbeco_R2	ATATTGCAGCAGTACGCACACA
E	Probe E_Sarbeco_P1	FAM-ACACTAGCCATCCTTACTGC GCTTCG-BBQ
RdRP	Primer RdRP_SARSr-F2	GTGARATGGTCATGTGTGGCGG
RdRP	Primer RdRP_SARSr-R1	CARATGTTAAASACACTATTAGCATA
RdRP	Probe RdRP_SARSr-P1	FAM-CCAGGTGGWACRTCATCMG GTGATGC-BBQ
RdRP	Probe RdRP_SARSr-P2	FAM-CAGGTGGAACCTCATCAGGA GATGC-BBQ

Primer and probe sequences for gene N are from the Hong Kong protocol (HKUMed, 2020). Primer and probe sequences for genes E and RdRp are from the Berlin protocol (Drosten *et al*, 2020). E, envelope membrane; N, nucleocapsid protein; RdRp, RNA-dependent RNA polymerase; rRT–PCR, real-time reverse transcriptase–polymerase chain reaction.

voltage 120 kVp, thickness 1.4 mm, increment of 1.4 mm, mean CTDIvol 19 mGy).

Sero-conversion assay

IgG antibodies against the S1/S2 antigens of SARS-CoV-2 using the LIAISON SARS-CoV-2 S1/S2 IgG Kit (DiaSorin S.p.A., Saluggia, Italy) were detected. The IgG antibody concentrations are expressed as arbitrary units (AU/ml) with values < 12 being interpreted as negative; between 12 and 15 as equivocal; and > 15 as positive. Dashed horizontal lines indicate the cutoff values.

Statistical analysis

NAK-binding assays

The concentration–response curve (CRC) fitting for NAK-binding assay as previously described was normalized by dividing by the mean of three replicates of the 0 nM treatment condition. Four-parameter logistic (4PL) curves were fit with the normalized assay signal as the response and $\log_{10}$ compound concentration as the independent variable using the R drc package (R version 3.6.0 and drc version 3.0). The curve top parameter was fixed to a value of one, while all other parameters were estimated in the curve fitting. Kd values were determined using the absolute half-maximum efficacy concentration (EC_{50}) values estimated from the logistic model.

IC_{50} values for cytokine signaling

IC_{50} values were determined by analyzing the mean fluorescence intensity (MFI) of cytokine-stimulated samples in the presence of the designated concentration of compound. For a given case (stimulation, cell type, and pSTAT combination), the MFI for unstimulated and stimulated cells was determined for each donor. To ensure that a biologically relevant signal was induced, CRCs were only analyzed when a consistent response to stimulus was observed as described below. Data for baricitinib were analyzed with a mixed-effects model having compound as a fixed effect and donor as a random effect.

Selection of cases for analysis, fitting, and selection of CRC curves for anti-cytokine activity of baricitinib

Two sets of criteria for reporting an IC_{50} value and computing a steady-state activity (SSACTIVITY) curve were used: one at the case level and another at the individual curve level. At the case level, the median across the six donors of the minimum stimulated to unstimulated ratio over two replicates is computed, and it is required that the median minimum ratio be above 1.5. Out of a total of 85 cases, 43 were selected according to these criteria. Once a case met this criterion, 4PL curves were fit to the curve response concentration data. If an individual curve had top outside of the 80–120% activity range or bottom outside of the (−20, 20%) range, the 4PL was refitted with these constraints. After a CRC was fit, the following quality criteria were evaluated: (i) R2 above 0.8; (ii) SE of $\ln(I\ IC_{50})$ below 10; and (iii) estimated IC_{50} is within a fivefold difference in the minimum and maximum experimented concentrations. A curve failing any of these criteria was discarded.

Estimation of daily percent inhibition

The individual 4PL CRCs were combined with population pharmacokinetic (PK) curves to calculate the average steady-state daily percent inhibition. The PK profiles of baricitinib were estimated from a two-compartment model with zero-order absorption that was developed using data from healthy volunteers from three phase 1 clinical trials with once-daily 2–20 mg or twice-daily 5 mg. Protein-binding effects were accounted for by replacing the *in vitro* IC_{50} with an adjusted IC_{50} value computed by dividing the IC_{50} value for each donor by the proportion of compound unbound. Protein-bound adjusted CRCs were constructed by replacing the *in vitro* IC_{50} value with the adjusted value. The average daily percent inhibition for a subject was obtained by entering the steady-state PK concentrations into the adjusted CRCs, computing the area under this curve, and dividing it by 24 h. Using the individual donor values for average daily percent inhibition, a mixed-effects model having compound as a fixed effect and donor as a random effect was fit. The reported estimates for population average SSACTIVITY are taken as the least-squares means from this model. No transformations were undertaken to keep the estimates of SSACTIVITY within the 0–100% range.

Data availability

Eli Lilly and Company data are available upon request at vivli.org. Access to data is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Access to data and documents will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org. In your request, include the following accession/reference numbers (GenBank accession number MT093571) so that

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The paper explained

Problem
There are few drugs that are useful to treat COVID-19, the largest medical crisis of this century. To try to solve this problem, using AI, we found that an oral, once-daily medicine, baricitinib, normally used to treat adult rheumatoid arthritis (RA), may be useful in both reducing viral propagation in cells, and to mitigate the cytokine signaling seen in the hyper-inflammatory stage of the disease. We wished to understand this further in various models and in a case series of patients.

Results
We found that baricitinib inhibited the signaling of cytokines we typically see as being present in hospitalized patients with COVID-19. Using samples from a previous randomized trial in RA, we showed statistically significant declines in IL-6 levels with baricitinib treatment. In liver spheroids designed to investigate SARS-CoV-2 infectivity and separately in kinase assays, we showed that baricitinib could reduce cellular infection by blockade of numb-associated kinase members used in viral propagation. In a small case series of patients in northern Italy with bilateral COVID-19 pneumonia, baricitinib therapy was associated with improvement in clinical, radiologic, and viral parameters along with a rapid decline in CRP and plasma IL-6 levels.

Impact
Finding new drugs in our armamentarium to treat COVID-19 would be enormously valuable. Here, we stitched together the anti-cytokine and anti-viral activity of baricitinib and studied it in a small number of hospitalized patients. This study represents rapid repurposing from AI to the laboratory to a potential bedside therapeutic and supports the testing of baricitinib in randomized controlled trials in COVID-19 patients.

we can identify the related publication and specific dataset that you are trying to access.

Expanded View for this article is available online.

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Author contributions
VK wrote the first draft of the manuscript. VK, VML, and REH designed the laboratory experiments, and analyzed and interpreted the data. JS, SO, GC, PJR, and MC wrote the clinical case series protocol, obtained ethical approval, collated case studies, and interpreted the data. JS, VK, SdB, SO, GC, VM, VML, AM, PJR, JART, BJN, REH, GR, NLB, DES, AC, AN, SY, Y-JT, AS, FB, and MC participated in the analyses and interpretation of data, wrote or critically reviewed the manuscript, and reviewed and approved the final version.

Conflict of interest
JS is editor-in-chief of Oncogene. JS has sat on a number of scientific advisory boards, including BenevolentAI, and consults with Lansdowne partners and Vitruvian, and since these findings in patients, consults with Eli Lilly and Company; he sits on the Board of Directors for BB Biotech Healthcare Trust. VML is the founder, CEO, and shareholder of HepaPredict AB. In addition, VML discloses consultancy work for EnginZyme AB. VM, AM, SO, MC, and GC report no conflicts of interest. PJR is an employee of BenevolentAI. VK, SdB, JART, BJN, REH, GR, NLB, DES, AN, and AC are employees and shareholders of Eli Lilly and Company.

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File No. SND/MA/20/000350
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Subsequent New Drug Division)

FDA Bhawan, Kotla Road,
New Delhi-110002.
Dated: 01-May-2021

To,
M/s. Natco Pharma Limited,
Natco House, Road No 2, Banjara Hills,
Hyderabad, Telangana (India) - 500034.

Sub: Grant of Permission to manufacture and marketing of Baricitinib API- Regarding.

Ref: Your application no. SND/CT21/BD/2020/22860 dated 02-12-2020.

Sir,

Please find enclosed herewith permission no. **MF/API/SND/65/2021 dated 01-May-2021** in Form CT-22 under Drugs & Cosmetics Acts and Rules thereunder and New Drug and Clinical Trial Rules, 2019 there under granted based on evaluation in consultation with Subject Expert Committee (SEC) as part of accelerated approval process considering the emergency situation and unmet medical need in light of Covid 19 outbreak for restricted emergency use in the country.

Please acknowledge receipt of the same.

Yours faithfully

(Dr. V. G. Somani)
Central Licensing Authority

Copy to:

1. **The Director, Drugs Control Administration, Drugs Control Bhavan, Vengalrao Nagar, Hyderabad – 500038.**
2. **DDC(I), CDSCO, Zonal office, Hyderabad, Telangana.**

सत्यमेव जयते

File No. SND/MA/20/000440

GOVERNMENT OF INDIA
Central Drugs Standard Control Organisation
Ministry of Health & Family Welfare
FDA BHAWAN, NEW DELHI – 110002 (INDIA)

FORM CT-22

(See rules 81, 82, 83 and 84)

PERMISSION TO MANUFACTURE NEW ACTIVE PHARMACEUTICAL INGREDIENT FOR SALE OR FOR DISTRIBUTION

Permission Number: MF/API/SND/65/2021 dated 01-May-2021

The Central Licencing Authority hereby grant permission to **M/s Natco Pharma Limited., Natco House, Road No 2, Banjara Hills, Hyderabad - 500034** (Name and full address with contact details of the manufacturer) to manufacture for sale the new active pharmaceutical ingredient manufactured by manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this permission.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).
1.	M/s. Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad – 500034, Telephone No.: 040-23547532, Fax: 040-23545298, E-Mail: clinical@natcopharma.co.in	M/s NATCO Pharma Limited (CHEMICAL DIVISION), MEKAGUDA(V), NANDIGAMA(M), RANGA REDDY(DIST.), Telangana (India) - 509 223 Telephone No.: 8548-249493 FAX: 8548-249496

3. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.

4. Details of the new active pharmaceuticals ingredient to be manufactured –**Baricitinib.**

Place: New Delhi
Date: 01-May-2021

(Dr. V. G. Somani)
Central Licensing Authority
Stamp

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

CDSCO CDSCO

Condition of Permission

1. The raw material (new bulk drug substance) shall confirm to the specifications approved by the Licensing Authority.
2. The labeling of the drugs shall confirm to the requirements specified in the Drugs and Cosmetics Rules, 1945.
3. The raw material (new bulk drug substance) can be sold to only those manufacturers who have permission, in writing, from Licensing Authority, either to use the drug for development purpose/Clinical trial/Bio-equivalence study or to manufacture the formulation for sale and distribution.
4. For manufacture of the formulation in the country, separate approval under Rule 81of New Drugs and Clinical Trial Rules, 2019 shall be obtained from the Licensing Authority.
5. If long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall continued to firmly establish the shelf-life and the complete stability data shall be submitted.
6. **The firm should submit IPC test report of Baricitinib API to CDSCO.**

File No. SND/MA/20/000344
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Subsequent New Drug Division)

FDA Bhawan, Kotla Road
New Delhi- 110002
Dated: 01-May-2021

To,

M/s. Natco Pharma Limited, Natco House,
Road No 2, Banjara Hills,
Hyderabad, Telangana (India) - 500034.

Sub: **Grant of Permission to manufacturing and marketing of Baricitinib Tablets 1mg, 2mg & 4mg - regarding.**

Ref: Your application no. SND/CT21/FF/2020/22814 dated 21.11.2020

Sir,

Please find enclosed herewith permission No. **MF/FF/SND/66/2021dated 01-May-2021** in Form CT-23 under Drugs & Cosmetics Acts and Rules thereunder and New Drug and Clinical Trial Rules, 2019 there under granted based on evaluation in consultation with Subject Expert Committee (SEC) as part of accelerated approval process considering the emergency situation and unmet medical need in light of Covid 19 outbreak for restricted emergency use in the country.

Please acknowledge receipt of the same.

Yours faithfully

(Dr. V. G. Somani)
Central Licensing Authority

Copy To:

1. **The Director, Drugs Control Administration, Drugs Control Bhavan, Vengalrao Nagar, Hyderabad - 500038**
2. **DDC(I), CDSCO, Zonal office, Hyderabad, Telangana.**

सत्यमेव जयते

GOVERNMENT OF INDIA
Central Drugs Standard Control Organization Ministry of Health & Family Welfare FDA BHAWAN, NEW DELHI – 110002 (INDIA)

FORM CT-23

(See rules 81, 82, 83 and 84)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

Permission Number: MF/FF/SND/66/2021dated 01-May-2021

The Central Licensing Authority hereby grant permission to **M/s Natco Pharma Limited., Natco House, Road No 2, Banjara Hills, Hyderabad - 500034** (Name and full address of authorised agent with contact details of the manufacturer) to manufacture for sale of pharmaceutical formulation manufactured by an manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this licence.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).
1.	M/s. Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad – 500034, Telephone No.: 040-23547532, Fax: 040-23545298	M/s Natco Pharma limited, Pharma Division, Kothur, Telangana (India) – 509228. Telephone No.: 8548257289 FAX: 8548257290

3. Details of pharmaceutical formulation:

Name of the new drug to be manufactured:	Baricitinib Tablets 1mg, 2mg, & 4 mg
Dosage form:	Tablet
Composition:	Each Film Coated Tablet Contains: Baricitinib.....1mg/2mg/4 mg
Indication:	Baricitinib, in combination with Remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
Shelf life with storage condition:	24 month, Store below 30° C, Keep out of reach of children.

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and ClinicalTrials Rules, 2019 under the Drugs and CosmeticsAct,1940.

Place: New Delhi
Date: 01-May-2021

(Dr. V. G. Somani)
Central Licensing Authority
Stamp

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

Condition for Grant of Approval/Permission

(i) The new drugs shall conform to the specifications approved by the Central Licencing Authority;

(ii) The labeling of the drugs shall conform to the requirements specified in the Drugs and Cosmetics Rules, 1945;

(iii) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by retail on the prescription of specialist for use in Hospital/ Institutional set up only" and the warning shall be in box with red back ground

(iv) As post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;

(v) All reported serious unexpected adverse reactions related to the drug shall be intimated to the Central Licencing Authority and regulatory action resulting from their review shall be complied with;

(vi) No claims except those mentioned above shall be made for the drug without prior approval of the Central Licencing Authority;

(vii) Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Central Licencing Authority before the drugs is marketed;

(viii) If long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.

(ix) **Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the county shall be got approved from the Central Licensing Authority before the drugs is marketed.**

(x) **Updated stability study data shall be submitted at periodic interval. If long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.**

(xi) **Written informed consent from each patient/or his representative prior to administration of the drug shall be obtained. Informed consent form to be used should contain in a language understandable to the patient/ or his representative the factual detail about the drug, its restricted emergency use approval, alternative therapy available etc. The copy of the informed consent form should be submitted to CDSCO before launching the drug product for marketing.**

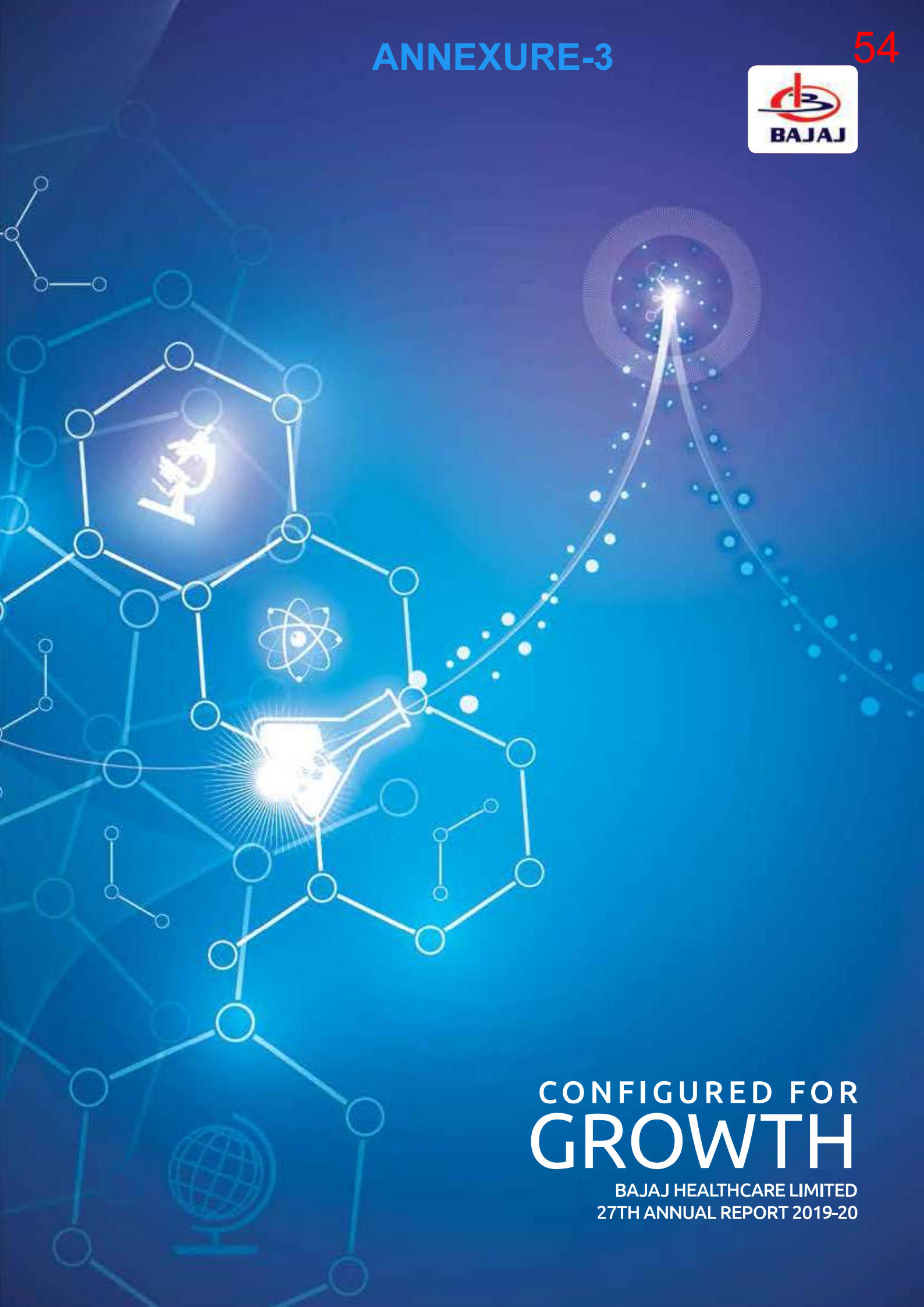
(xii) **The Label of the product should mention "For use in hospital/ institutional set up only".**

(xiii) **The Package Insert containing all details including the information as above and Informed Consent Form should be provided along with the drug product for use in hospital/ institutional.**

(xiv) **Active surveillance data of all treated patients should be submitted to CDSCO on monthly basis.**

(xv) **The Risk Management Plan including active Post Marketing Surveillance (PMS) and reporting of Serious Adverse Events (SAEs) etc. should be submitted to CDSCO within one month of approval of the drug product.**

(xvi) **Firm should conduct Phase IV Clinical Trial study and accordingly, the firm should submit Phase IV CT protocol to CDSCO within 15 days of approval.**



CONFIGURED FOR GROWTH

BAJAJ HEALTHCARE LIMITED
27TH ANNUAL REPORT 2019-20

FORWARD-LOOKING STATEMENTS

IN THIS ANNUAL REPORT, WE HAVE DISCLOSED FORWARD-LOOKING INFORMATION TO ENABLE INVESTORS TO COMPREHEND OUR PROSPECTS AND TAKE INFORMED INVESTMENT DECISIONS. THIS REPORT AND OTHER STATEMENTS - WRITTEN AND ORAL - THAT WE PERIODICALLY MAKE, MAY CONTAIN FORWARD-LOOKING STATEMENTS THAT SET OUT ANTICIPATED RESULTS BASED ON THE MANAGEMENT'S PLANS AND ASSUMPTIONS. WE HAVE TRIED WHEREVER POSSIBLE TO IDENTIFY SUCH STATEMENTS BY USING WORDS SUCH AS 'ANTICIPATES', 'ESTIMATES', 'EXPECTS', 'PROJECTS', 'INTENDS', 'PLANS', 'BELIEVES' AND WORDS OF SIMILAR NATURE IN CONNECTION WITH ANY DISCUSSION OF FUTURE PERFORMANCE. WE CANNOT GUARANTEE THAT THESE FORWARD-LOOKING STATEMENTS WILL BE REALISED, ALTHOUGH WE BELIEVE WE HAVE BEEN PRUDENT IN OUR ASSUMPTIONS. THE ACHIEVEMENT OF RESULTS IS SUBJECT TO RISKS, UNCERTAINTIES AND EVEN INACCURATE ASSUMPTIONS. SHOULD KNOWN OR UNKNOWN RISKS OR UNCERTAINTIES MATERIALISE, OR SHOULD UNDERLYING ASSUMPTIONS PROVE INACCURATE, ACTUAL RESULTS COULD VARY MATERIALLY FROM THOSE ANTICIPATED, ESTIMATED OR PROJECTED. WE UNDERTAKE NO OBLIGATION TO PUBLICLY UPDATE ANY FORWARD-LOOKING STATEMENTS, WHETHER AS A RESULT OF NEW INFORMATION, FUTURE EVENTS OR OTHERWISE.

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THE story of Bajaj Healthcare Limited (BHL) continues to be intertwined with it's core philosophy of creating a differentiated niche.

The Company has continuously strived to widen its horizon and grow exponentially.

Even as we made strides ahead, but at the same time, we ensured that we are rooted to our core and at every opportunity we focused on strengthening them.

Our road to success has been defined by the configurations we undertook to strengthen our cores, from manufacturing to research and development.

Thus, today, BHL has emerged as a company who has been able to create a niche that is ring-fenced by significant competitive advantages.

At BHL, we configured our cores to develop such a business model that helped us grow from strength to strength, year after year.

The result is evident in the numbers:

FY20 proved to be an extremely challenging year. The slowdown global and national economy dented most bottomlines in FY20, BHL's profit after tax profit enhanced by 38%.

The slowdown affected margins; BHL's PBT margin expanded 1,340 bps to 7.85%.

THE BIG PICTURE

Largest
World's largest manufacturer of Chlorhexidine base

Largest
India's largest manufacturer of Ascorbic Acids

51+
Countries of presence

50+
Clients portfolio

6
Manufacturing facilities

80+
Products manufactured in API, Intermediates & Formulations

7,776 TPA
BHL's API & Intermediates manufacturing capacity

38%
PAT growth in FY20

1,104
million pcs p.a.
BHL's Formulation manufacturing capacity

200+
Finished dosage formulations manufacturing approval

5
New molecules launched in FY20

₹ 3,755 .45
million
Market capitalisation as on June 30, 2020



Bajaj Healthcare Limited.
Manufacturer of APIs, Intermediates and Finished Formulations.

Amongst one of the emerging global manufacturers of high-volume and high-value pharmaceutical products.

Grew at 249%, over the last decade, while expanding margins.

AND NOW **RECONFIGURED** TO ACCELERATE GROWTH EVEN FASTER.



WHAT YOU NEED TO KNOW ABOUT BAJAJ HEALTHCARE LIMITED

Values navigating our existence

Our Vision

- Our vision is to be a leading pharmaceutical company in India and to become a significant global player by providing high quality and affordable products.
- Commitment to continuous improvement and innovation.
- To develop environment friendly system.
- Contributing towards better healthcare through innovation.

Our Mission

- Innovation and excellence with customer satisfaction.
- Our mission at Bajaj Healthcare Limited is to become a global leader in manufacturing of APIs and Pharmaceuticals with high standards of quality and technical services.
- Our mission is to provide cost-effective products with reliable quality and delivery within a short span of time.
- To achieve excellence in our products and services and to build long term relationships with our customers.



A respectable track record

Incorporated in 1993, Maharashtra-based Bajaj Healthcare Limited is one of India's emerging large scale and vertically integrated pharmaceutical manufacturer for quality-conscious customers across the globe.

Bajaj Healthcare Limited (BHL) differentiates itself from its competitors through its unrivalled combination of market-leading product portfolio and track record in innovation, its expert knowledge of the pharmaceuticals market, longstanding and sustainable relationships with the partners, and a highly talented and engaged workforce.

Our purpose

BHL aims to create new niches in the markets of its presence to ensure that its market share remains strong and our product portfolio remains innovative. It intends to enhance our global relevance with the help of a unique business model and wide spread offerings.

Generate profitable growth in our core markets

Realise global opportunities in the emerging pharmaceuticals market

Continue to step-change of our business capabilities

Build trust and respect in the market and communities of our presence

To focus on smart acquisitions to strengthen portfolio and sustain growth

Our world-class products that have strengthened our recall

Over the years, BHL has metamorphosed into a specialty company and focused on development, manufacturing and supply of Active Pharmaceutical Ingredients (APIs), Intermediates and Finished Dosage Formulations (FDFs) for the globally renowned companies across pharmaceutical, nutraceuticals and food industries.

API: We focus on efficiently manufacturing high-quality and high-value APIs in key therapeutic categories.

Intermediates: We focus manufacturing intermediates which form a key input component for its API and FDF manufacturing, thereby ensuring a steady demand for our products.

Finished Dosage Formulation (FDFs): We focus on manufacturing tablets, capsules, and powders which find application in key therapeutic segments.

Our professional and knowledgeable management team

BHL is headed by Mr. Sajankumar R. Bajaj (Chairman & Managing Director) and Mr. Anil C. Jain (Joint Managing Director) who, in turn, are supported by a competent managerial team with an experience of more than 10 years. With the promoters having an enriching industry experience of more than 25 years, the Company has been highly successful in taking advantage of key decision taken by them and different business opportunities.

Our culture

Our workforce is central to our ability to succeed. As we continue to transform our culture and capabilities to meet the demands of tomorrow, our employees' integrity, pride and spirit are paramount. We will continue to focus on employee engagement to create a culture which makes us proud and helps us deliver on our long-term goals.



OUR MANUFACTURING CAPACITIES

...that have enhanced our preparedness

BHL has periodically enhanced its capacities to address consumer demands

Product category	Facility location	Product	Certifications
Active Pharmaceutical Ingredients (APIs) and intermediates	1. Savli, Gujarat 2. Tarapur, Maharashtra 3. Panoli, Gujarat	Ascorbic Acid, CH Base and Its Derivatives, Citicoline Sodium, Carbamazepine, Theobromine, Ferrous Ascorbate, Doxofylline, Oxcarbazepine, Choline Bitartrate and its derivatives Octenidine Hydrochloride, Calcium Phosphoryl Chlorine Cloride, among others.	ISO 9001:2015 ; HACCP certification since 2012; Star-Kosher and OK Kosher certification; GMP certification; Certificate from CDSCO i.e. Written Confirmation for exporting products into European Union (EU)Countries; EU-GMP Certification from Croatia; MFDS (KFDA) Certificate; Certificate of Suitability (CEP) for the product- Chlorhexidine Gluconate 20% Solution from EDQM authority; MFDS (KFDA) Certificate for the product- Theobromine; Halal Certificate; FSSAI License from FDA, Gujarat; FSSC 22000 from TUV NORD CERT GmbH, Germany; WHO-GMP Certificate from FDA, Gujarat
Finished Dosage Formulation (FDF)	Vadodara, Gujarat	Cellin 500, Septran DS Tablet, Aspirin Gasto Resistant Tablets and Ecosprin Tablet, among others.	ISO 9001:2015 ISO 9001:2015 certified for its Quality Management Systems; WHO – GMP certification for the manufacturing of Capsules, Oral Powder and Tablets; FSSAI from FDA, Gujarat; Certificate of product registration from FDA, Philippiness for Hydroxychloroquine sulphate

BHL'S STORY OF EVOLUTION

Key inflection points in BHL's existence

1993
Bajaj Healthcare Limited, started its journey with the establishment of its first API manufacturing plant at Tarapur

2006
BHL strengthened its manufacturing capabilities with the acquisition of an API manufacturing unit at Salvi, Gujarat

2008
Strengthened BHL's portfolio with the commencement of formulation operations at its Manjusar plant at Gujarat

2014
Further enhanced BHL's portfolio with the acquisition of intermediates manufacturing unit at Boisar, Gujarat. Bolstered BHL's API manufacturing capacity with the acquisition of another API manufacturing unit at Panoli, Gujarat



2016
BHL got listed on the stock exchange, on BSE- SME Platform

2019
Migrated from BSE-SME Platform to BSE main board

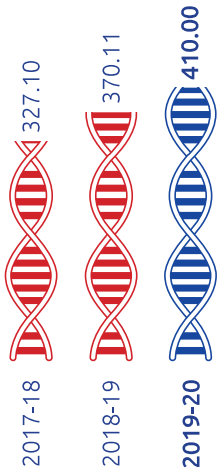
2020
Further strengthen portfolio with the acquisition of another intermediate manufacturing unit at MIDC, Tarapur, Maharashtra. As a part of this acquisition, BHL is all set to acquire four manufacturing facilities, comprising of three API manufacturing facilities and one engineering unit

RECALIBRATED CORE DELIVERED GROWTH

Numbers behind the story.

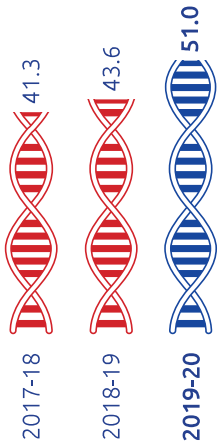
P&L Metrics

Revenue from operations (₹ in crores)



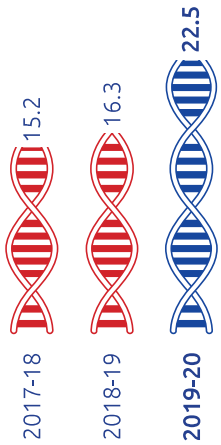
7.9%
3-year CAGR

EBIDTA (₹ in crores)



7.3%
3-year CAGR

PAT (₹ in crores)



14%
3-year CAGR

Debtors Turnover Ratio

4.67% in FY19 **4.60%** in FY20

Inventory Turnover Ratio

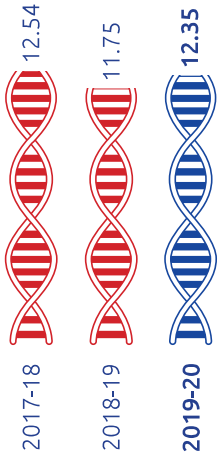
7.70% in FY19 **7.74%** in FY20

Interest Coverage Ratio*

4.46% in FY19 **6.37%** in FY20

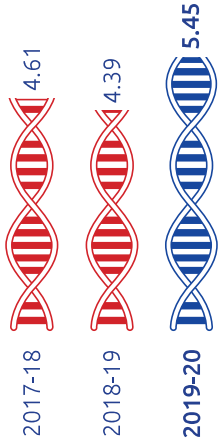
* Interest Coverage Ratio changed more than 25% during the year, owing to decrease in interest paid during the year.

EBIDTA Margin (%)



23.6%
Growth over last two years

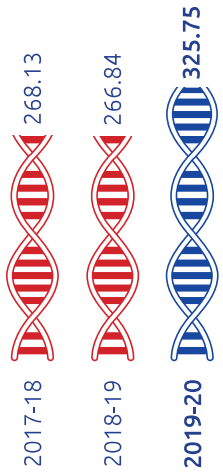
PAT Margin (%)



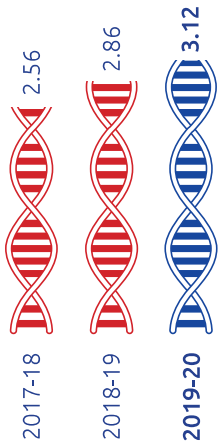
48.2%
Growth over last two years

Balance Sheet Metrics

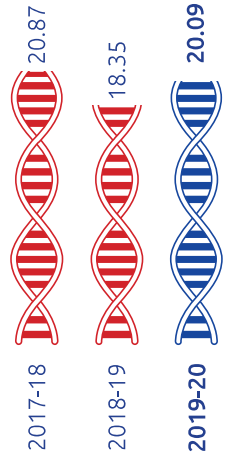
Total Assets
(₹ in crores)



Fixed Asset turnover ratio
(in times)

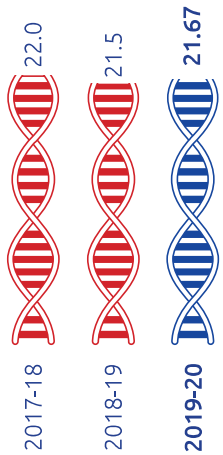


Return on Net Worth (RoNW)
(%)



11%
Growth over last two years

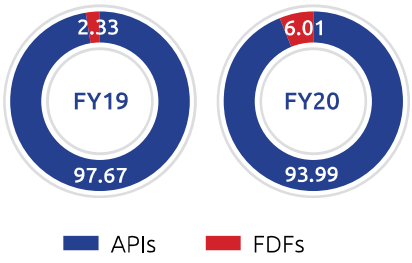
Return on Capital Employed (RoCE)
(%)



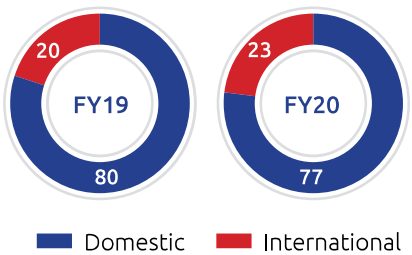
1.2%
Growth over last two years

Sales breakup

Product wise (%)



Revenue by Geography (%)



OUR GROWING PRESENCE



- Algeria
- Argentina
- Australia
- Bangladesh
- Belgium
- Brazil
- Canada
- Chile
- China
- Colombia
- Costa Rica
- Dominican Republic
- Ecuador
- Ecuador
- Egypt
- El Salvador
- France
- Germany
- Ghana
- Greece
- Guatemala
- Indonesia
- Iraq
- Israel
- Japan
- Jordan
- Kenya
- Malaysia
- Mexico
- Morocco
- Netherlands
- New Zealand
- Peru
- Poland
- Saudi Arabia
- Singapore
- South Africa
- Spain
- Sudan
- Syria
- Taiwan R.O.C
- Turkey
- United Arab Emirates
- United States
- Uruguay

OUR STRONG CLIENT-BASE

Sun Pharma Ltd.

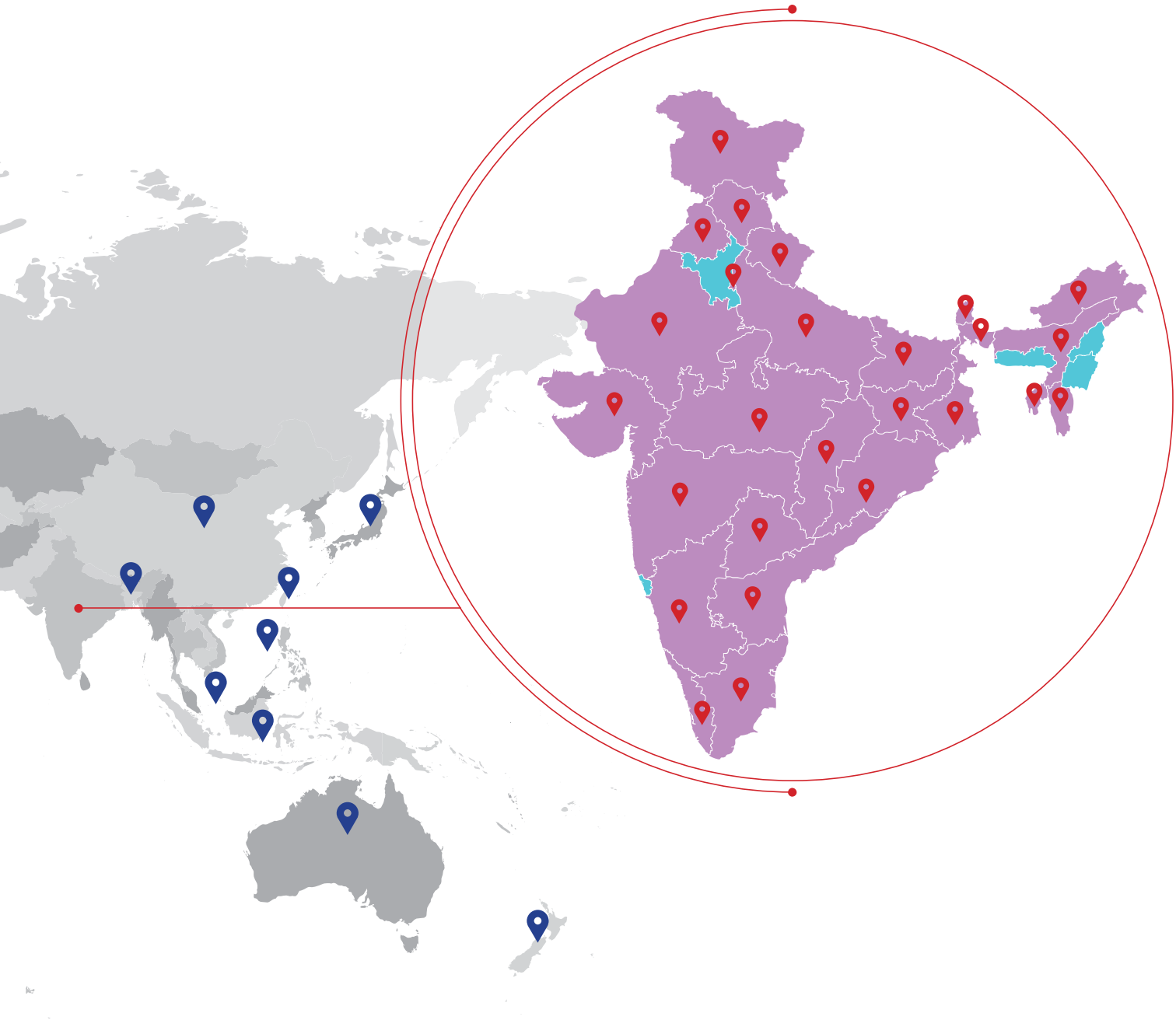
Pfizer Ltd.

Abbott Healthcare P. Ltd.

Glaxosmithkline Pharmaceuticals Ltd.

Lonza Group

Bajaj Medical Llc



Nestle Group

Evonik Industries AG

Koye Pharmaceuticals Limited

Usv Pvt.Ltd.

Intas Pharmaceutical Ltd.

Interquim S.a.

CHAIRMAN & MANAGING DIRECTOR MESSAGE

BAJAJ HEALTHCARE, TODAY, STANDS ON AN IMPORTANT JUNCTURE OF GROWTH, WHERE WE EXPECT TO ACCELERATE MUCH FASTER THAN WHAT WE HAVE ACHIEVED TILL NOW!



Mr. Sajankumar R. Bajaj, reviews the performance of the Company in 2019-20 and chalks out future growth path.

Dear shareholders,

I am happy to present you the 27th annual report of the Company. The year 2019-20 was the watershed financial year in BHL's history. Over the past few years, we have worked relentlessly to graduate from a commodity-driven company to a value-driven company. In line with this tenant, we have tried to create a robust research and development team working on molecules nearing patent expiry. We are happy to announce that in 2019-20, we launched five new molecules in the premium segment and are expected to guarantee the future growth of the Company in terms of revenue and profitability.

Performance review 2019-20

We report a revenue of ₹ 413.18 crores in 2019-20, a growth of 11.3% over 2018-19. Our focused approach on enhancing profitability over the past few years helped us increase our EBIDTA by 17% over 2018-19 and our PAT by 37.9% over 2018-19.

Despite our investments in business-strengthening initiatives, we continue to possess a strong balance sheet with a long-term gearing of 0.14 times and a cash and cash Equivalents balance of ₹ 4.16 crores.



Business strengthening initiatives

As we continued to strengthen our financial performance, we equally concentrated on strengthening our core, the results of which should become more visible over the foreseeable future. These initiatives included a proactive investment in research that should deepen our presence and should establish BHL as a more broad-based player with a relevance across a wider range of businesses and regions.

- Over the past few years, the Company focused on taking itself to the next big league in the API segment. We invested in strengthening our research capabilities with the induction of competent manpower. We also focused on developing a pipeline of molecules which are slated for patent expiry in the near future. This has helped us to successfully introduce five new molecules during 2019-20. These are high-value and low-volume products, and are expected to strengthen our profitability in the coming years. Moreover, the Company embarked on building another state-of-the-art research and development center (expected to commission by October 2020) in Baroda to further bolster our research strengths.
- One of our major achievement during the year was the GMP approvals from the European customers and the South Korean customers. These approvals revalidated our stringent quality-control parameters. With these two approvals, we are now present across the world's major regulated pharmaceutical markets, with exports contributing to about 23% of our revenues in 2019-20. The road to this achievement was challenging. To achieve these approvals, we realigned our processes, invested in cutting-edge equipment, recruited experienced industry professionals, and extensively trained our existing employees to match international standards. Achieved after rigorous planning and implementation for the past three years, these approvals are not just going to strengthen the Company's performance in the coming years but would also help us expand our market base. Our standard operating procedure helps us in streaming the processes while resulting into an overall efficiency improvement.
- Furthermore, the Company is strengthening its manufacturing capabilities through the acquisition of assets of Vet Pharma Limited including land and building. In a post balance sheet development, we have acquired another API manufacturing unit in Maharashtra. The targeted assets have installed manufacturing capacities of 111 metric tons per month and are capable of manufacturing bulk drugs and Active Pharmaceutical Ingredients (APIs) like mefenamic acid, artemether, lumefantrine, aceclofenacalbendazole, and nimesulide. The existing product portfolios of these assets are highly complementary to our current priorities and future priorities. Going forward, this transaction ensures our access to additional portfolio opportunities within a very short period of time. Plus, the above mentioned units have additional capacities, useful to manufacture the value-added products. The full impact of the acquisition will be experienced from 2020-21 onwards.
- In a bid to become more self-reliant in line with the Prime Minister's vision of an 'Aatmanirbhar Bharat,' we have acquired a land parcel at Dahej with the required environment clearance (approximately 9 acres) that will be dedicated towards our backward integration initiatives and reduce our dependence on imported chemicals from China.

23%

We are now present across the world's major regulated pharmaceutical markets, with exports contributing to about 23% of our revenues in 2019-20.



Governance

At Bajaj Healthcare, we believe in a principle of transparency that is validated by the high level of governance in our organization. We have a well-diversified Board of Directors engaged in timely and transparent communication with our entire universe of stakeholders.

People

We consider people as our key resource and invest heavily in developing our "people" resources. We have invested in an inductive work environment, well-defined training programs, and detailed career progression plans. A testimony to our employee-centric initiatives: out of our 715 employees, more than 60% have been working for more than 10 years! A testimony of the Company's employee-centric initiatives.

Impact of COVID-19

The world-wide coronavirus pandemic drastically changed the way businesses operations are being carried out across the world and across organizations, and we are no different. In turn, we quickly facilitated a work-from-home initiative. It helped us prevent our employees from exposure to the coronavirus.

Health first - that is the underlying message that the COVID-19 pandemic has re-asserted. The pandemic is a health as well as an economic crisis and hence the role of the pharmaceutical industry has become very critical. The pandemic has shaken the global economy but has given the world an opportunity to correct decades of under investment in healthcare.

Over the past many years governments across the world have given more importance to controlling healthcare costs to balance their overall budgets. The COVID-19 pandemic and the economic costs that it has extracted may force governments to reconsider this presumption and try to strike a balance between providing adequate healthcare and the ability to fund it.

Road Ahead

We have an optimistic outlook towards the coming years. Our continuous study of molecules going off-patent is helping us create a steady product pipeline, with opportunities to add significant value to the topline as well as the bottom-line. By launching 2-5 new molecules every year, we plan to strengthen our position as a value-added API manufacturer in the market.

60%

A testimony to our employee-centric initiatives: out of our 715 employees, more than 60% have been working for more than 10 years!



Our acquisition of assets over the last few years has helped us prepare for the marketing of the near patent expiry molecules. This inorganic route of expansion has helped us keep our balance sheet light and gain a significant head-start in becoming ready for the market.

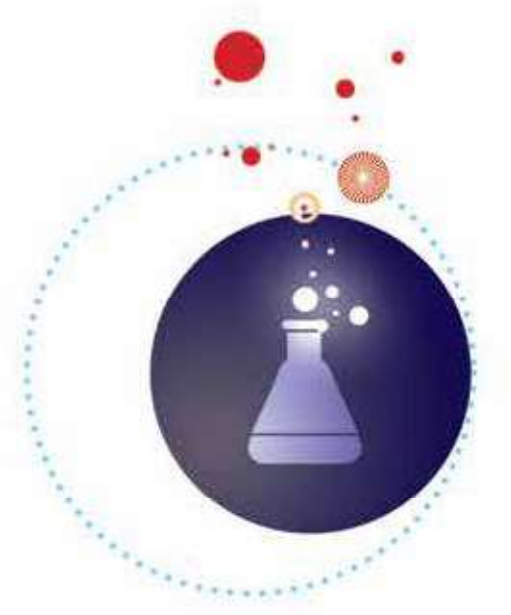
Additionally, we have shifted from just API manufacturer to a combination of formulations and APIs. These constant reconfigurations have not only helped maintain our growth momentum but also enable us to stay ahead of the competetion.

BHL's sterling performance, during the year under review, through the economic maelstrom is a testament to our robust business strategy, diversified businesses and operating fundamentals.

Riding on these initiatives, we expect to emerge as a ₹ 1,000+ crore company in the next 3 years.

Note of thanks

I am thankful to all our stakeholders for trusting our business model and staying invested in our business. We stand at an important juncture in our history and expect to prosper exponentially more than what we have achieved in the past 27 years!



SUSTAINING GROWTH MOMENTUM

BY RECONFIGURING OUR REVENUE BASE

FOR A MAJOR PART OF OUR EXISTENCE, BHL HAS BEEN PERCEIVED AS A COMPANY WHO IS STUCK IN THE LOW MARGIN AND HIGH-VOLUME GAME.

But a meaningful understanding of our business expansion strategy would reveal that we relentlessly focused on improving our manufacturing efficiencies and undertook strategic acquisitions, leading to some of the highest margins in the products we compete in.

Over the years, we strengthened our ability to enhance margins and revenues.

We did so by...

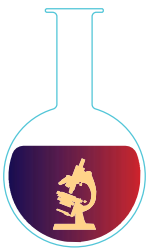
Progressively evolving our product mix from Intermediates to APIs to FDFs. Our FDF sales contributed to 6% of our revenue in FY20 compared to just 2% in FY19. Every year, we use more of our APIs for captive consumption to manufacture FDFs. While we offer all three components of the value chain, an increasing number of our customers are being converted from the purchase of APIs to lucrative formulations.

Enhancing our presence in the key therapeutic areas such as pain management, anti-malaria and tapeworm infection in the API segment which are high on value and low on volume. We focused on regular new product addition to our portfolio to support commercial launches on patient expiry.

Altered our sales mix towards value-added products in the pharma value chain – from a 100% API business in 2007, the sales mix altered to 94% to 6% between APIs and FDFs in FY20.

Leveraged our cost advantage in API manufacturing to forward integrate into generic FDF manufacturing.

Making Bajaj Healthcare Limited future-ready

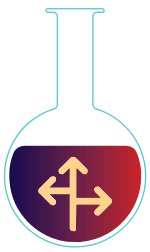


Research and innovation:
Creation of strong R&D team

Investment in cutting-edge infrastructure

Continuous development of off-patent molecules

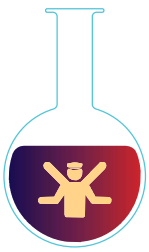
Annual introduction of 2-5 molecules



Market expansion:
Strong manufacturing practices

Creation of well-defined SOPs

Expansion in newer export markets

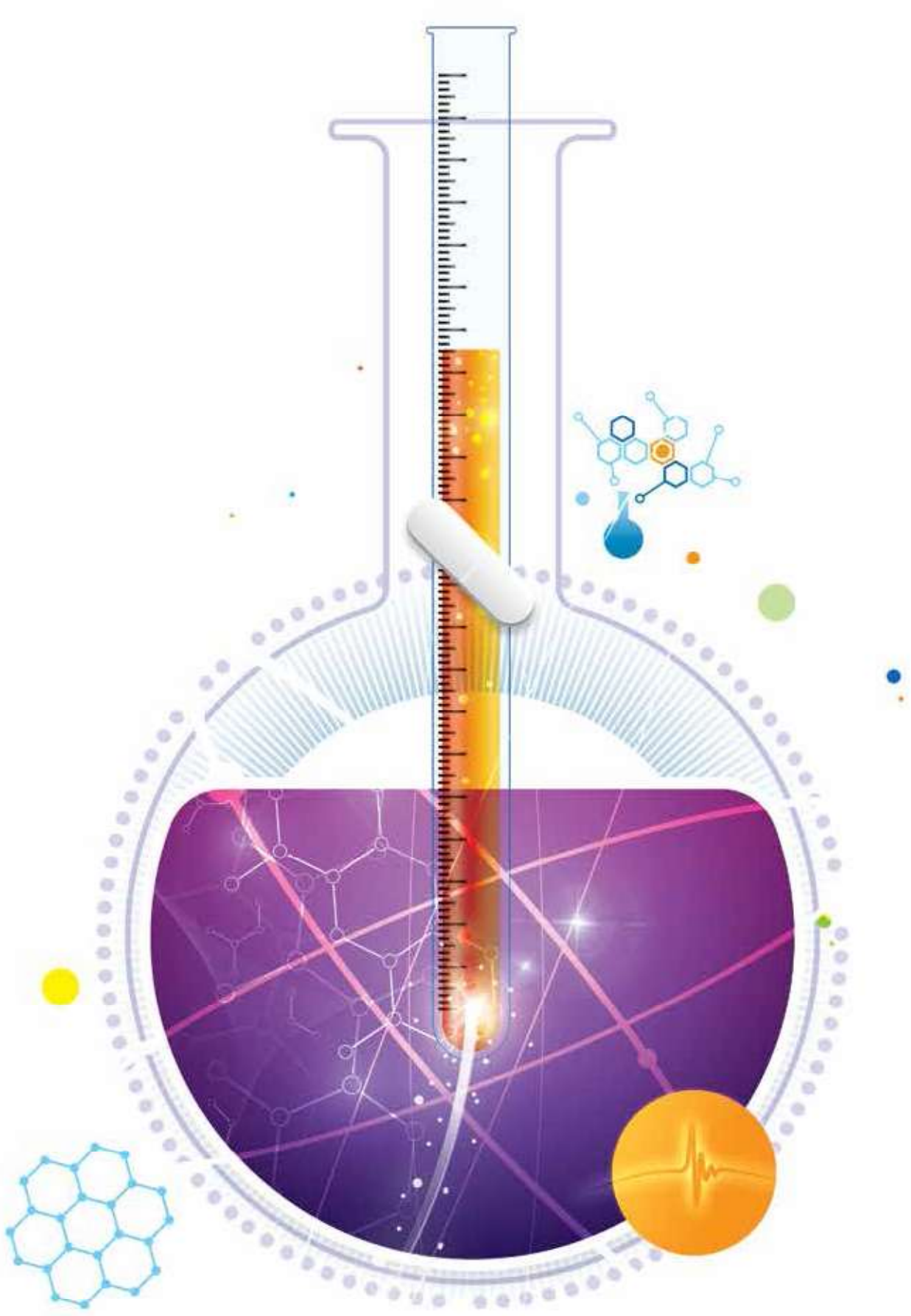


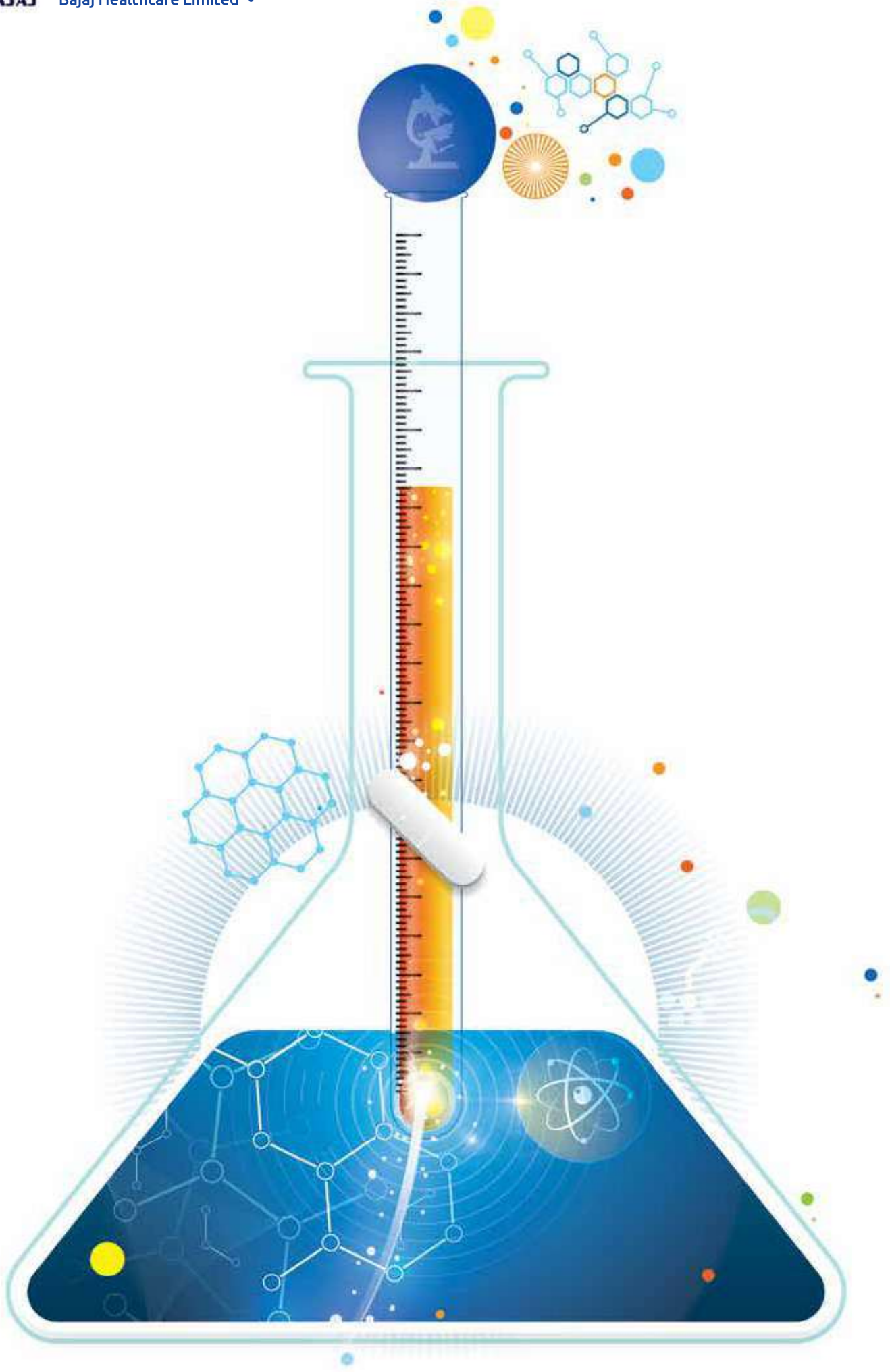
Inorganic expansion route:
Acquisition of stressed assets

Quick turnaround of these assets

Marginal investments in upgrading assets

Faster scale-up





TO SUSTAIN GROWTH MOMENTUM

ENHANCING OUR RESEARCH AND DEVELOPMENT (R&D) COMPETITIVENESS

EXPERTS OPINED THAT BHL IS MAJORLY A MANUFACTURING FOCUSED PHARMACEUTICAL COMPANY WITH LIMITED RESEARCH CAPABILITIES.

A more accurate portrayal of our business model would reveal how we are building on our competitive advantage i.e. R&D to grow wallet share while simultaneously investing in new R&D opportunities to grow revenue and improve margins.

R&D is a critical component of our growth engine, because we believe that R&D would help us to create a wider basket of products of an improving quality at a progressively lower cost. Further, effective research and new product development helps take our business ahead.

The different R&D strengthening initiatives taken by the company over the last few years are depicted by the fact our new molecule launches over the past few years.

We strengthened our R&D capabilities by...

- Forming a strong R&D team comprising of experienced professionals
- Possess a pool of talented and experienced scientists including organic/analytical chemists to provide support to our R&D through documentation and validation of test results as per ICH guidelines and assist the regulatory affairs to prepare high quality
- Undertaking regular training programs to keep ourselves updated
- Ensuring that our R&D division has the required accreditations
- Investing latest technologies to bolster capacity and ensure quality
- Equipped with fume-hoods, sophisticated equipment and facilities for carrying out synthetic research and scale-up activities to develop new process technology for APIs under safe conditions
- Department of Scientific and Industrial Research (DSIR), India certified R&D laboratory

To drive its business growth in a profitable way, the Company created a focused R&D unit to service the growing needs of its API and FDF Segment.

Result, today our R&D facility is being accredited by Department of Scientific & Industrial Research, Ministry of Science and Technology, GOI.

The importance of R&D segment cannot be over-stated. Continuous focus on R&D helped us is substantially shrinking the product transfer time from the lab to pilot scale to the commercial scale. It not only ensured a seamless conversion but also helped in improving asset utilisation at downstream facilities and improve revenue generation.

Proactive reverse engineering has helped us to reduce our dependence on our external partners for input raw-materials.

BHL'S COMPETITIVE ADVANTAGE

Leadership: The Company is among the leading global manufacturers of high-volume APIs including Ascorbic Acid, CH Base and its derivatives among others. Additionally, BHL has expanded its business scope over the years with extending its presence in the intermediates and finished dosage formulations (FDF).

Experienced management: The promoters of the Company has been long associated with the pharmaceutical industry, nearly three decades, and has a proven background and rich experience in the pharmaceutical industry. Further, the top management is being aided by a team of experienced professionals having technical, operational and business development experience. The top managements enriching industry experience has enabled the Company successfully mitigate the challenges and grab on the opportunities.

Economies of scale: The Company's has in place six state-of-the-art manufacturing facilities spread across India. The facilities can accommodate large-scale customers; the Company is amongst the top five suppliers to the regulated markets for its product portfolio. The Company is the one of the leading manufacturers of Neutraceuticals in domestic market – Ascorbic Acid IP, Sodium Ascorbate, Ferrous Ascorbate. BHL is the largest manufacturer of CH Base and its derivatives in the world, and India's largest manufacturer of Vitamin-C.

Integration: While most pharmaceutical manufacturers focus on one product vertical (APIs or FDFs), BHL invested in all three – APIs, Intermediates and Finished Dosage Formulations (FDFs), which enables the Company to add value throughout the manufacturing value chain.





Approvals: All of the Company's facilities are approved by some of the most demanding global regulatory authorities, making it possible for the Company to market products in countries marked by relatively low competition and attractive realisations.

Flexibility: Being spread across the pharmaceutical manufacturing value chain enables the Company to offer quality and wide range products to its customers across the value chain. Thereby offering BHL's customers with flexibility and also enabled the Company to widen its geographical presence.

Diversified customer base: The Company has been in the business for nearly three decades and over the years, the Company has continuously expanded its product portfolio. This wide spread product range across three segments has enabled the Company established a strong customer base and an unyielding marketing setup. Further, each of BHL's manufacturing unit functions as an independent division and garners customer base of its own. Supervised by the core marketing team of the Company, this strategy enabled the BHL build a diversified and strong customer base. This also helps de-risk the business from an excessive dependence on a handful of large clients.

Wide product range: From a couple of products in 2000, the Company today had more than 80 products in its portfolio. Also, the Company ensured that it has marked its presence in the key therapeutic areas, to ensure a steady demand for its products. This has enabled the Company to successfully meet the customers demand for the latest product and also undertake market expansion activities for its suppliers.

Value-addition products: APIs accounted for 100% of the Company's sales when it went into business in 1993; the Company increased the non-API proportion of its sales from scratch to 6%, over the last decade year.

Operational excellence: The Company periodically implemented operational excellence programme and technological upgrade programme that helped debottleneck operating units and enhance capacities for only a marginal capital outlay, strengthening profitability. These dedicated upgradation programme has enabled the Company to offer quality products at a competitive price and enhance profitability.

WHAT MAKES BHL DIFFERENT?

As a growth focused company, we are a dedicated pharmaceutical products manufacturer across some of the key product segments. It has helped our customers to sell more while enabling them to reduce cost and manage their business risk.

We are able to do so because of the scale of our manufacturing and our investment in R&D, innovation, process improvement, quality control, great service and our people.

Our scale

Enables us to serve large customers efficiently on a multinational basis

- Our presence across the three segments and in some of the major markets such as Europe and the US enables us to serve wide array of customers and with short lead-times
- Long-standing relationships with a wide range of multinational and globally renowned pharma companies

Investment in R&D and innovation

Adds value to our customers

- Forward thinking approach
- Progressive investment in R&D
- Strong in-house quality management system
- Technology know-how

Total value approach

Aligns us with our customers need who seek to maximise their efficiency

- Presence across the value chain
- Wide array of products across key therapeutic areas
- Leverage relationships; through timely, and quality-consistent delivery

Our people

We employ dedicated, skilled and motivated people, and invest in ensuring that they understand how to play their part in the success of the business. We work hard to integrate new colleagues, including those who join from manufacturing facilities acquired by BHL, as quickly and smoothly as possible. Our strong corporate values underpin our culture and behaviours and are central to how wider value is created for our business and stakeholders.



We help our customers achieve more

More sales > Wide range of products | Timely availability | Consistent quality

Managed risk > Stringent quality controls | Sustainable business practice | Accreditation by international regulatory agencies | Regulatory compliance

Lower cost > Economies of scale | Integrated manufacturing | Presence across the value chain

HOW WE HAVE ENHANCED SHAREHOLDER'S VALUE?

BHL enhanced value for its shareholder's through various long-term initiatives.



Tangible value-addition

Revenue growth: The Company grew sales (revenues and volumes) across markets and products through enhanced capacities, global approvals from authorities and customers and increasing demand for its products. The Company is amongst the leading manufacturers in its product lines for the regulated markets.

12.96%
CAGR revenue growth from operation over the last five years

Improving profitability: The Company climbed the value-chain from APIs to Finished Dosage Formulations (FDFs). BHL grew its API business from ₹ 115.03 crores in FY10 to ₹ 385.37 crores in FY20 and FDF's business from ₹ 02.34 crores in FY10 to ₹ 24.64 crores in FY20. Further, enhanced its presence in regulated markets while building on capacities through strategic acquisitions. This has enabled BHL to sustainably grow its bottom-line.

22.4%
CAGR PAT growth over the last five years

Strengthening fundamentals: BHL consistently grew its free cash flows through a strategic volume and value-driven initiatives, maintained a prudent ratio between the need to reward shareholders and business investments. In the last three years, the Company deployed retained earnings to repay debt, undertake portfolio strengthening acquisitions, enhance shareholder's return and strengthen investor recall.

26.05%
Grew shareholder's fund over the last three years

Business reinvestment: BHL, over the years, reinvested in enhancing its production capacity with the objective to make growth sustainable. BHL undertook several acquisitions since its inception. The cumulative gross block addition in the years leading to FY20 was funded through a prudent mix of debt and accruals while maintaining a healthy debt equity ratio.

15%
Grew gross block over the last three years



Why BHL is an ideal investment opportunity?

We invest where there is long-term growth.
We have delivered industry-leading performance, time and again, by continuing to execute our robust long-term growth strategy with passion and with perfection.

We have always put our customers first and diligently focused on partnering in their success.
We have consistently delivered profitable growth, 9 years out of our last 10 years we reported profitable growth.

We ensured that our capital allocation was disciplined and was in line with our strategy. Our ROCE grew every year over the last five years.
We are committed towards continuous enhancement of our operational efficiency and R&D capabilities.

HOW BHL HAVE RECONFIGURED OVER THE YEARS?

We were a volume driven Company earlier.	We are a volume and value driven company today.
We were only API manufacturing company earlier.	We today have a presence across the value-chain from APIs to FDFs.
We were primarily an India and the regulated market focused company earlier.	We have a multinational product presence today from the regulated markets to the pharmerging ones.
We were a relatively small company earlier with a singular marketing focus.	We are a 715 employee organization today, comprising of engineers and R&D professionals.
We earlier focused on introducing products that plugged market place gaps.	We launch new products that represent new therapies and applications, creating new markets instead.
We were a pure-play API manufacturer earlier, with a couple of manufacturing units.	With six manufacturing facilities, we are today one of the leading pharmaceutical products manufacturer from India.
We earlier focused on vanilla generic products only.	We now generate revenues from a mix of generics, off-patented products, important intermediates and critical FDFs.
We were a manufacturing driven pharmaceutical company earlier.	We are a quality-focused and research driven company today.

OUR STRATEGY FOR DRIVING GROWTH

Our strategy is to build a leading and future-focused pharmaceutical company powered by advanced research and development and effective product portfolio. As we implement our strategy, we have four priorities to shape our future and help us continue to create value for our Company, stakeholders and society. This is delivered via our four strategic goals.

To lead the way sustainability

Reduce our carbon footprint

Protecting natural resources by making the most of natural resources used

Reducing waste and disposing the wastes responsibly

To realise the potential of our people

Ensuring the safety of our people

Creating an environment that our people are proud of and where they can give their best

Building individual and organizational capability

To delight our customers

Delivering on our commitments for top quality pharmaceutical products and within the given time

Providing a wide range of products to choose from with a presence across the value chain

Driving innovation while focusing on a research-based approach

Expanding manufacturing scope by adding new products to the portfolio

To double our size and profitability

Driving organic market share gains by enhancing our international presence into newer market

Maximizing the opportunities from the acquired manufacturing facilities and focus on inorganic growth opportunities

Regularly investing in R&D to develop custom and consistent manufacturing process, and also to synthesize efficient and technologically advanced products

Expand our formulation manufacturing capacity to help increase BHL's presence in the global market and also increase the loan licensing work



OUR BUSINESS MODEL

Our business model is focused on garnering the maximum value from our input resources and drive sustainable growth over the long-term.

Resources we use → **Activities we perform**

Financial capital

We use a prudent mix cash, equity and debt to meet our financial commitments, finance our acquisitions, to invest in enhancing our R&D and manufacturing facilities. This enables us to expand our product portfolio, technical capabilities, geographic reach and manufacturing capacity.

Intellectual capital

We use our longstanding expertise and market data to develop and market our products. We hold trade-marks that protect the long-term investments required for our business growth.

Human capital

We depend on the skills and creativity of our employees to discover, develop and produce new molecules and deliver them to our clients.

Manufacturing capital

We have extensive manufacturing capabilities with six ultra-modern facilities, focused on operational excellence and efficiency.

Technological capital

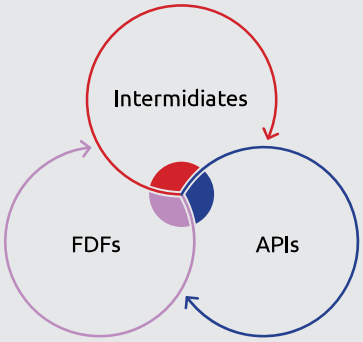
Marked by contemporary technologies and driven by research-focused insight, BHL's competitive advantage is its research expertise.

Relationships

We work very closely with our clients and partner with them to develop products matching their specific needs, enabling us to meet growth objective.

Sustainable product portfolio

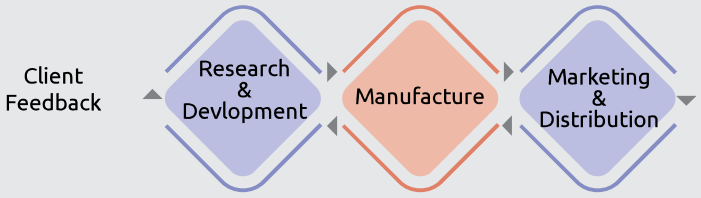
We manufacture a wide range of pharmaceutical products across the three different segments strategy based on our multi-decadal industry expertise



We strategized to mark our presence in key therapeutic areas such as pain management, anti-malaria and tapeworm infection among others to ensure that we have a steady demand for our products.

We focused on keeping the right-balance between volume and value driven products to sustain our growth momentum.

We undertook reverse engineering to emerge as a vertically integrated pharmaceutical manufacturing company.



Focused R&D

In FY20, we delivered new molecules for a variety of illnesses and received key approvals for molecules. Our consistent investment in research and development has fuelled this progress. We have been constantly investing in R&D, where our team has been able to passionately translate science and technology into pharmaceutical products and manufacturing processes, meeting global regulatory standards.

Key supporting activities

- Implemented stringent **quality-control management system**, ensuring high quality and consistent product quality.
- Formed **experienced sales and marketing team** to broad-base BHL's product presence and to form international tie-ups
- Focus on understanding the clients need accurately and working closely with them to build a **formidable relationship**.

Build a dedicated employee base: To help BHL fulfil it's purpose of reimagining a leading pharmaceutical products manufacturer, we focused on reconfiguring

the way we work to unleash the talent and creativity of our people. We focused on making our culture a driver of innovation, performance and reputation, and a source of sustainable competitive advantage.



Outputs we generate

For our clients

- High quality, affordable medicines
- Widen product portfolio to help them cater a wider segment
- Products tailored to clients' needs

For our investors

- Sustained business growth
- Regular return on investment
- A pipeline of products ensuring long-term growth
- Focused R&D investment
- Strong balance sheet position

For our people

- Creating a dynamic and rewarding place to work with clear development opportunities.
- We're creating an organization where people are inspired, curious and unbossed.

For our business partners

- We are rethinking how we work, embracing new technologies and building better productivity into our company to free resources that we can invest in innovation and help boost returns.
- Regular investment in R&D training to build on our capabilities

For the society and environment

- Focused on managing carbon footprint, offering quality employment opportunities and better health outcomes

Value we create

10.76%
y-o-y Sales growth

17%
EBIDTA margin

21.67%
ROCE

₹ 2.41 crores
Technology leadership through R&D investment

₹ 57.58 crores
Exchequer contribution in FY20

₹ 17.44 crores
Invested in upgrading manufacturing facilities

₹ 49.05 lakhs
Contributed towards different social activities

DELIVERING ON OUR SOCIAL COMMITMENT

An organisation's true success is not defined by the financial success it has achieved for its shareholders, rather it defined by the positive change it has been able to bring to the communities where they operate and thrive. Believing in this ethos, we embarked on different sustainable development of the society through different direct and indirect participation for the larger community.

How we ensured our participation?

Investment in CSR programmes | Focus on sustainability | Empowering communities by creating employment and self-employment opportunities | Upliftment of underprivileged sections of the society | Reducing the environment impact of our operations | Help creating a healthy community | Help the larger community fight against the pandemic Covid-19.











CORPORATE INFORMATION

Board of Directors:

Mr. Sajankumar R. Bajaj
Chairman & Managing Director

Mr. Anil C. Jain
Managing Director

Ms. Namrata S. Bajaj
Whole Time Director

Mr. Dhananjay S. Hatle
Whole Time Director

Mr. Rupesh H. Nikam
Whole Time Director & Chief Financial Officer

Mr. Pakshal A. Jain
Whole Time Director

Mr. Hemant R. Karnik
Independent Director

Mr. Ram B. Banarse
Independent Director

Mr. Avinash Dalal
Independent Director

Mr. Loukik D. Tipnis
Independent Director

Mr. Luke B. Fernandez
Independent Director

Ms. Kejal N. Shah
Independent Director

Company Secretary

Mr. Aakashkumar Keshari

Statutory Auditors

M/s. Paresh Rakesh & Associates
Chartered Accountants
103, Namrata CHS, Bldg No. 15,
Shastri Nagar, Link Road, Goregaon (West),
Mumbai- 400 104.

Chief Financial Officer

Mr. Rupesh H. Nikam

Registered Office:

602-606, Bhoomi Velocity Infotech Park,
Plot No.B-39, B-39a, B-39 A/1,
Road No.23 Wagle Industrial Estate,
Thane (West), Thane - 400 604.
CIN L99999MH1993PLC072892
E-mail Id: investors@bajajhealth.com

Website: www.bajajhealth.com

Registrar & Transfer Agent

Link Intime India Private Limited
C-101, 24*7 Park, L B S Marg,
Vikhroli West, Mumbai-400083.
E-mail Id: rnt.helpdesk@linkintme.co.in

Website: www.linkintime.co.in

Bankers

Saraswat Bank

Standard Chartered Bank

Citi Bank

SVC Bank

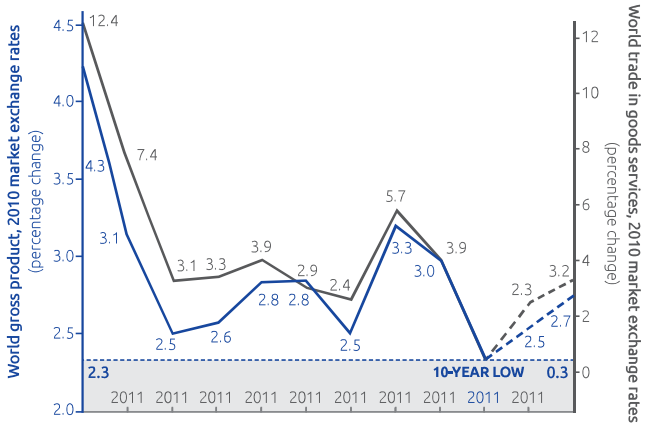
Management Discussion and Analysis

Global economy overview and outlook

2017 and the first half of 2018, saw the global economy witness robust growth of around 3.8%. But, since then the global economy saw a constant decline in the GDP growth, reflecting the effect of a confluence of several geopolitical factors such as the growing trade tensions between the US and China, US sanctions on certain major oil-producing nations, failure of the Brexit negotiations and also due to slowdown in some of the key emerging economies of the globe.

Escalating trade disputes and the deepening climate crisis, coupled with recession fears, tapering merchandise trade volumes, and capacity constraints in several developed economies, resulted in the global economy recording its lowest growth rate of the decade. Growing at just 2.3% in 2019, the global economy ended up having the slowest global economic expansion since the world financial crisis in 2008-2009.

World GDP growth and Trade growth



(Source: https://unctad.org/en/PublicationsLibrary/wesp2020_summary_en.pdf)

Despite the short-term risks and uncertainties surrounding the policy measures adopted by the developed and emerging nations, the industry experts had opined modest acceleration in global growth in 2020 and 2021. It is expected that the global economy would grow at 2.5% in 2020 and 2.7% in 2021.

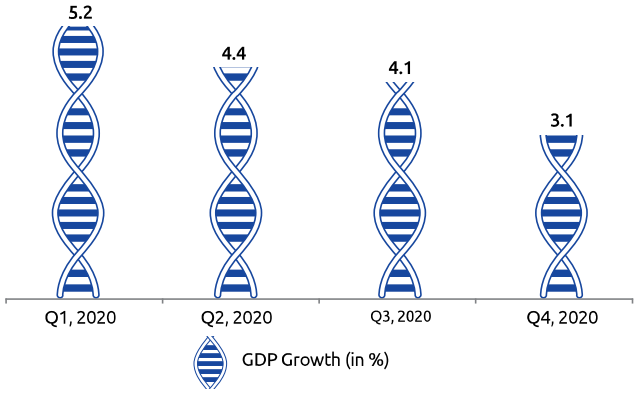
However, the outbreak of the pandemic COVID-19 in early 2020 has not only resulted in a mammoth health crisis but also pushed the global economy towards a severe economic fallout. As a result of the pandemic, the global economy is projected to contract sharply by 3% in 2020, much more compared to the 2008-09 financial crisis. As economies across the globe continue to adapt to the 'new normal', the global economy is projected to grow by 5.8% in 2021 as economic activity normalizes aided by policy support.

Indian economy overview and outlook

The brightest spot in the global economic map, the Indian economy retained its position as the sixth-largest economy and emerged as the fastest-growing trillion-dollar economy in 2018 driven by strong consumption demand and steady growth in some of the key sectors.

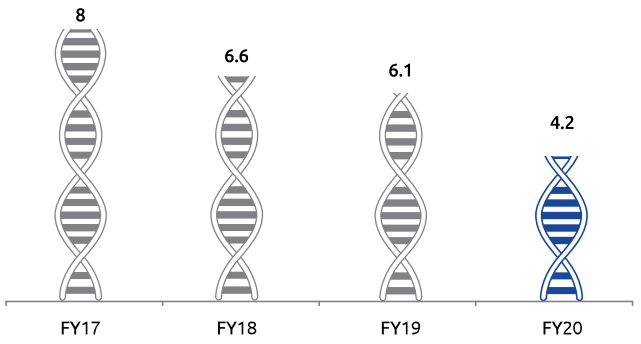
However, since early 2019 the economy witnessed a slowdown in economic activities in some of the key sectors and also witnessed tapering of the domestic demand. In 2018-19, the Indian economy grew at 6.1%. However, in 2019-20, the economic growth slowed to an 11-year low of 4.2% and for the last quarter of FY20, the GDP growth fell to just 3.1%, the lowest growth rate in the last 44 quarters. A fall in consumption, lack of private investments, and sluggish exports are being blamed for sluggish GDP growth.

Quarterly (FY20) growth of the Indian Economy



(Source: https://economictimes.indiatimes.com/news/economy/indicators/indias-gdp-growth-in-q4-fy20-sinks-to-11-year-low/articleshow/76099894.cms)

Y-O-Y growth of the Indian Economy (in %)



(Source: https://economictimes.indiatimes.com/news/economy/indicators/indias-gdp-growth-in-q4-fy20-sinks-to-11-year-low/articleshow/76099894.cms)

Low wages and income inequality resulted in diminishing domestic demand and emerged as the biggest roadblock in India's path for sustainable economic growth. Degrowth in the services sector further complicated the situation. The slowdown in the GDP growth also contributed to an increase in fiscal deficit mainly on account of lower aggregate demand, lower fiscal revenue, lower economic activity, and higher fiscal expenditure on account of the measures to address the economic slowdown.

COVID-19 impact on the Indian economy

The pandemic COVID-19 is the first and foremost human disaster in 2020 and is unprecedented in recent human history.

Since the pandemic outbreak in late March 2020, the Indian government announced a nationwide lockdown to stem the spread of the virus. While the lockdown may have been necessary, but as a side-effect, the nation witnessed a screeching halt in almost all the major economic activities. It resulted in massive job losses, income loss, and dramatic curtailment of production and infrastructural activities among others.

Consumption demand, the bedrock of the Indian economy, also witnessed a steep fall due to the collapse of incomes, and rampant job losses.

According to the International Monetary Fund, the Indian economy is likely to see a sharp contraction of 4.5% in 2020 due to COVID-19 and the subsequent lockdown. However, experts expect that the Indian economy to bounce back in 2021 with a robust 6% growth on the back of the assumption that the economic activity is likely to see a gradual pick up in the latter half of FY21 and an uptick in demand in the second half.

Global pharma industry

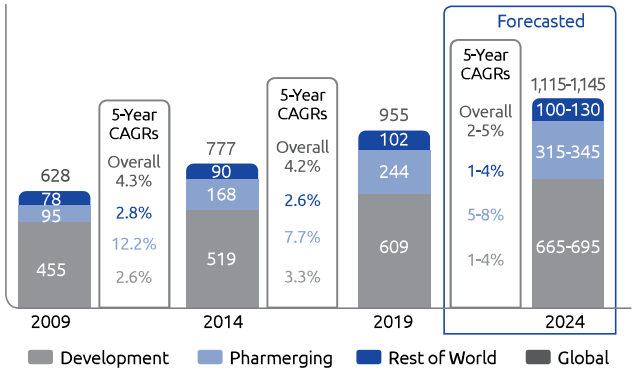
The global research-based pharmaceutical industry has entered a new era of medicine development due to the recent progress in pharmaceutical science and technology. Emerging technologies are creating transformative opportunities for life sciences, and scientific achievements are on a record pace. Evolving research methods have opened up several promising horizons with an array of possibilities offered by personalized medicines, and by harnessing the power of big data. The innovative pharmaceutical industry both drives and is being driven by medical progress.

Despite operating in an uncertain environment owing to the persisting issues of cost and supply-chain disruptions, the global pharma industry is positioned to grow in excess of USD 1.5 trillion by 2023 after growing at a CAGR of 6.3%. Growth of the global pharma industry is likely to be driven by the aging global population, rising purchasing power leading to better health care access, rising focus on tapping the specialty disease market, growing R&D pipelines, and favorable government policies.

The principal growth of the global pharmaceutical sector is expected to come out of the United States and pharmerging markets, reporting 4-7% and 5-8% CAGR respectively. In the United States, overall spending growth is driven by a range of factors including new product uptake and brand pricing, while it is offset by patent expiries and generics.

In terms of spending, the global healthcare spending is expected to grow at 5% annually between 2019 and 2023. This acceleration is likely to be driven by a variety of factors such as expanding healthcare coverage in emerging markets, growing needs of the current pandemic situation, new treatment methods, aging, population, and increasing labour wages. Global spending on medicines stood at about USD 1.0 trillion in 2019, which is likely to grow at 3-6% to about USD 1.1 trillion by 2024.

Expected global medicine spending is projected



(Source: https://heatinformatics.com/sites/default/files/images-videosFileContent/global-medicine-spending-and-usage-trends.pdf)

Worldwide prescription drug sales are projected to have a positive CAGR of 6.9% between 2019-24 with sales expected to reach USD 1.18 trillion.

Drivers of growth

- Accelerated drug approvals
- Increased potential for an additional USD 109 billion from orphan drug sales
- Amplified sales from oncology therapies

Oncology is expected to have almost a 20% share of the worldwide market by 2024 and a 11.4% in CAGR growth.

Worldwide orphan drug sales are expected to have double the CAGR of non-orphan drugs, at 12.3% over the 2019-24 period.

Global medical devices market was valued at USD 425.5 billion in 2018 and is expected to reach USD 612.7 billion by 2025.

Global generics drug market

Growing at a CAGR of 6.9%, the global generic drugs market is estimated to reach a value of USD 441.89 billion by 2028. Generic drugs are bio-equivalents of brand-name drugs in terms of strength, quality, dosage, form, effect, side effect, intended use and route of administration. More than 80% of the total global generic market is accounted for by ten key markets like USA, Canada, Germany, the UK, France, Spain, Italy, Japan, China and India.

With major therapeutics coming off patent and increasing demand for low cost medication, several big players are moving into the generic drugs market, spearheaded by leading pharma companies, and specialist pharma organisations especially in pharmerging markets.

Indian pharmaceutical industry

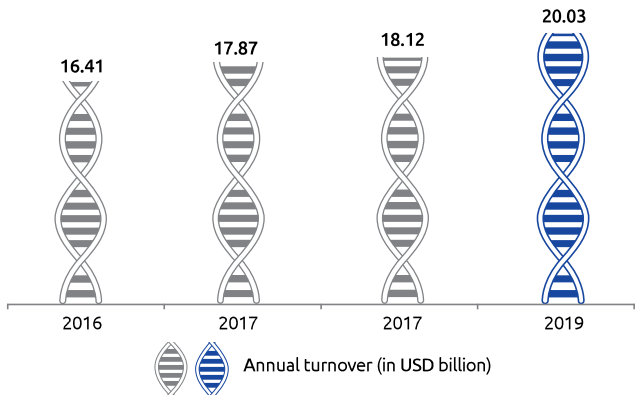
Nourished by increased spending, improved accessibility and growing exports, India's pharmaceutical sector has showcased sustainable growth over the last few years despite being shrouded by dark clouds of pricing and cost headwinds.

Source to nearly 60,000 generic brands across 60 therapeutic categories and manufacturer of more than 500 different Active Pharmaceutical Ingredients (APIs), the Indian pharmaceutical industry today ranks 3rd worldwide for production of generic medicines in terms of volume and 10th in terms of value. India fulfils 20% of global demand for generic medicines in terms of volume and supplies over 60% of the global demand for various vaccines and Antiretroviral (ARV) drugs.

The pharmaceutical industry is indeed a sector of pride, as India is the only country with largest number of US-FDA compliant Pharma plants (more than 262 including APIs) outside of USA, has nearly 1,400 WHO-GMP approved pharmaceutical plants, and 253 European Directorate of Quality Medicines (EDQM) approved plants with modern state-of-the-art-technology.

Home to more than 3,000 pharma companies with a strong network of over 10,500 manufacturing facilities, the Indian pharmaceutical market grew by 9.8% in 2019 to reach USD 20.03 billion from USD 18.12 billion in 2018.

Annual turnover of the Indian Pharmaceutical industry

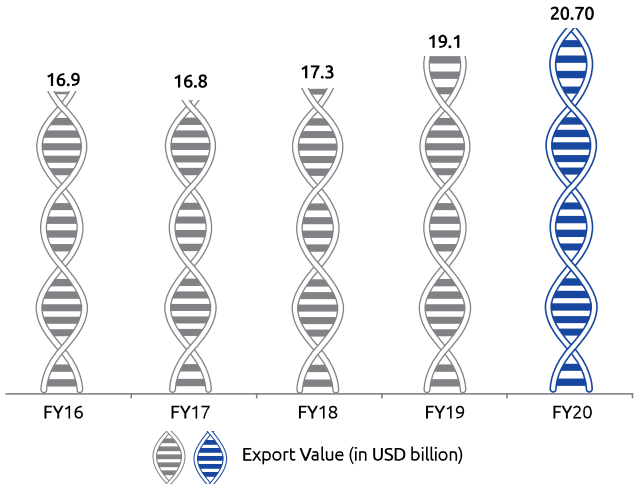


(Source: https://www.ibef.org/download/Pharmaceuticals-August-2020.pdf)

With the rising share of the Indian generic drugs, the domestic generic drug market is expected to reach USD 27.9 billion in 2020.

India's ability to manufacture high quality, low priced medicines, presents a huge business opportunity for the domestic players in the industry. With the cost of production nearly 33% lower than that of the US and backed by strong R&D, over the years, the Indian pharma industry has emerged as a competitive player in the export market. Capitalizing on these factors, pharmaceutical export from India, which include bulk drugs, intermediates, drug formulations, biologicals, Ayush & herbal products, and surgical, reached USD 20.70 billion in FY20. The biggest export destination for Indian pharma products is the US. In FY20, 32.1% of India's pharma exports were to North America, followed by 17.96% to Africa and 15.70% to the European Union. India's formulation exports to increase at 10-11% compound annual growth rate (CAGR) from fiscals 2020-25, compared with 6-7% CAGR over the previous five years. According to the data released by Department for Promotion of Industry and Internal Trade (DPIIT), the Indian drugs and pharmaceuticals sector attracted cumulative FDI inflow worth USD 16.50 billion between April 2000 and March 2020.

Pharmaceutical Exports from India (USD billion)



(Source: https://www.ibef.org/download/Pharmaceuticals-August-2020.pdf)

Korean Pharmaceutical market

An aging population and rising life expectancy have contributed to a strong demand for medicines in the country. The pharmaceutical industry in Korea is evolving in reaction to the government's funding for R&D and anti-illegal rebate initiatives, with leading organizations the earliest to respond to the evolving climate. Further R&D spending is being spent on new medicines, and bio-similars, despite high growth rates in global markets. The Korean pharmaceutical industry is likely to grow at a CAGR of 2.5% over the 2020–25 period.

Expected to grow at a CAGR of about 5-6% over the next five years, Indian pharma exports to semi-regulated markets is expected to touch USD 9 billion by fiscal 2025. Characterized by lower penetration of healthcare facilities, low per capita consumption of medicines, high population growth rates, a wide base of patients with acute and chronic diseases, and low penetration of generics, Africa and many Asian countries have emerged as the key semi-regulated markets in the recent years.

Active Pharmaceutical Ingredients (APIs)

Domestic API consumption is expected to reach USD 18.8 billion by FY22.

Biosimilar

The Indian domestic biosimilar market is expected to reach USD 40 billion by 2030 as the Government intends to allocate USD 70 million for local players to develop Biosimilar.

Contract Research and Manufacturing Services (CRAMS)

Fragmented with more than 1,000 players, the Indian CRAMS industry has posted 48% CAGR between FY15-18 and expected to witness a strong growth over 25% over 2018-21.

Formulations

India is the largest exporter of formulations in terms of volume with 14% market share and 12th in terms of export value. It expects to sustain double-digit growth over the next five years.

Government of India's (GOI's) Key Initiatives and Policy Support

- GOI's 'Pharma Vision 2020' aimed at making India a global leader in end-to-end drug manufacturing and thereby reduced the approval time for new facilities to boost investment
- Under Budget 2020-21, allocation to the Ministry of Health and Family Welfare is ₹ 65,012 crores (USD 9.30 billion)
- GOI allocated ₹ 34,115 crores (USD 4.88 billion) towards the National Health Mission under which rural and urban people will get benefited
- To hasten the growth of the sector, the government allowed 100% FDI is allowed under automatic route
- Exemptions to drugs manufactured through indigenous R&D from price control under NPPP-2012
- The GOI allocated ₹ 6,400 crores (USD 915.72 million) towards health insurance scheme Ayushman Bharat – Pradhan Mantri Jan Arogya Yojana (AB-PMJAY)
- According to Economic Survey 2019-20, the Government enhanced its healthcare expenditure in FY20, from 1.2% in FY15 to 1.6% in FY20
- The GOI announced National Health Protection Scheme plan in 2018-19. It is the largest Government funded healthcare programme across the globe, and is expected to benefit 100 million poor families in the country by providing a cover of up to ₹ 5 lakhs (USD 7,723.2) per family per year for secondary and tertiary care hospitalization.

Key growth opportunities for the Indian pharmaceutical industry

Enhanced medical spending: With medical spending in India projected to grow at 9-12% over the next five years, India is likely to become one of the top 10 countries in terms of medicine spending and which likely to propel the growth of the Indian pharmaceutical industry further.

Patent expiry: The Indian generics industry can benefit substantially from the patent cliff as patents for branded molecules with cumulative global sales of over USD 251 billion are expected to expire between 2018 and 2024, opening new opportunities for the industry. Further, about 120 drugs are expected to go off-patent over the next 10 years; with expected worldwide revenue between USD 80 to USD 250 billion.

Key challeges faced by the Indian Pharmaceautical sector

Lack of a stable pricing and policy environment: Frequent and unexpected changes to domestic pricing policy have created an uncertain environment for investments and innovations. According to IPA, untill both the government and stakeholders work together to develop a plan to produce affordable drugs for Indian patients, the Indian pharma industry may find it difficult to reach its true potential.

Lack of capabilities in the innovation space: India lacks behind in the innovation space compared to other developing nations. The government needs to invest in research initiatives and talent in order to grow India's innovation quotient. Clinical trials should also be supported and subjectivity in certain regulatory decision-making removed.

Dependence on external markets: India is heavily reliant on other countries for intermediates and active pharmaceutical ingredients (APIs), with approximately 80% of the APIs used in India fulfilled by China. The country is therefore at the mercy of supply disruptions and unpredictable price fluctuations. Implementing improvements to infrastructure would help in the development of internal facilities to stabilise supply.

High quality compliance scrutiny: India experienced the highest number of FDA inspections since 2009; therefore, continued investment into upgrading quality standards is likely to divert capital away from other areas of development such as R&D and distract from growth.

COVID-19 and its impact on the Indian pharmaceutical industry

Forming a part of the essential commodities, the Indian pharma industry was given special permission by the Government of India to operate in a restricted environment after following all the government-mandated norms. Despite all the government support, the industry faced a few challenges just like the other industries. The major challenges faced by the industry are listed below.

Disruptions in Supply Chain

- Restricted and limited sea/cargo transport capacity is likely to impact sales in semi-regulated markets
- The cost of exports has also gone up owing to demand and supply mismatch
- Supply of ancillary products such as packaging materials and bottle caps were limited and time-consuming owing to restricted transport

Delay in Approvals

- Delayed foreign inspections by USFDA is likely to result in a delay in pre-approval inspections and clearances of major plants under OAI/ warning letters of Indian players
- This would, in turn, lead to a delay in approvals of key products for Indian players

Slower traction for key products

- An extended lockdown in many of the key export countries has resulted in limited MR visits to doctors, which in turn resulted in slower take-up of new products
- Further, the lockdown is likely to result in slower adoption of biosimilars

Reduced earnings

- Slower exports are likely to negatively impact export revenue growth for most players
- Weakness in emerging market currencies is also likely to impact earning for players
- Rising transportation cost has also resulted in enhanced input cost, which intron may impact profitability

Growth driver of the Indian pharma industry

- Increasing fatal diseases
- Enhanced accessibility of drugs
- Rising penetration of health insurance
- A growing number of stress-related diseases due to change in lifestyles
- Better diagnostic facilities
- Enhanced usage of data analytics to understand demand patterns
- Increasing penetration of chemists especially online
- Metro and Tier-I market to drive growth
- Rural market to enhance its share

Road ahead

Increased spending, improved accessibility, and growing exports are some of the key factors that are likely to drive the growth of the domestic pharmaceutical industry. Going forward, better growth in domestic sales would also depend on the ability of companies to align their product portfolio towards chronic therapies for diseases such as cardiovascular, anti-diabetes, anti-depressants, and anti-cancers, which are on the rise.

Further, the Indian government is proactively undertaking the necessary steps to reduce costs, bring down healthcare expenses, and help India emerge as 60,000 pharma products manufacturing hub. Speedy introduction of generic drugs into the market has remained in focus and is expected to benefit the Indian pharmaceutical companies. Also, the thrust on rural health programmes, lifesaving drugs, and preventive vaccines augurs well for Indian pharmaceutical companies.

On the exports front, the industry expects its next wave of growth could come from increasing exports to large and traditionally underpenetrated markets such as Japan, China, Africa, Indonesia, and Latin America, which would help the industry meet its aspiration of becoming the world's largest supplier by volume. Given all these favourable factors, the Indian pharmaceutical industry is expected to grow to USD 100 billion, while medical device market is expected to grow USD 25 billion by 2025. Further, India's biotechnology industry comprising bio-pharmacauticals, bio-services, bio-agriculture, bio-industry, and bioinformatics is expected grow at an average growth rate of around 30% (on a y-o-y basis) to reach USD 100 billion by 2025.

Company overview

Founded in 1993, Bajaj Healthcare Limited (BHL) is an established player in the Indian pharmaceutical industry and one of the fastest-growing mid-cap pharmaceutical companies in India. A bulk drug manufacturer, BHL's product line focuses on the manufacturing of Active Pharmaceutical Ingredients (APIs), Intermediates, and Formulations.

With a widespread international and domestic presence, the Company's product line has helped BHL successfully serve

various globally renowned companies in the pharmaceuticals, nutraceuticals, and food industries with a spirit of scrupulousness. Backed by six state-of-the-art manufacturing facilities and strong R&D capabilities, the Company is a major player in India with a keen focus on the development, manufacturing, and supply of amino acids, nutritional supplements, and active pharmaceutical ingredients (API). However, recently, the Company has undertaken a shift in its business strategy and from being a volume-based player to a value-driven player. The Company's manufacturing facilities are accredited with accreditations such as EU-GMP Certificate from Agency of Medicinal Products and Medical Devices, Croatia, Certificate of Suitability (CEP), KFDA Certificate, ISO 9001:2015 Certificate, WHO-GMP Certificate, GMP Certificate, FSSAI License, FSSC 22000, and HACCP Certificate among others. and focuses on manufacturing products such as Ascorbic Acid, Chlorhexidine Base, Carbamazepine, Chlorhexidine Gluconate 20% Solution, Oxcarbazepine, Doxofylline, Citicoline Sodium, and Choline Bitartarte among others.

In FY 2019-20, the Company acquired Intermediates manufacturing Unit at MIDC, Tarapur Maharashtra and also agreed to acquire Four Manufacturing facilities, comprising of three APIs manufacturing facilities, one Engineering Unit, at MIDC, Tarapur Maharashtra along with an Industrial Plot at Dahej, Gujarat.

Business segment review

Business Vertical-I

Active Pharmaceutical Ingredients (APIs)

Vertical status in Company:	1
Revenues, 2019-20:	₹ 385.37 crores
Revenue proportion:	93%
API's share in the export business:	23%

Over the years Bajaj Healthcare Limited has emerged as one of the leading API manufacturers from India. The Company has six API manufacturing facilities spread across different states in India and are accredited by international regulatory agencies. Contributing more than 90% to the overall revenue mix, API manufacturing forms the core business of the Company. Additionally, more of BHL' APIs are being used for captive consumption. The API vertical will continue to be critical to the Company's success since it the starting point for the Company's FDI vertical. Major products within the vertical are Ascorbic Acid CH Base and Its Derivatives, Citicoline Sodium, Carbamazepine, Theobromine and Ferrous Ascorbate among others. Bajaj Healthcare Limited is one of the leading manufacturers of Neutraceuticals in the domestic market – Ascorbic Acid IP, Sodium Ascorbate, and Ferrous Ascorbate.

With a strong in-house product registration team for export of APIs, the Company has strong international presence in more than 50 countries with an aggregate API manufacturing capacity of 726 MT per month.

Over the years the Company adopted several R&D enhancing measures, like setting up of a new in-house R&D centre, undertake extensive training, and strategic acquisitions, to extend its product offerings in the API space.

Talking Points, 2019-20

- Introduced 5 new molecules during the year
- Enhanced sales by 7% during the year
- Enhanced manufacturing capacity by 111 MT / month, thanks to strategic acquisitions

Blueprint for FY21

Going forward, we plan to focus on the products which are currently under development such as Brivaracetam, Alogliptin, Tigecycline, Ertapenem, Rivaroxaban, Acotiamide Hydrochloride, and Leflunomide BP / EP / USP Olmesartan Medoxomil BP / EP / USP, among others, as most of these products are likely to go off patent soon.

The Company expects to see strong direct sales from the API vertical along with an increase in captive consumption to fuel FDF business growth. Also commissioning and stabilisation of the newly acquired facilities would be an area of focus for the Company going forward. To focus on domestic market for APIs Vildagliptin, Ticagrelor, Theobromine, and Ascorbic Acid, and for APIs Vildagliptin, Sitagliptin, Deferasirox, Chlorhexidine Gluconate, Fosfomycin, Theobromine, and Octenidine Hydrochloride in the global market. Also, we plan to undertake more API product registrations in the international market.

We also intend to grow our presence in the international market from 51 countries to 100 countries over the next few years.

BHL's Star Performing Product

Ascorbic Acid

With a substantial market share, BHL is one of the leading manufacturers of Ascorbic Acid with dedicated manufacturing facility.

Application industries

- Used in Food and Beverage industry as a Preservative, Antioxidant, and Acidity Regulator
- Used as Nutritional Supplement and Antioxidant for Cosmetics & Pharmaceuticals
- Used in skin and hair care products
- Used in treatment of diseases like Scurvy, prevention of Cardiovascular Diseases and as a treatment for common cold

Business Vertical-II

Finished Dosage Formulations (FDFs)

Vertical status in Company:	2
Revenues, 2019-20:	₹ 24.64 crores
Revenue proportion:	7%

Backed by state-of-the-art formulation manufacturing facility complied with USFDA, TGA (Australia), MHRA (UK), the Company entered into the formulations business in 2008 and represents the highest end of the value chain. The Company entered this business in 2008 through an installed capacity of 92 million pieces per month. Today, FDF accounts for 7% of the Company's revenues. BHL's FDF facility in Vadodara, Gujarat, comprises automated processes, robust infrastructure and superior quality systems that efficiently produce FDFs.

BHL's offers multiple FDF forms comprising tablets, caplets, capsules and oral powders in bulk.

Highlights 2019-20

- Increased revenues by 186% from ₹ 8.62 crore in FY19 to ₹ 24.64 crore in FY20
- Recruited human capital in several key positions

Blueprint for FY21

Moving forward, our key focus would revolve around adding more products in our FDF portfolio through extensive research and strategic acquisitions. Also, we would focus on widening our customer base with the FDF segment.

Business Vertical-III

Intermediates

Vertical status in Company:	3

One of the few manufacturers of speciality intermediates like Calcium Phosphoryl Choline Chloride (CPCC) & Chlorhexidine (CH Base), BHL's intermediates manufacturing capacity today stands at 94 MT per annum. This has given the company a sustainable competitive edge in terms of economies of scale and cost advantages. Presently, the intermediates business supports its API manufacturing and are consumed in-house only.

During the year, BHL acquired Vetpharma Limited to boost its intermediates manufacturing facility.

Moving forward, we intend to focus on launching 7 new products through reverse engineering in intermediates segment by 2022.

Credit Rating
BBB/Positive: Long term
A3+: Short term
by CRISIL

Financial overview

Key financial metrics

Parameters	FY 2018-19	FY 2019-20	Growth (%)
Revenue from operations (in ₹ crores)	370.17	410.01	10.76
EBITDA (in ₹ crores)	43.60	51.02	17.03
PBT (in ₹ crores)	24.17	32.45	34.26
PAT (in ₹ crores)	16.31	22.50	37.95
Earnings per share (in ₹)	11.82	16.31	37.99

Analysis of the profit and loss statement

Revenues: Revenues from operations reported a 10.76% growth from ₹ 370.17 crores in 2018-19 to reach ₹ 410.01 crores in 2019-20. Other income of the Company accounted for only 0.77% share of the Company's revenue pie, reflecting the Company's dependence on its core business operations.

Expenses: Total expenses of the Company increased by 9.73% from ₹ 346.98 crores in 2018-19 to ₹ 380.74 crores primarily due to rise in the raw-material cost and employee cost, among others. Raw-material costs (65.44% of the Company's revenue from operations) increased 9.37% from ₹ 245.33 crores in 2018-19 to ₹ 268.32 crores in 2019-20. Employee expenses, accounting for 6.88% share of revenues, increased by ₹ 3.81 crores (15.49%) from ₹ 24.62 crores in 2018-19 to ₹ 28.43 crores in 2019-20.

Profitability: Company's EBITDA increased to ₹ 51.02 crores in 2019-20 compared to ₹ 43.60 crores in 2018-19. Net profit for the year stood at ₹ 22.50 crores compared to ₹ 16.31 crores in the previous year. PAT grew by 37.95% during the year. Operating profit margin for the year stood at 12.35% compared to 11.75% in the previous year, whereas net profit margin stood at 5.45% in 2019-20 as against 4.39% in 2018-19.

Analysis of the Balance Sheet

Sources of funds

- The net worth of the Company increased by 26.03% from ₹ 88.88 crores as on 31st March, 2019 to ₹ 112.02 crores as on 31st March, 2020 owing to increase in reserves and surplus. The Company's equity share capital comprising 137.99 lakhs equity shares of ₹ 10 each, enhanced by 100% during the year under review.
- The capital employed by the Company stood at ₹ 149.51 crores as on 31st March, 2020 as compared to ₹ 179.48 crores as on 31st March, 2019.
- Long-term debt of the Company increased by 25.75% to ₹ 32.49 crores as on 31st March, 2020 owing to the external loans undertaken to fund our acquisitions. The long-term debt-equity ratio of the Company stood at par in 2019-20 compared 2018-19. Finance cost decreased by 19.56% from ₹ 8.02 crores in 2018-19 to ₹ 6.45 crores in 2019-20. Interest coverage ratio in 2019-20 stood at 6.37 compared to 4.46 in the previous year.

Applications of funds

Fixed assets (gross) of the Company increased by 8.13% from ₹ 222.23 crores as on 31st March, 2019 to ₹ 240.31 crores as on

31st March, 2020. Depreciation and amortisation marginally increased by 12.64% from ₹ 93.74 crores in 2018-19 to ₹ 105.59 crores in 2019-20.

Working capital management

Current assets of the Company increased by 31.64% from ₹ 137.17 crores as on 31st March, 2019 to ₹ 180.57 crores as on 31st March, 2020. The current and quick ratios of the Company stood at 1.23 and 1.05, respectively in 2019-20 compared to 1.17 and 1.05, respectively in 2018-19.

Trade receivables as on 31st March, 2020 stood at ₹ 100.13 crores, representing 70-80 days of as on 31st March, 2020. The entire receivables are considered good and secure.

Cash and cash equivalents decreased 47.10 % from ₹ 7.86 crores as on 31st March, 2019 to ₹ 4.16 crores as on 31st March, 2020.

Margins

Better product mix, increased volume withless than a linear increase in expenses helped the Company report better margins during the year under review. The EBITDA margin for the FY2019-20 stood at 12.35% as compared to 11.75% in FY2018-19.

Human resources

BHL believes that its competitive advantage lies within its people. The Company's people bring to the stage a multi-sectoral experience, technological experience and domain knowledge. The Company also believes in working as a team to meet targets and hence puts emphasis on providing equal opportunitiesto all employees.

The Company's HR culture is rooted inits ability to subvert age-old norms in a bid to enhance competitiveness. The Company always takes proactive decisions whichare in alignment with the professional and personal goals of employees, there by achieving an ideal work-life balance and enhancing pride association. BHL's employee count stood at 715 as on 31st March, 2020.

Quality and Compliance

BHL always believed in quality of products and patient safety. This is being achieved through the implementation of best quality systems, creating a right quality culture and periodic training of employees. We always had a vision to be ahead of the curve in business and are investing significantly in the digitalisation program of the key quality systems like Quality Management Systems (QMS), Document Control, Change Control, Internal Audit, Data Management, Policy Management, Training Records Management, and CAPA Management among others on a continuous basis to further strengthen our core. We continue to sustain avery high level of transparency with our customers, regulators, statutory bodies, and employees. Our accreditations include the regulatory approvals from the top regulatory authorities from some of the stringently regulated pharma markets. As a proactive organisation, we have started the implementation of our very aggressive plans for expanding our quality function including investments in laboratories and newer analytical capabilities and technologies to make BHL a future ready organisation.

Risk management at Bajaj Healthcare Limited

BHL leverages it deep domain expertise and management insight to undertake proactive risk mitigating measures that helped strengthen BHL's viability across verticals, products, geographies and market cycle. The Company has also implemented an integrated risk management strategy to review and assesses the significant risk on regular basis to help ensure that there is robust system of internal control in place. Governed by a strong compliance's ethic, BHL relies heavily on risk management and forecasting frame work to manage competitive, economic, financial, geo-political and social risks. Further, the Company has put out in place a response mechanism that helped BHL mitigate environmental, operational and business risk and minimize impact on business.

Industry risk

A slowdown in the pharma industry may negatively impact the performance of the company.

Mitigation

- The Global pharma industry is expected to grow at over 6% over the next few years.
- Ageing global population, improving standards of living, and innovation in manufacturing making medicines cheaper, among others is likely to drive the demand for the pharma industry
- Indian pharma industry is likely to grow at 10% - 12% over the next couple of years and medicine spending is also likely to see double digit growth over the foreseeable future.

Regulatory risk

Any change in regulation might dent the growth of the Company as it can impact production

Mitigation

- Every product manufactured by the Company is passed through extensive R&D checks and stringent quality control tests as per international norms and standards.
- All manufacturing units of the company are in 100% conformance with the guidelines issued by the different regulatory bodies across the world.
- The Company regularly invests in plant automation which has helped meet the regulatory compliances.

Technology obsolescence risks

The Company can be a victim of technology obsolescence, if timely technological upgradations are not taken into consideration.

Mitigation

The Company regularly monitors its technology quotient and also undertakes periodic up-gradation measures to keep itself apprised with the latest technology.

Geographical risk

Presence in one market or over dependence on any one region could result in stagnant revenues.

Mitigation

- The Company has a business presence in more than 51 countries across the world including countries like the USA and UK.

- The Company entered 10 new countries in the last 5 years.
- Two of the biggest pharma markets in the world i.e. the USA and the UK account for only 64% of the Company's revenue.

Competition risks

The Company operates in a competitive environment and, as such, may experience increased competition that could adversely affect BHL's sales, operating margins and market share. Further, introduction of new products by competitor may impair the BHL's competitive advantage and lead to erosion of revenue.

Mitigation

- The Company has a continued focus on its operating performance from manufacturing to R&D to distribution to ensure that it continues to service the needs of its clients efficiently and in a timely manner. Further, the Company parodically enhanced its offerings basket to stay ahead of the curve.
- The Company has further developed unique capabilities to innovate on product offering across the market customized as per the client's need, this gives BHL an edge over its competition.

Foreign currency risk

The Company is exposed to foreign currency risk arising primarily owing to its business presence in a number of foreign countries. Therefore, exposing the company to fluctuation in currency movements.

Mitigation

- Foreign exchange rate exposures are managed by the Company by utilizing forward foreign exchange contracts.
- The Company enters into forward foreign exchange contracts to manage the risk associated with anticipated future business transactions denominated in foreign currencies.
- The Company's senior management team reviews and manages the foreign exchange risk in a systematic manner. Undertakes regular monitoring of exposures, seeks proper advice from market experts, and undertakes hedging of exposures, among others.

Internal Control Systems and Adequacy

Commensurate with the size and nature of operations, the Company has adequate systems of internal control and procedures covering all financial and operating functions. It believes that a strong internal control framework is one of the most indispensable factors of Corporate Governance. Continuous efforts are being made to enhance the controlling system's response to unauthorised use or losses. The audit committee supervises all aspects of internal functioning and advises corrective action as and when required.

Cautionary statement

Certain statement in the Management Discussions and Analysis describing the Company's objectives, projections, estimates, expectations may be "forward looking statements" within the meaning of applicable securities laws and regulations. Actual results vary significantly from the forward-looking statements contained in the documents due to various risk and uncertainties. These risk and uncertainties include the effect of economical and political condition in India, volatility in interest rates, new regulations, and Government policies that may impact the Company's business as well as its ability to implement strategy. The Company does not undertake to update these statements.

Directors' Report

To,
The Members
Bajaj Healthcare Limited

Your Directors have pleasure in presenting their 27th Board Report together with the Audited Financial Statements for the financial year ended 31st March, 2020.

Financial Performance of the Company

(₹ in Lakhs)

	Year Ended 31st March, 2020	Year Ended 31st March, 2019
Gross Income	41,318.74	37,114.55
Profit before Interest, Depreciation & Tax	5,102.39	4,359.76
Finance Charges	644.92	801.78
Provision for Depreciation	1,212.33	1,141.00
Profit before Tax	3,245.12	2,416.97
Less: Current Tax / Deferred Tax	995.15	785.94
Net Profit after Tax	2,249.97	1,631.03
Surplus carried to Balance Sheet	2,249.97	1,631.03
Earnings Per Share	16.31	11.82

The Company's gross revenue for the year increased to ₹ 41,318.74 lakhs as compared to last year's ₹ 37,114.55 lakhs increased by 11.33% over the previous year, which includes the Domestic Turnover of ₹ 31,733.62 lakhs as compare to last year's Domestic Turnover was ₹ 29,536.67 lakhs, and the Export Turnover of ₹ 9,267.22 lakhs as compared to last year's export turnover of ₹ 7,480.71 lakhs.

The net profit after tax during the year amounted to ₹ 2,249.97 lakhs as compared to net profit of ₹ 1,631.03 lakhs in the previous year increased by 38% over the previous year.

Dividend

In order to conserve the resources for future business requirements, your Directors do not recommend dividend for the year under review.

Deposits

The Company has not accepted any deposit from public during the year under review and as such, there are no outstanding deposits in terms of the Companies (Acceptance of Deposits) Rules, 2014.

Change in Nature of Business

There are no changes in the nature of business of the Company. However, the Company has commenced new business in Agro Sector during the year under review.

Extract of Annual Return

The extract of Annual Return as required under sub-section (3) of Section 92 of the Companies Act, 2013 ('the Act') in form MGT-9 is provided as '**Annexure-I**' to this Report and is also made available on the website of the Company at www.bajajhealth.com

Transfer to Reserves in terms of Section 134 (3) (J) of the Companies Act, 2013:

The Company has not transferred any amount to General Reserves for the financial year 2019-2020.

Transfer of Unpaid and Unclaimed Dividend to Investor Education and Protection Fund ("IEPF")

Pursuant to the provisions of Section 124 of the Act and Investor Education and Protection Fund Authority (Accounting, Audit, Transfer and Refund) Rules, 2016 (IEPF Rules), the declared dividends, which remains unpaid or unclaimed for a period of 7 (seven) years from the date of its transfer to unpaid dividend account is required to be transferred by the Company to Investor Education and Protection Fund (IEPF). Details of unpaid dividend is a part of Report on Corporate Governance that forms part of this Annual Report.

Material Changes and Commitments Affecting the Financial Position of the Company which have Occurred Between the end of the Financial Year to which the Financial Statement Relates and the Date of the Report

The Company acquired intermediates manufacturing Unit at MIDC, Tarapur Maharashtra and also has agreed to acquire four manufacturing facilities, comprising of three Active Pharmaceutical Ingredients (APIs) manufacturing facilities and

one engineering facility, at MIDC, Tarapur Maharashtra and 9 acres of an industrial plot at Dahej, Gujarat.

COVID-19 Pandemic:

The COVID-19 pandemic has negatively impacted the global economy, disrupted global supply chains and workforce participation due to "work-from-home" restrictions by various governments' worldwide and created significant volatility and disruption of businesses. For the Company, the focus immediately shifted to ensuring the health and well-being of all employees. Although there were uncertainties due to the pandemic, the manufacturing operations of the Company was well managed with the underlying support of the key personnel of the Company. The initial disruption faced in handling secondary operations including the distribution channels was gradually streamlined in the month of May. The Company have taken all the steps necessary to adapt itself to emerging changes and the new normal.

Information about Subsidiary / JV / Associate Company

The Company has no Subsidiary, Joint venture or Associate Company.

Share Capital

Bonus Shares

The Company has issued and allotted 68,99,600 bonus shares to the Equity Shareholders in the ratio of 1:1 (i.e. one fully paid up equity share of ₹ 10/- each for one fully paid up equity share) on 11th April, 2019.

Buy Back of Securities / Sweat Equity / Employees Stock Option Plan

During the year under review, the Company has not bought back any of its securities nor issued any Sweat Equity Shares nor provided any Stock Option Scheme to the employees during the year under review.

Directors and Key Managerial Personnel

The Board has an optimum combination of Executive and Non-Executive Independent Directors and is headed by an Executive Chairman, Mr. Sajankumar R. Bajaj. The Board of the Company is diverse in terms of qualification, competence, skills and expertise which enables it to ensure long term value creation for all the stakeholders.

Director retires by rotation

In accordance with the provisions of Section 152 of the Act and the Articles of Association of the Company, Mr. Dhananjay S. Hatle (DIN 00226390), an Executive Director is retiring by rotation at the ensuing Annual General Meeting (AGM) and is eligible for re-appointment.

Appointment/Re-appointment of Directors

On the recommendation of the Nomination and Remuneration Committee, the appointment of Mr. Luke B. Fernandez (DIN: 08188583) and Ms. Kejal N. Shah (DIN: 08608399) as Non-executive Independent Directors of the Company for a term of 5 (five) years w.e.f. 30th June, 2020 is proposed by the Board for the approval of the shareholders at the ensuing AGM of the Company.

On the recommendation of the Nomination and Remuneration Committee, the appointment of Mr. Pakshal A. Jain (DIN: 08776385) as an Executive Director of the Company for a term of 3 (three) years w.e.f. 30th June, 2020, is proposed by the Board for the approval of the shareholders at the ensuing AGM of the Company.

The term of office of Mr. Sajankumar R. Bajaj as Chairman and Managing Director of the Company has expired on 31st March, 2020. The Board at their meeting held on 30th June, 2020, on the recommendation of the Nomination and Remuneration Committee, has proposed the re-appointment of Mr. Sajankumar R. Bajaj as Chairman and Managing Director of the Company for a period of 3 (three) years with effect from 1st April, 2020, for the approval of shareholders at the ensuing AGM of the Company.

The term of office of Mr. Anil C. Jain as Managing Director of the Company has expired on 31st March, 2020. The Board at their meeting held on 30th June, 2020, on the recommendation of the Nomination and Remuneration Committee has proposed the re-appointment of Mr. Anil C. Jain as Managing Director of the Company for a period of 3 (three) years with effect from 1st April, 2020, for the approval of shareholders at the ensuing AGM of the Company.

The term of office of Mr. Dhananjay S. Hatle (DIN 00226390), Ms. Namrata S. Bajaj (DIN 05327071) and Mr. Rupesh H. Nikam (DIN 07007815) as Whole Time Directors of the Company has also expired on 31st March, 2020. The Board at their meeting held on 30th June, 2020, on the recommendation of the Nomination and Remuneration Committee, has proposed the re-appointment of Mr. Dhananjay S. Hatle, Ms. Namrata S. Bajaj and Mr. Rupesh H. Nikam as Whole Time Directors of the Company for a period of 3 (three) years with effect from 1st April, 2020, for the approval of shareholders at the ensuing AGM of the Company.

Mr. Hemant R. Karnik and Mr. Ram B. Banarse were appointed as Independent Director of the Company for the period of five years w.e.f. 08th January, 2016 and 14th January, 2016 respectively. The terms of Mr. Hemant R. Karnik and Mr. Ram B. Banarse are going to expire on 07th January, 2021 and 13th January, 2021 respectively. The Board of Directors on recommendation of the Nomination and Remuneration Committee have proposed the re-appointment of Mr. Hemant R. Karnik and Mr. Ram B. Banarse as Independent Director (Non-Executive) of the Company for a period of 5 (five) years with effect from 8th January, 2021 and 14th January, 2021 respectively, for the approval of shareholders at the ensuing AGM of the Company.

Resignation of Director

Mr. Vidyut Shah (DIN 02578165), Non-Executive Independent Director of the Company has resigned with effect from 12th June, 2020 from the directorship of the Company.

As stipulated under the Regulation 36(3) of SEBI (Listing Obligation and Disclosure Requirements) Regulations, 2015 (hereinafter referred as "Listing Regulations"), brief resume of the Directors proposed to be appointed/re-appointed is furnished along with the Explanatory Statement to the Notice to the 27th Annual General Meeting of the Company.

Key Managerial Personnel

Pursuant to the provisions of Sections 2(51), and 203 of the Act, read with the Companies (Appointment and Remuneration of Managerial Personnel) Rules, 2014, Key Managerial Personnel of

the Company as on 31st March 2020 are Mr. Sajankumar R. Bajaj , Managing Director, Mr. Rupesh H. Nikam, Whole-time Director & Chief Financial Officer and Mr. Aakash Keshari, Company Secretary & Compliance Officer.

Independent Director(s)

The Company has received necessary declarations from all Independent Directors of the Company under the provisions of section 149(7) of the Act, that they meet the criteria of independence as laid down in section 149 (6) of the Act and applicable provisions of the Listing Regulations. The terms and conditions of appointment of Independent Directors are disclosed on the website of the Company.

As per the Companies (Appointment and Qualifications of Directors) Fifth Amendment Rules, 2019, all the Independent Directors of the Company have registered with the Indian Institute of Corporate Affairs for inclusion of their names in the comprehensive repository maintained by the Ministry of Corporate Affairs.

In the opinion of the Board, the Independent Directors of the Company fulfil the conditions specified under the Act and Listing Regulations and are independent of the management.

Number of Meetings of the Board

During the year, 6 (six) Board Meetings were convened and held. The intervening gap between the meetings was within the period prescribed under the Act. The details of meetings of the Board are provided in the Report on Corporate Governance that forms part of this Annual Report.

Performance evaluation of the Board

The formal annual evaluation has been done by the Board of its own performance and that of its Committees and Individual Directors on the basis of evaluation criteria specified in the Nomination and Remuneration policy of the Company.

The performance evaluation of the Chairman, non-independent Directors and Board as a whole was also carried out by the Independent Directors at their separate meeting held as on 13th February, 2020 inter alia to:

i. To evaluate the performance of non-independent directors and the Board as a whole;

ii. To evaluate performance of the Chairman and Managing Director of the Company; and

iii. To evaluate the quality, quantity and timelines of flow of information between the executive management and the Board.

The suggestions made at the meeting of the Independent Directors were communicated to the Board Chairman and the Executive Director for taking appropriate steps. All Independent Directors were present at the meeting. The Directors expressed their satisfaction with the evaluation process.

Committees of the Board

With a view to have a more focused attention on various facets of business and for better accountability, the Board has constituted a set of Committees in accordance with the requirements of the Act and Listing Regulations. The Board supervises the execution of its responsibilities by the Committees and is responsible for their action. The statutorily mandated Committees constituted under the provisions of the Act and Listing Regulations are Audit Committee, Nomination and Remuneration Committee, Corporate Social Responsibility (CSR) Committee and Stakeholders' Relationship Committee. A detailed note on the composition of the Committees, terms of reference and other such details of the above mentioned Committees are provided in the Report of Corporate Governance forming part of this Annual Report.

Nomination and Remuneration Policy

Pursuant to the provisions of Section 178 of the Act and Regulation 19 of Listing Regulations and on recommendation of the Nomination and Remuneration Committee, the Board of Directors has adopted a policy on Criteria for Selection and Appointment of Directors, Senior Management Personnel and their remuneration. Nomination and Remuneration policy is applicable to all Directors, Key Managerial Personnel (KMP), Senior Management team and other employees of the Company. The said policy has been annexed to this Report and marked as "Annexure-A" and is also available on the Company's website www.bajajhealth.com

VIGIL Mechanism / Whistle Blower Policy

As per the provisions of Section 177(9) and (10) of the Act, the Company has adopted a Whistle Blower Policy for establishing vigil mechanism for the Employees and Directors to report to the Audit Committee Chairman, genuine concerns, unethical behavior and irregularities, if any noticed by them, in the Company which can adversely affects Company's operations. The same is reviewed by the Audit Committee from time to time. No concerns or irregularities have been reported by Employees/ Directors till date. The said policy is available on the Company's website www.bajajhealth.com

Insider Trading Code

The Company has adopted an 'Code of Conduct to regulate, monitor and report trading by designated persons in Listed or Proposed to be Listed Securities' ("the Code") in accordance with the requirements of the Securities and Exchange Board of India (Prohibition of Insider Trading) Regulations, 2015 (PIT Regulations). This Code is displayed on the Company's website. The object of the PIT Regulations is to curb the practice of insider trading in the securities of a listed Company.

The Code is applicable to Promoters and Promoter's Group, all Directors and such Designated Employees who are expected to have access to unpublished price sensitive information relating to the Company. The Company Secretary is the Compliance Officer for monitoring adherence to the said Regulations.

Business Responsibility Reporting

The Business Responsibility Report of the Company for the year ended 31st March, 2020, forms part of the Annual Report and marked as "Annexure-B".

Risk Management

The Company implemented an integrated risk management approach though which it reviews and assesses significant risks on

a regular basis to ensure that a robust system on risk controls and mitigation is in place. Senior management periodically reviews this risk management framework to keep update and address emerging challenges.

Statement in Respect of Adequacy of Internal Financial Controls with Reference to the Financial Statements

Adequate internal control system commensurate with the nature of the Company's business and size and complexity of its operations are in place and have been operating satisfactorily. Internal Control systems comprising of policies and procedure are designed to ensure reliability of financial reporting, timely feedback on achievement of operational and strategic goals, compliance with policies, procedure, applicable laws and regulations and that all assets and resources are acquired economically, used efficiently and adequately protected.

Auditors

Statutory Auditors & their report

M/s. Paresh Rakesh & Associates, Chartered Accountants, were appointed as Statutory Auditors of the Company at the 22nd AGM held on 30th September, 2015 to hold office until the conclusion of the 27th AGM of the Company.

Pursuant to the recommendation of the Audit Committee, the Board of Directors of the Company at their meeting held on 14th September, 2020 has recommended the appointment of M/s. Chaturvedi & Agarwal, Chartered Accountants (Firm Registration No. 101717W) as Statutory Auditors of the Company, for a term of Five consecutive years, from the conclusion of 27th AGM till the conclusion of 32nd AGM of the Company, subject to the approval of shareholders of the Company at their ensuing AGM.

In this regard, M/s. Chaturvedi & Agarwal, Chartered Accountants have submitted their written consent that they are eligible and qualified to be appointed as Statutory Auditors of the Company in terms of Section 139 of the Act and also satisfy the criteria provided in Section 141 of the Act.

The Auditors' Report for the year under review does not contain any reservation, qualification or adverse remarks and all the comments mentioned in the Auditors' Report to the Shareholders are self-explanatory and do not need further explanation.

Cost Auditors & their report

As per Section 148 of the Act read with the Companies (Cost Records and Audit) Amendment Rules, 2014, the cost audit records maintained by the Company in respect of its Drugs & Pharmaceuticals business is required to be audited by a Cost Accountant in practice. In this connection, the Board of Directors of the Company has on the recommendation of the Audit Committee, approved the appointment of N. Ritesh and Associates, Cost Accountants as the Cost Auditors of the Company for the year ending 31st March, 2021. M/s. N. Ritesh and Associates have vast experience in the field of cost audit and have conducted the audit of the cost records of the Company for the past several years under the provisions of the Act.

In accordance with the provisions of Section 148(3) of the Act read with Rule 14 of the Companies (Audit and Auditors) Rules, 2014, the remuneration payable to the Cost Auditors as recommended by the Audit Committee and approved by the Board has to be ratified by the members of the Company at the ensuring AGM. Accordingly, appropriate resolution forms part of the Notice convening the AGM. The Board seeks your support in approving the proposed remuneration plus out-of-pocket expenses payable to the Cost Auditors for the Financial Year ending 31st March, 2021.

The Cost Audit Report for the year ended on 31st March, 2019 does not contain any reservation, qualification or adverse remark.

Internal Auditor and their report

Pursuant to the provisions of Section 138 of the Act read with the Companies (Accounts) Rules, 2014, Ms. Neha Gupta, Cost Accountant has been appointed as Internal Auditor of the Company for the financial year 2020-21.

The Internal Auditor submits her reports to the Audit Committee on periodic basis. Based on the report of Internal Audit, management undertakes corrective action in their respective areas and thereby strengthens the controls.

Secretarial Auditor and their report

Pursuant to the provisions of Section 204 of the Act and the Companies (Appointment and Remuneration of Managerial Personnel) Rules, 2014, the Company has appointed Mr. Haresh Sanghvi, Practicing Company Secretary, Mumbai as a Secretarial Auditor to conduct Secretarial Audit of the Company. Report of the Secretarial Audit in Form MR-3 for the financial year ended 31st March, 2020 is enclosed as **Annexure-II** to the Report. The said report does not contain any observation or qualification requiring explanation and the remarks mentioned in the report are self-explanatory.

Reporting of fraud by Auditors

There was no instance of fraud during the year under review, which required the Statutory Auditors, Internal Auditor, Cost Auditor or/and the Secretarial Auditor to report to the Audit Committee and/or the Board under Section 143(12) of Act and Rules framed thereunder.

Compliance with Secretarial Standards

The Company has complied with the applicable mandatory Secretarial Standards.

General Disclosures

Related Party Transactions

All transactions entered into with related parties as defined under the Companies Act, 2013 during the financial year were in the ordinary course of business and on an arm's length pricing basis and do not attract the provisions of Section 188 of the Act. There were no materially significant transactions with the related parties during the financial year which were in conflict with the interest of the Company and hence, enclosing of Form AOC-2 is not required. Suitable disclosure as required by the Accounting Standard (AS 18) has been made in the notes to the Financial Statements.

Particulars of Loans, Guarantee and Investments

Pursuant to Section 186 of the Act read with the Companies (Meetings of Board and its Powers) Rules, 2014, details of loans made, guarantee issued, investments made or securities provided by the Company have been disclosed in the Financial Statements.

Cash Flow Analysis

The cash flow statement for the year ended 31st March, 2020 is annexed with the financial statements.

Particulars of Employees

Information required in accordance with Section 197 (12) of the Act read with Rule 5(1) and 5(2) of the Companies (Appointment and Remuneration of Managerial Personnel) Rules, 2014 are forming part of the Board's Report for the year ended 31st March, 2020 is annexed and marked as **Annexure-III** to Board's Report.

Disclosure under Sexual Harassment of Women at Workplace (Prevention, Prohibition and Redressal) Act, 2013

The Company has always believed in providing a safe and harassment free workplace for every individual working in the Company's premises through various practices and always endeavors to provide an environment that is free from discrimination. All employees are treated with dignity with a view to maintain a work environment free of sexual harassment whether physical, verbal or psychological. The Company has in place, policy on Prevention, Prohibition and Redressal of Sexual Harassment for women at workplace in accordance with the requirements of Sexual Harassment of women at workplace (Prevention, Prohibition and Redressal) Act, 2013. An Internal Complaints Committee (ICC) has been setup as per the statutory requirements, to redress complaints regarding sexual harassment.

During the year 2019-20, ICC did not receive complaints of sexual harassment from any employees.

Significant and Material Orders passed by the Regulators or Courts or Tribunals

There are no significant and material orders passed by the Regulators/Courts that would impact the going concern status of the Company and its future operations.

Management Discussion and Analysis Report

Management Discussion and Analysis for the year under review is provided as separate section forming part of the Annual Report.

Corporate Governance

Report on Corporate Governance and Certificate of the Auditors of the Company regarding compliance of the conditions of Corporate Governance as stipulated in Part C of Schedule V of the Listing Regulations, are provided in a separate section forming part of the Annual Report.

Directors' Responsibility Statement

The Board of Directors acknowledge the responsibility for ensuring compliance with the provisions of Section 134(3)(c) read with Section 134(5) of the Act, in the preparation of annual accounts for the year ended on 31st March, 2020 and confirm that:

a. in the preparation of the annual accounts, the applicable accounting standards had been followed along with proper explanation relating to material departures;

b. the directors had selected such accounting policies and applied them consistently and made judgments and estimates that are reasonable and prudent so as to give a true and fair view of the state of affairs of the company at the end of the financial year and of the profit and loss of the company for that period;

c. the directors had taken proper and sufficient care for the maintenance of adequate accounting records in accordance with the provisions of this Act for safeguarding the assets of the Company and for preventing and detecting fraud and other irregularities;

d. the directors had prepared the annual accounts on a going concern basis;

e. the directors had laid down internal financial controls to be followed by the Company and that such internal financial controls are adequate and were operating effectively; and

f. the directors had devised proper systems to ensure compliance with the provisions of all applicable laws and that such systems were adequate and operating effectively.

Corporate Social Responsibility

As a part of its initiative under the "Corporate Social Responsibility" (CSR) drive, the Company has undertaken projects in the area of rural development and education. These projects are in accordance with Schedule VII of the Act and the Company's CSR policy. The Report on CSR activities as required under the Companies (Corporate Social Responsibility Policy) Rules, 2014 is annexed and marked as **Annexure-IV** which forms an integral part of this Report.

Energy Conservation, Technology Absorption, Research & Development and Foreign Exchange Earnings and Outgo

The information on conservation of energy, technology absorption and foreign exchange earnings and outgo stipulated. Under section 134(3) (m) of the Act read with Rule 8(3) of the Companies (Accounts) Rules, 2014, are as follows:

I. Conservation of Energy:

Steps taken on Energy Conservation –

Many steps towards energy conservation has taken & implemented successfully.

a. Commissioned low pressure steam turbine. This works on back pressure of steam boiler & generates electrical power of 100 KW/HR.

b. Installed Solar Panels of capacity of 700 KW in vacant land of factory premises.

c. To prevent heat loss replaced old insulation of reactors and cold well of brine storage tank.

d. Installed softener plant capacity of 10 M3/HR to improve cooling water quality and efficient running of chilling plant. This prevents scaling & ensure better heat transfer & saves energy.

e. Installed DM plant to improve boiler feed water quality and run efficient. This saves scaling in tubes & enhances life of boiler tubes.

f. Replaced the condenser of Brine Plant 2 by higher capacity to run machine efficient.

g. Replaced steam trap by float type. This controls live steam wastage & helps improving steam savings.

II. Technology Absorption:

a. Cooling tower blades replaced by new designed FRP Pumps.

b. For distillation column, old structured packing replaced with new one.

c. Mercury vapour lamps replaced by LED Lamps.

III. Research & Development:

a. R&D Laboratory of Bajaj Healthcare Limited is already approved by DSIR (Department of Scientific and Industrial Research), India.

b. We added efficient fume-hoods, sophisticated equipment and facilities for carrying out synthetic research and scale-up activities to develop new process technology for APIs under safe conditions.

c. R&D works on different generic molecules are under process. Some of products have been commercialised at plant scale using environment friendly routes.

d. With the regular progression in the business, our company intends to emphasise on further expansion of R&D facilities for development of technologically advanced, asymmetric active pharmaceutical ingredients.

e. To achieve highest level of challenges of R&D activities, Bajaj Healthcare Limited has developed a talented pool of scientists including organic/analytical chemists provide support to our R&D through documentation and validation of test results as per ICH guidelines and assist the regulatory affairs to prepare high quality technical packages and drug master files.

f. The Company has obtained approval for In-house R & D Facility from the Department of Scientific and Industrial Research (DSIR) vide letter No. TU/IV-RD/4031/2019 dated 01st May, 2019 for the purpose of section 35(2AB) of the Income Tax Act, 1961 valid till 31st March 2022 subject to the condition underline therein.

h. There under, the company has claimed a weighted deduction of 150% of the following expenditure incurred wholly and exclusively for the Research & Development Activity so approved.

(₹ in Lakhs)

Nature of Expenditure	2019-20	2018-19
Revenue Expenditure:		
Salary Expenses of R&D Personnel	68.00	102.03
R & D Chemical Purchase	117.06	45.42
Stores & Spares & Consumables in R & D	6.01	-
Travelling & Other Exp.	1.04	0.18
Common Utilities Expenses	30.85	23.21
Capital Expenditure:		
Laboratory Equipment	18.03	61.55
TOTAL	**241.00**	**232.39**

IV. Foreign Exchange Earning and Outgo

Earnings:

Foreign Currency inflow amounting to ₹ 94,65,58,475/-

Outgo:

Foreign Currency outgo amounting to ₹ 1,21,12,30,528/-

Environment and Pollution Control

The Company is well aware of its responsibility towards a better and clean environment. Our efforts in environment management go well beyond mere compliance with statutory requirements. The Company has always maintained harmony with nature by adopting eco-friendly technologies and upgrading the same from time to time incidental to its growth programs.

Statutory Compliances

The Company has complied with all the statutory requirements. A declaration regarding compliance of the provisions of the various statutes is also made by the Chief Financial Officer at each Board Meeting. The Company ensures compliance of the ROC, SEBI Regulations and various statutory authorities.

Acknowledgements

Your Directors express their gratitude to various Central and State Government Departments, Organizations and Agencies for their continued help and co-operation extended by them. The Directors also gratefully acknowledge all stakeholders of the Company viz. customers, members, dealers, vendors, banks, and other business associates for the excellent support received from them during the year. The Board also wishes to express its gratitude and record its sincere appreciation for the commitment and dedicated efforts put in by all the employees more particularly ensuring business as usual in spite of COVID-19 impact.

The Directors express their special thanks to Mr. Sajankumar R. Bajaj, Chairman & Managing Director for his untiring efforts for the progress of the Company.

For and on behalf of the Board of Directors
of **Bajaj Healthcare Limited**

Sd/-
Sajankumar R. Bajaj
Chairman and Managing Director
DIN: 00225950

Date: 14th September, 2020
Place: Thane

Annexure-I

Form No. MGT-9

EXTRACT OF THE ANNUAL RETURN AS ON THE FINANCIAL YEAR ENDED 31ST MARCH, 2020

(Pursuant to section 92(3) of the Companies Act, 2013 and Rule 12(1) of the Companies (Management and Administration) Rules, 2014)

I. Registration and other Details

i.	**CIN**	:	L99999MH1993PLC072892
ii.	**Registration Date**	:	15th July, 1993
iii.	**Name of the Company**	:	BAJAJ HEALTHCARE LIMITED
iv.	**Category**	:	Company Limited by shares
	Sub-Category of the Company	:	Indian Non-Government Company
v.	**Address of the Registered Office and contact details**	:	602-606, Bhoomi Velocity Infotech Park, Plot No.B-39, B-39A, B- 39A/1, Road No.23, Wagle Industrial Estate, Thane (West) - 400 604 Tel: (91) 22 66177400. Email:investors@bajajhealth.com; Website: www.bajajhealth.com
vi.	**Whether Listed Company**	:	Yes, Listed -BSE Limited Migrated to main board of BSE Limited w.e.f. 29th May 29, 2019
vii.	**Name, Address and Contact details of Registrar and Transfer Agent:**		M/s. Link Intime India Private Limited. C-101, 24*7 Park, L B S Marg, Vikhroli West, Mumbai - 400083. Website: www.linkintime.co.in

II. Principal Business Activities

All the business activities contributing 10% or more of the total turnover of the Company

Sr. No.	Name and Description ofmain products	NIC Code of the Product	% to total turnover of the Company
1.	Manufacturing of Bulk Drugs & Pharmaceutical Products	210	99.23

III. Particular of Holding, Subsidiary and Associate Companies

Sr. No.	Name and Address CIN/GLN	Holding/ Subsidiary/ Associate	% of Shares Held	Applicable Section
		Not applicable		

IV. Share Holding Pattern (Equity Share Capital Breakup as percentage of Total Equity)

(i) Category-wise Share Holding

Category of shareholders	No. of shares held at the beginning of the year (As on 1st April, 2019)				No. of shares held at the end of the year (As on 31st March, 2020)				% Change during the year
	Demat	Physical	Total	% of total Shares	Demat	Physical	Total	% of total Shares	
A. Promoters									
(1) Indian									
a) Individual/HUF	45,66,000	-	45,66,000	66.178	91,32,000	-	91,32,000	66.178	-
b) Central Govt	-	-	-	-	-	-	-	-	-
c) State Govt (s)	-	-	-	-	-	-	-	-	-
d) Bodies Corp.	75,000	-	75,000	1.087	1,50,000	-	1,50,000	1.087	-
e) Banks / FI	-	-	-	-	-	-	-	-	-
f) Any Other	-	-	-	-	-	-	-	-	-
Directors	-	-	-	-	-	-	-	-	-
Directors Relatives	-	-	-	-	-	-	-	-	-
Person Acting in Concern	-	-	-	-	-	-	-	-	-
Sub-total (A) (1)	**46,41,000**	**-**	**46,41,000**	**67.265**	**92,82,000**	**-**	**92,82,000**	**67.265**	**-**

Category of shareholders	No. of shares held at the beginning of the year (As on 1st April, 2019)				No. of shares held at the end of the year (As on 31st March, 2020)				% Change during the year
	Demat	Physical	Total	% of total Shares	Demat	Physical	Total	% of total Shares	
(2) Foreign									
a) NRIs -									
Individuals	-	-	-	-	-	-	-	-	-
b) Other –									
Individuals	-	-	-	-	-	-	-	-	-
c) Bodies Corp.	-	-	-	-	-	-	-	-	-
d) Banks / FI	-	-	-	-	-	-	-	-	-
e) Any Other	-	-	-	-	-	-	-	-	-
Sub-total (A) (2)	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**-**
Total shareholding of Promoter (A) =(A)(1)+(A)(2)	**46,41,000**	**-**	**46,41,000**	**67.265**	**92,82,000**	**-**	**92,82,000**	**67.265**	**-**
B. Public Shareholding									
1. Institutions									
a) Mutual Funds	-	-	-	-	-	-	-	-	-
b) Banks / FI	-	-	-	-	-	-	-	-	-
c) Central Govt	-	-	-	-	-	-	-	-	-
d) State Govt(s)	-	-	-	-	-	-	-	-	-
e) Venture Capital Funds	-	-	-	-	-	-	-	-	-
f) Insurance Companies	-	-	-	-	-	-	-	-	-
g) FIIs	-	-	-	-	-	-	-	-	-
h) Foreign Venture Capital Funds	-	-	-	-	-	-	-	-	-
i) Others	-	-	-	-	-	-	-	-	-
Sub-total (B)(1):-	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**NIL**	**-**
2. Non-Institutions:									
a) Bodies Corp.									
i) Indian	14,45,200	4,35,000	18,80,200	27.251	30,09,519	4,35,000	34,44,519	24.962	-2.289
ii) Overseas	-	-	-	-	-	-	-	-	-
b) Individuals									
i) Individual shareholders holding nominal share capital upto ₹ 1 lakh	1,02,800	-	1,02,800	1.490	1,70,884	-	1,70,884	1.238	-0.252
ii) Individual shareholders holding nominal share capital in excess of ₹ 1 lakh	2,74,400	-	2,74,400	3.977	8,96,259	-	8,96,259	6.495	2.518
c) Others (specify)									
Trusts	-	-		-	-	-	-	-	-
Clearing member	400	-	400	0.006	594	-	594	0.004	-0.002
Market Maker	-	-	-	-	-	-	-	-	-
Foreign Nationals	-	-	-	-	-	-	--	-	-
Non Resident Indians (Repat)	800	-	800	0.012	4,944	-	4,944	0.036	0.024
Non Resident Indians (Non-Repat)	-	-	-	-	-	-	-	-	-
Foreign Companies	-	-	-	-	-	-	-	-	-
Overseas Corporate Bodies	-	-	-	-	-	-	-	-	-
Independent Directors	-	-	-	-	-	-	-	-	-
HUF	-	-	-	-	-	-	-	-	-
Sub-total (B)(2):	**18,23,600**	**4,35,000**	**22,58,600**	**32.736**	**40,82,200**	**4,35,000**	**45,17,200**	**32.736**	**-0.001**
Total Public Shareholding (B)=(B)(1)+ (B)(2)	**18,23,600**	**4,35,000**	**22,58,600**	**32.735**	**40,82,200**	**4,35,000**	**45,17,200**	**32.736**	**-0.001**
C. Shares held byCustodian for GDRs & ADRs	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Grand Total (A+B+C)	**64,64,600**	**4,35,000**	**68,99,600**	**100**	**1,33,64,200**	**43,50,00**	**1,37,99,200**	**100**	**-**

(ii) Shareholding of Promoters

Shareholders Name	No. of shares held at the beginning of the year (As on 1st April, 2019)			No. of shares held at the end of the year (As on 31st March, 2020)			% Change in share holding during the year
	No. of Shares	% of total Shares of the company	%of Shares Pledged / encumbered to total shares	No. of Shares	% of total Shares of the company	%of Shares Pledged / encumbered to total shares	
Mr. Sajankumar R. Bajaj	24,07,000	34.88	N.A	48,14,000	34.88	N.A	-
Ms. Babita Bajaj	3,76,000	5.45	N.A	7,52,000	5.45	N.A	-
Ms. Namrata S. Bajaj	4,04,000	5.86	N.A	8,08,000	5.86	N.A	-
Ms. Nihita Bajaj	4,04,000	5.86	N.A	8,08,000	5.86	N.A	-
Mr. Anil C. jain	3,59,000	5.20	N.A	7,18,000	5.20	N.A	-
Mr. Padma A. jain	76,000	1.10	N.A	1,52,000	1.10	N.A	-
S. K. R. Bajaj HUF	5,40,000	7.83	N.A	10,80,000	7.83	N.A	-
Bajaj Health & Nutrition Private Limited	60,000	0.87	N.A	1,20,000	0.87	N.A	-
Bansal Pharma Limited	15,000	0.22	N.A	30,000	0.22	N.A	-
TOTAL	**46,41,000**	**67.27**	**N.A**	**92,82,000**	**67.27**	**N.A**	**-**

(iii) Change in Promoters' Shareholding (please specify, if there is no change)

	No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
	No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
Mr. Sajankumar R. Bajaj				
At the beginning of the year	24,07,000	34.88		
Changes during the year:				
Add: Bonus Shares (11th April, 2019) 24,07,000 shares			48,14,000	34.88
At the End of the year			48,14,000	34.88
Ms. Babita S. Bajaj				
At the beginning of the year	3,76,000	5.45		
Changes during the year:				
Add: Bonus Shares (11th April, 2019) 3,76,000 shares			7,52,000	5.45
At the End of the year			7,52,000	5.45
Ms. Namrata S. Bajaj				
At the beginning of the year	4,04,000	5.86		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 4,04,000 shares			8,08,000	5.86
At the End of the year			8,08,000	5.86
Ms. Nihita S. Bajaj				
At the beginning of the year	4,04,000	5.86		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 4,04,000 shares			8,08,000	5.86
At the End of the year			8,08,000	5.86
Mr. Anil C. Jain				
At the beginning of the year	3,59,000	5.20		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 3,59,000 shares			7,18,000	5.20
At the End of the year			7,18,000	5.20
Ms. Padma A. Jain				
At the beginning of the year	76,000	1.10		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 76,000 shares			1,52,000	1.10
At the End of the year			1,52,000	1.10

	No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
	No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
S K R Bajaj HUF				
At the beginning of the year	5,40,000	8.00		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 5,40,000 shares			10,80,000	8.00
At the End of the year			10,80,000	8.00
Bajaj Health & Nutrition Private Limited				
At the beginning of the year	60,000	0.89		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 60,000 shares			1,20,000	0.89
At the End of the year			1,20,000	0.89
Bansal Pharma Limited				
At the beginning of the year	15,000	0.23		
Changes during the year				
Add: Bonus Shares (11th April, 2019) 15,000 shares			30,000	0.23
At the End of the year			30,000	0.23

(iv) Shareholding Pattern of top ten Shareholders (other than Directors, Promoters and Holders of GDRs and ADRs):

			No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
			No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
1.	**Progyan Construction and Engineers Pvt Ltd**					
	At the beginning of the year		5,28,900	7.666		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	5,28,900	11th April, 2019			
	At the End of the year				10,57,800	7.666
2.	**Maa Sharada Distributors Private Limited**					
	At the beginning of the year		4,35,000	6.30		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	4,35,000	11th April, 2019			
	At the End of the year				8,70,000	6.30
3.	**Shri Ravindra Media Ventures**					
	At the beginning of the year		2,70,300	3.918		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	2,70,300	11th April, 2019		5,40,600	3.918
	Sell	(1,00,000)	26th July, 2019		4,40,600	3.193
	Sell	(1,00,000)	2nd August, 2019		3,40,600	2.468
	Buy	2,00,000	31st March, 2020		5,40,600	3.918
	At the End of the year				5,40,600	3.918
4.	**Escorp Asset Management Limited**					
	At the beginning of the year		2,37,600	3.444		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	2,37,600	11th April, 2019		4,75,200	3.444
	Sold	(250)	1st November, 2019		4,74,950	3.442
	Sold	(450)	15th November, 2019		4,74,500	3.439
	Sold	(700)	6th March, 2020		4,73,800	3.434
	Sold	(100)	13th March, 2020		4,73,700	3.433
	At the End of the year				4,73,700	3.433

			No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
			No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
5.	**Vinod Harilal Jhaveri**					
	At the beginning of the year		1,45,200	2.104		
	Changes during the year:					
	Particulars	**Shares**	**Date**			
	Bonus	1,45,200	11th April, 2019		2,90,400	2.104
	At the End of the year				2,90,400	2.104
6.	**Tia Enterprises Private Limited**					
	At the beginning of the year		143600	6.68		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	1,43,600	11th April, 2019		2,87,200	2.081
	Sold	(49,600)	15th November, 2019		2,37,600	1.722
	At the End of the year				2,37,600	1.722
7.	**Shashank Pravinchandra Doshi**					
	At the beginning of the year		Nil	Nil		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Buy	97,200	22nd November, 2019		97,200	0.704
	Buy	21,600	13th March, 2020		1,18,800	0.861
	Buy	4,500	20th March, 2020		1,23,300	0.894
	At the End of the year				1,23,300	0.894
8.	**Hetal Shashank Doshi**					
	At the beginning of the year		Nil	Nil		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Buy	1,10,150	22nd November, 2019		1,10,150	0.798
	At the End of the year				1,10,150	0.798
9.	**Bipin Chabildas Shah**					
	At the beginning of the year		51,600	0.748		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	51,600	11th April, 2019		1,03,200	0.748
	At the End of the year				1,03,200	0.748
10.	**MBM Bearings (Rajasthan) Private Limited**					
	At the beginning of the year		68,000	0.986		
	Changes during the year					
	Particulars	**Shares**	**Date**			
	Bonus	68,000	11th April, 2019		1,36,000	0.986
	Sold	(37,600)	15th November, 2019		98,400	0.713
	At the End of the year			98,400	0.713	

(v) Shareholding of Directors and Key Managerial Personnel:

			No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
			No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
Mr. Sajankumar R. Bajaj						
At the beginning of the year			24,07,000	34.88		
Changes during the year:						
Particulars	**Shares**	**Date**				
Bonus	2,407,000	11th April, 2019			48,14,000	34.88
At the End of the year					48,14,000	34.88

			No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
			No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
Ms. Namrata S. Bajaj						
At the beginning of the year			4,04,000	5.86		
Changes during the year						
Particulars	**Shares**	**Date**				
Bonus	4,04,000	11th April, 2019			8,08,000	5.59
At the End of the year					8,08,000	5.86
Mr. Anil C. Jain						
At the beginning of the year			3,59,000	5.2		
Changes during the year						
Particulars	**Shares**	**Date**				
Bonus	3,59,000	11th April, 2019			7,18,000	5.2
At the End of the year					7,18,000	5.2
Mr. Dhananjay S. Hatle						
At the beginning of the year			6,000	0.09		
Changes during the year						
Particulars	**Shares**	**Date**				
Bonus	6,000	11th April, 2019			12,000	0.09
At the End of the year					12,000	0.09
Mr. Rupesh H. Nikam, Director & CFO						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Vidyut Shah (Independent Director) (6)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Hemant R. Karnik (Independent Director)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Ram Banarase (Independent Director)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Pakshal A. Jain, Director(1)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Avinash Dalal (Independent Director) (2)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Loukik D. Tipnis (Independent Director) (3)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL
Mr. Luke Fernendez (Independent Director) (4)						
At the beginning of the year			NIL	NIL		
Changes during the year				No Change During the year		
At the End of the year					NIL	NIL

	No. of shares held at the beginning of the year (As on 1st April, 2019)		Cumulative at the end of the year (As on 31st March, 2020)	
	No. of shares	% of total shares of the company	No. of shares	% of total shares of the company
Ms. Kejal N. Shah (Independent Director) [5]				
At the beginning of the year	NIL	NIL		
Changes during the year	No Change During the year			
At the End of the year			NIL	NIL
Mr. Aakash Keshari (Company Secretary)				
At the beginning of the year	NIL	NIL		
Changes during the year	No Change During the year			
At the End of the year			NIL	NIL

[1] Mr. Pakshal A. Jain has been appointed as director w.e.f. 30th June, 2020.
[2] Mr. Avinash Dalal has been appointed as director w.e.f. 22nd April, 2019.
[3] Mr. Loukik D. Tipnis has been appointed as director w.e.f. 22nd April, 2019.
[4] Mr. Luke B. Fernandez has been appointed as director w.e.f. 30th June, 2020.
[5] Ms. Kejal N. Shah has been appointed as director w.e.f. 30th June, 2020.
[6] Mr. Vidyut Shah has been resigned from the Directorship of the Company w.e.f. 12th June, 2020.

V. Indebtedness

Indebtedness of the Company including interest outstanding/accrued but not due for payment.

(In ₹)

	Secured Loans excluding deposits& LC	Unsecured Loans	Deposits	Total Indebtedness
Indebtedness at the beginning of the financial year:				
i) Principal Amount	77,32,87,672	3,39,73,966	NIL	80,72,61,638
ii) Interest due but not paid	-	-	-	-
iii) Interest accrued but not due	-	-	-	-
Total (i+ii+iii)	**77,32,87,672**	**3,39,73,966**	**NIL**	**80,72,61,638**
Change in Indebtedness during the financial year				
Addition/(Reduction)	12,59,41,308	(2,39,44,566)	NIL	10,19,96,744
Net Change	12,59,41,308	(2,39,44,566)	NIL	10,19,96,744
Indebtedness at the end of the financial year				
i) Principal Amount	89,92,28,980	1,00,29,400	NIL	90,93,21,380
ii) Interest due but not paid	-	-	-	-
iii) Interest accrued but not due	-	-	-	-
Total (i+ii+iii)	**89,92,28,980**	**1,00,29,400**	**NIL**	**90,92,58,380**

VI. Remuneration of Directors and Key Managerial Personnel

A. Remuneration to Managing Director, Whole-Time Directors and/or Manager:

(In ₹)

Particulars of Remuneration	Mr. Sajankumar R. Bajaj (Chairman and Managing Director)	Mr. Anil C. Jain (Managing Director)	Mr. Dhananjay S. Hatle (Whole Time Director)	Ms. Namrata S. Bajaj (Whole Time Director)	Mr. Rupesh H. Nikam (Whole Time Director & CFO)	Total Amount
Gross salary						
(a) Salary as per provisions contained in section 17(1) of the Income-tax Act, 1961	48,00,000	46,00,000	13,58,535	10,15,000	16,15,440	1,33,88,975
(b) Value of perquisites u/s 17(2) Income-tax Act, 1961	-	-	-	-	-	-
(c) Profits in lieu of salary under section 17(3) Income-tax Act, 1961	-	-	-	-	-	-

(In ₹)

Particulars of Remuneration	Mr. Sajankumar R. Bajaj (Chairman and Managing Director)	Mr. Anil C. Jain (Managing Director)	Mr. Dhananjay S. Hatle (Whole Time Director)	Ms. Namrata S. Bajaj (Whole Time Director)	Mr. Rupesh H. Nikam (Whole Time Director & CFO)	Total Amount
Stock Option	-	-	-	-	-	-
Sweat Equity	-	-	-	-	-	-
Commission - as % of profit - others						
Others	-	-	-	-	-	-
Total (A)	**48,00,000**	**46,00,000**	**13,58,535**	**10,15,000**	**16,15,440**	**1,33,88,975**
Ceiling as per the Act	**within the limits as approved by the Shareholders**					

B. Remuneration to Other Directors:

(In ₹)

Particulars of Remuneration	Total Amount					
Independent Directors	**Mr. Vidyut J. Shah**	**Mr. Hemant R. Karnik**	**Mr. Ram B. Banarse**	**Mr. Loukik D. Tipnis**	**Mr. Avinash Dalal**	**Total Amount**
• Fee for attending board / committee meetings	1,20,000	1,20,000	60,000	45,000	35,000	1,80,000
• Commission		-	-	-		
• Others	-	-	-			-
Total (1)	**1,20,000**	**1,20,000**	**60,000**	**45,000**	**35,000**	**3,80,000**
Other Non-Executive Directors						
• Fee for attending board / committee meetings	-					
• Commission	-					
• Others	-					
Total (2)	**-**					
Total (B)=(1+2)	**3,80,000**					
Total Managerial Remuneration	**1,37,68,975**					
Overall Ceiling as per the Act	**NA**					

VI. Remuneration to Key Managerial Personnel other than MD/Manager/WTD

(In ₹)

Particulars of Remuneration	Mr. Sajankumar R. Bajaj	Mr. Rupesh H. Nikam (CFO)	Mr. Aakashkumar Keshari (Company Secretary)	Total Amount
Gross salary				
(a) Salary as per provisions contained in section 17(1) of the Income-tax Act, 1961	48,00,000	16,15,440	7,48,859	71,64,229
(b) Value of perquisites u/s 17(2) Income-tax Act, 1961	-	-	-	-
(c) Profits in lieu of salary under section 17(3) Income-tax Act, 1961	-	-	-	-
Stock Option	-	-	-	-
Sweat Equity	-	-	-	-
Commission - as % of profit - others				
Others	-	-	-	-
Total	**48,00,000**	**16,15,440**	**7,48,859**	**71,64,229**

VII. Penalties / Punishment/ Compounding of Offences

Type	Section of the Companies Act	Brief Description	Details of Penalty / Punishment / Compounding fees imposed	Authority [RD/ NCLT/Court]	Appeal made, if any (give details)
A. COMPANY					
Penalty					
Punishment			NIL		
Compounding					
B. DIRECTORS					
Penalty					
Punishment			NIL		
Compounding					
C. OTHER OFFICERS IN DEFAULT					
Penalty					
Punishment			NIL		
Compounding					

Annexure-II

Form No. MR-3

SECRETARIAL AUDIT REPORT

For the Financial Year Ended 31st March, 2020

(Pursuant to section 204(1) of the Companies Act, 2013 and Rule No.9 of the Companies (Appointment and Remuneration Personnel) Rules, 2014]

The Members,

BAJAJ HEALTHCARE LIMITED
602-606, Bhoomi Velocity Infotech Park,
Plot No. B-39, B-39A, B-39 A/1, Rd No.23,
Wagle Ind. Estate Thane West 400604

I have conducted the secretarial audit of the compliance of applicable statutory provisions and the adherence to good corporate practices by **BAJAJ HEALTHCARE LIMITED** (hereinafter called the "Company") for the audit period covering the financial year ended on 31st March, 2020. Secretarial Audit was conducted in a manner that provided me a reasonable basis for evaluating the corporate conducts/statutory compliances and expressing my opinion thereon.

Based on my verification of the Company's books, papers, minute books, forms and returns filed and other records maintained by the Company and also the information provided by the Company, its officers, agents and authorized representatives during the conduct of secretarial audit, I hereby report that in my opinion, the Company has, during the audit period covering the financial year ended on 31st March 2020, generally complied with the statutory provisions listed hereunder and also that the Company has proper Board processes and compliance mechanism in place to the extent, in the manner and subject to the reporting made hereinafter:

1. I have examined the books, papers, minute books, forms and returns filed and other records maintained by the Company for the financial year ended on 31st March 2020, according to the provisions of:
   - (i) The Companies Act, 2013 (the Act) and the rules made thereunder;
   - (ii) The Securities Contracts (Regulation) Act, 1956 ('SCRA') and the rules made thereunder;
   - (iii) The Depositories Act, 1996 and the Regulations and Bye-laws framed thereunder;
   - (iv) The following Regulations and Guidelines prescribed under the Securities and Exchange Board of India Act, 1992 ('SEBI Act'):-
     - (a) Securities and Exchange Board of India (Substantial Acquisition of Shares and Takeovers) Regulations, 2011;
     - (b) Securities and Exchange Board of India (Prohibition of Insider Trading) Regulations, 2015;
     - (c) Securities and Exchange Board of India (Issue of Capital and Disclosure Requirements) Regulations, 2018;
     - (d) Securities and Exchange Board of India (Depositories and Participants) Regulations, 2018; and
     - (e) Securities and Exchange Board of India (Listing Obligations and Disclosure Requirement) Regulations, 2015
2. There were no actions/ events in pursuance of following Regulations of SEBI requiring compliance thereof by the Company during the period under review:
   - (i) Securities and Exchange Board of India (Share Based Employee Benefits) Regulations, 2014;
   - (ii) Securities and Exchange Board of India (Delisting of Equity Shares) Regulations, 2009;
   - (iii) Securities and Exchange Board of India (Buyback of Securities) Regulations, 2018;
   - (iv) Securities and Exchange Board of India (Issue and Listing of Debt Securities) Regulations, 2008; and
   - (v) Securities and Exchange Board of India (Registrars to an Issue and Share Transfer Agents) Regulations, 1993 regarding the Companies Act and dealing with client
3. Provisions of Foreign Exchange Management Act, 1999 and the rules and regulations made thereunder to the extent of Foreign Direct Investment, Overseas Direct Investments, External Commercial Borrowings were not attracted during the year under review;
4. Based on the information provided and review of the Compliances Report of Managing Director taken on record by the Board of the Company and also relying on the representation made by the Company and its Officers, in my opinion adequate system and process exists in the Company to monitor and ensure compliances with the provisions of general and other industry and sector specific Laws and Regulations applicable to the Company, as identified and confirmed by the management of the company and listed in Annexure-A to this report.

5. I have also examined compliance with the applicable clauses of the following:

   (i) Secretarial Standards (SS-1 and SS-2) issued by The Institute of Company Secretaries of India; and

   (ii) Listing Agreements entered into by the Company with BSE Limited.

During the audit period, the Company has generally complied with the provisions of the Act, Rules, Regulations, Guidelines, Standards mentioned above and there are no material non-compliances that have come to my knowledge except:

(i) Delay in filing of e-Form DPT-3 in accordance with the provisions of Section 76 of the Companies Act, 2013 and the rules framed thereunder; and

(ii) Details on "change in Return on Networth" in accordance of Para (B)(1)(j) of Schedule V of SEBI (LODR), 2015 were inadvertently missed out in the Annual Report for FY 2018-19.

I further report that compliances of finance and tax laws and maintenance of financial records and books of accounts has not been reviewed in this Audit since the same have been subject to review by statutory Auditors and other designated professionals.

I further report that:

1. The Board of Directors of the Company is duly constituted with proper balance of Executive Directors, Non-Executive Directors and Independent Directors. During the period under review. The changes in the composition of the Board of Directors that took place during the period under review were carried out in compliance with the provisions of the Act.
2. Adequate notice is given to all directors to schedule the Board Meetings, agenda and detailed notes on agenda were generally sent in advance, and a system exists for seeking and obtaining further information and clarifications on the agenda items before the meeting and for meaningful participation at the meeting.
3. All decisions at Board Meetings and Committee Meetings were carried out unanimously as recorded in the minutes of the meetings of the Board of Directors or Committees of the Board, as the case may be.

I further report that there are adequate systems and processes in the Company commensurate with the size and operations of the company to monitor and ensure compliance with applicable laws, rules, regulations and guidelines.

I further report that during the audit period under report, no event/action occurred which had a major bearing on the Company's affairs in pursuance of the above referred laws, rules, regulations, guidelines, standards, etc.

Haresh Sanghvi
Practicing Company Secretary
FCS 2259/COP No. 3675
UDIN: F002259B000706919

Date: 10th August, 2020
Place: Mumbai

Note: This report is to be read with my letter of even date which is annexed as **ANNEXURE-B** and forms an integral part of this report.

ANNEXURE - a

List of applicable laws to the Company

a) The following laws and regulations, as amended from time to time, are applicable specifically to the Company given its business:

i. The Drugs & Cosmetics Act, 1940;
ii. The Drugs (Control), Act, 1950;
iii. The Narcotics Drugs and Psychotropic Substances Act, 1985;
iv. The Pharmacy Act, 1948;
v. The Drugs and Magic remedies (Objectionable Advertisements) Act,1954;
vi. The Poisons Act, 1919;
vii. The Petroleum Act, 1934;
viii. The Legal Metrology Act, 2009;
ix. The Indian Boiler Act,1923;

b) All General Laws related to Direct and Indirect Taxation, Labour Laws and other incidental laws as applicable.

Haresh Sanghvi
Practicing Company Secretary
FCS 2259/COP No. 3675
UDIN: F002259B000706919

Date: 10th August, 2020
Place: Mumbai

ANNEXURE - b

The Members,

BAJAJ HEALTHCARE LIMITED
602-606, Bhoomi Velocity Infotech Park,
Plot No. B-39, B-39A, B-39 A/1, Rd No.23,
Wagle Ind. Estate Thane West 400604

My report of even date is to be read along with this letter:

1. Maintenance of secretarial record is the responsibility of the management of the Company. My responsibility is to express an opinion on these secretarial records based on my audit.
2. I have followed the audit practices and processes as were appropriate to obtain reasonable assurance about the correctness of the contents of the secretarial records. The verification was done on test basis to ensure that correct facts are reflected in secretarial records. I believe that the processes and practices I followed, provide a reasonable basis for my opinion.
3. I have not verified the correctness and appropriateness of financial records and Books of Accounts of the Company.
4. Whenever required, I have obtained the management representation about the compliance of laws, rules and regulations and major events during the audit period. Due to ongoing COVID-19 pandemic and consequent lock-down imposed, I could not verify the compliance documents physically for the period under review and the reliance has been placed on the scanned documents obtained through electronic mode.
5. The compliance of the provisions of corporate and other applicable laws, rules, regulations, standards is the responsibility of management. My examination was limited to the verification of procedures on test basis.
6. The Secretarial Audit Report is neither an assurance as to the future viability of the Company nor of the efficacy or effectiveness with which the management has conducted the affairs of the Company.

Haresh Sanghvi
Practicing Company Secretary
FCS 2259/COP No. 3675
UDIN: F002259B000706919

Date: 10th August, 2020
Place: Mumbai

Annexure-III

Disclosure pursuant to Section 197(12) of the Companies Act, 2013 read with rule 5 of the Companies (Appointment and Remuneration of Managerial Personnel) Rules, 2014.

i) The percentage increase in remuneration of each director, Chief Financial Officer, Chief Executive Officer, Company Secretary or Manager, if any, in the financial year 2019-20, ratio of the remuneration of each director to the median remuneration of the employees of the company for the financial year.

Sr. No.	Name of the Director/KMP and Designation	% increase in Remuneration in the financial year 2019-20	Ratio of the remuneration of each director to the median remuneration of the employees.
1	Mr. Sajankumar R. Bajaj (Chairman & Managing Director)	Nil	21.67: 1
2	Mr. Anil C. Jain (Managing Director)	27.78	20.77:1
3	Mr. Dhananjay S. Hatle Whole Time Director (WTD)	9.56	6.13:1
4	Mr. Namrata S. Bajaj Whole Time Director (WTD)	Nil	4.58:1
5	Mr. Rupesh H. Nikam Whole Time Director (WTD) & Chief Financial Officer (CFO)	8.20	7.29:1
7.	Mr. Aakashkumar Keshari (Company Secretary & Compliance Officer)	14.70	03.30:1

ii) The percentage increase in the median remuneration of employees in the financial year;

The % increase in median remuneration of employee is 9.85%.

iii) The number of permanent employees on the rolls of company

There are 715 employee on pay rolls of the Company as on 31st March, 2020. The detailed break-up of our employees is as under:

PARTICULARS	Total Numbers of Employees including worker
Head Office, Mumbai	67
Tarapur Unit	114
Savli Unit	407
Manjusar Unit	93
Panoli Unit	34
TOTAL	**715**

iv) Average percentile increase already made in the salaries of employees other than the managerial personnel in the last financial year and its comparison with the percentile increase in the managerial remuneration and justification thereof and point out if there are any exceptional circumstances for increase in the managerial remuneration.

Average percentile increase in the salaries of employees other than the managerial personnel is 14.52% during the year under review.

v) Affirmation that the remuneration is as per the remuneration policy of the company

Remuneration paid during the year ended 31st March, 2020 is as per the remuneration policy of the Company.

Annexure-IV

Annual Report on Corporate Social Responsibility (CSR) Activities

1. **A brief outline of the Company's CSR Policy, including overview of the projects or programs proposed to be undertaken and a reference to the web-link to the CSR Policy and projects or programmers':**

   The Company has framed a CSR Policy in compliance with the provisions of the Companies Act, 2013.

   CSR Policy is aimed at demonstrating care for the community through its focus on education & skill development, health & wellness and environment sustainability including biodiversity, energy & water conservation. Also embedded in this objective is support to the marginalized cross section of the society by providing opportunity to improve their quality of life.

   The projects undertaken by the Company are within the broad framework of schedule VII of the Companies Act, 2013.

2. **The Composition of the CSR Committee:**

   Mr. Sajankumar R. Bajaj – Chairman

   Mr. Ram B. Banarse – Member

   Mr. Rupesh H. Nikam – Member

   The Terms of Reference of the Committee are as follows:-

   a) To frame the CSR Policy and its review from time- to-time.

   b) To ensure effective implementation and monitoring of the CSR activities as per the approved policy, plans and budget.

   c) To ensure compliance with the laws, rules & regulations governing the CSR and to periodically report to the Board of Directors.

3. **Average net Profits for last three years:** ₹ 20,18,14,028/-

4. **Prescribed CSR Expenditure (two per cent. of the amount as in item 3 above):** ₹ 40,36,280/-

5. **Details of CSR spent during the financial year:**

   a) **Total amount spent for the financial year:** ₹ 49,05,000/-

   b) **Amount unspent, if any:** NIL

   c) **Manner in which the amount spent during the year:**

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sr. No.	**CSR project or activity identified**	**Sector in which project is covered**	**Projects or programs (1) Local area (2) Specify the State and district where projects or programs was undertaken**	**Amount outlay (budget) project or program wise**	**Amount spent on the projects or programs. Sub-heads (1) Direct expenditure (2) Overheads**	**Cumulative expenditure upto the date of reporting**	**Amount spent direct or through agency**
1.	Donation to Shree Sadguru Swani Akhandand Trust -Opening a hostel for adivasi women	Promoting education, including special education And environment	Sad Guru Dham, Tyiyodas Jyotiling Tirth, Taluka-Dharampur, Valsad (Gujrat)	Year wise- ₹ 1,20,00,000 Total Budget- ₹ 5,00,00,000	₹ 21,54,000/-	₹ 3,91,24,000/-	Directly
2.	Donation to Dhandhan Welfare Society for eradicating poverty and malnutrition's	Eradicating poverty and malnutrition	Village Dhandhan, Dist. Sikar, Rajasthan	Year wise- ₹ 75,00,000 Total Budget- ₹ 5,00,00,000	₹ 27,51,000/-	₹ 1,41,66,000/-	Directly

6. **Reasons for not spending the 2% of average net profit of last three financial years.** Not applicable

7. **Responsibility statement of the CSR Committee:**
   The implementation and monitoring of CSR Policy is in compliance with CSR objectives and Policy of the Company.

ANNEXURE- A

REMUNERATION POLICY
OF
BAJAJ HEALTHCARE LIMITED

For the Members of Board and Executive Management

1. Preamble:

1.1 The remuneration policy provides a framework for remuneration paid to the members of the Board of Directors ("Board"), Key Managerial Personnel ("KMP") and the Senior Management Personnel ("SMP") of the Company (collectively referred to as "Executives"). The expression "senior management" means personnel of the company who are members of its core management team excluding Board of Directors comprising all members of management one level below the executive directors, including the functional heads.

1.2 The policy would be reviewed every year by the Nomination and Remuneration Committee of the Board of Directors.

2. Aims & Objectives

2.1 The aims and objectives of this remuneration policy may be summarized as follows:

2.1.1 The remuneration policy aims to enable the company to attract, retain and motivate highly qualified members for the Board and Executive level.

2.1.2 The remuneration policy seeks to enable the company to provide a well-balanced and performance-related compensation package, taking into account shareholder interests, industry standards and relevant Indian corporate regulations.

2.1.3 The remuneration policy will ensure that the interests of Board members & Executives are aligned with the business strategy and risk tolerance, objectives, values and long-term interests of the company and will be consistent with the "pay-for-performance" principle.

2.1.4 The remuneration policy will ensure that remuneration to Directors and Executives involves a balance between fixed and incentive pay reflecting short and long-term performance objectives appropriate to the working of the company and its goals.

3. Principles of remuneration

3.1 **Support for Strategic Objectives:** Remuneration and reward frameworks and decisions shall be developed in a manner that is consistent with, supports and reinforces the achievement of the Company's vision and strategy.

3.2 **Transparency:** The process of remuneration management shall be transparent, conducted in good faith and in accordance with appropriate levels of confidentiality.

3.3 **Internal equity:** The Company shall remunerate the board members and the Executives in terms of their roles within the organization. Positions shall be formally evaluated to determine their relative weight in relation to other positions within the Company.

3.4 **External equity:** The Company strives to pay an equitable remuneration, capable of attracting and retaining high quality personnel. Therefore the Company will remain logically mindful of the ongoing need to attract and retain high quality people and the influence of external remuneration pressures.

3.5 **Flexibility:** Remuneration and reward offerings shall be sufficiently flexible to meet both the needs of individuals and those of the Company whilst complying with relevant tax and other legislation.

3.6 **Performance-Driven Remuneration**: The Company shall entrench a culture of performance driven remuneration through the implementation of the Performance Incentive System.

3.7 **Affordability and Sustainability:** The Company shall ensure that remuneration is affordable on a sustainable basis.

4 Nomination and Remuneration Committee

4.1 Members of the Committee shall be appointed by the Board and shall comprise of three or more non-executive directors out of which not less than one-half shall be independent directors.

4.2 The Committee shall be responsible for

4.2.1 Formulating framework and/or policy for remuneration, terms of employment including service contracts, policy for and scope of pension arrangements, etc for Executives and reviewing it on a periodic basis;

4.2.2 Formulate the criteria for determining qualifications, positive attributes and independence of a director and recommend to the Board a policy, relating to the remuneration for the Director.

4.2.3 Identifying persons who are qualified to become directors and who may be appointed as Executives in accordance with the criteria laid down in this policy, recommend to the Board their appointment and removal and carry out their evaluation.

4.2.4 Formulating terms for cessation of employment and ensure that any payments made are fair to the individual and the company, that failure is not rewarded and that the duty to mitigate loss is fully recognised;

4.3 The Committee shall:

4.3.1 review the ongoing appropriateness and relevance of the remuneration policy;

4.3.2 ensure that all provisions regarding disclosure of remuneration, including pensions, are fulfilled;

4.3.3 obtain reliable, up-to-date information about remuneration in other companies;

4.3.4 ensure that no director or Executive is involved in any decisions as to their own remuneration.

4.4 Without prejudice to the generality of the terms of reference to the Nomination and Remuneration Committee set out above, the Committee shall:

4.4.1 operate the Company's share option schemes (if any) or other incentives schemes (if any) as they apply to. It shall recommend to the Board the total aggregate amount of any grants to employees (with the specific grants to individuals to be at the discretion of the Board) and make amendments to the terms of such schemes (subject to the provisions of the schemes relating to amendment);

4.4.2 liaise with the trustee / custodian of any employee share scheme which is created by the Company for the benefit of employees or Directors and Director should possess the highest personal and professional ethics, integrity and

4.4.3 review the terms of executive Directors' service contracts from time to time.

5 Procedure for selection and appointment of the Board Members

5.1 Board membership criteria: The Committee, along with the Board, reviews on an annual basis, appropriate skills, characteristics and experience required of the Board as a whole and its individual members. The objective is to have a Board with diverse background and experience in business, government, academics, technology and in areas that are relevant for the Company's global operations. In evaluating the suitability of individual Board members, the Committee takes into account many factors, including general understanding of the Company's business dynamics, global business and social perspective, educational and professional background and personal achievements. In addition, Directors must be willing to devote sufficient time and energy in carrying out their duties and responsibilities effectively. They must have the aptitude to critically evaluate management's working as part of a team in an environment of collegiality and trust. The Committee evaluates each individual with the objective of having a group that best enables the success of the Company's business.

5.2 Selection of Board Members/ extending invitation to a potential director to join the Board.

6. Procedure for selection and appointment of Executives other than Board Members

6.1 The Committee shall actively liaise with the relevant departments of the Company to study the requirement for management personnel, and produce a written document thereon;

6.2 The Committee may conduct a wide-ranging search for candidates for the positions of Employees within the Company, within enterprises controlled by the Company or within enterprises in which the Company holds equity, if any, and on the human resources market;

6.3 The professional, academic qualifications, professional titles, detailed work experience and all concurrently held positions of the initial candidates shall be compiled as a written document;

6.4 A meeting of the Committee shall be convened, and the qualifications of the initial candidates shall be examined on the basis of the conditions for appointment of the Employees;

6.5 Before the selection of Employee, the recommendations of and relevant information on the relevant candidate(s) shall be submitted to the Board of Directors;

6.6 The Committee shall carry out other follow-up tasks based on the decisions of and feedback from the Board of Directors. One of the roles of the Committee is to periodically identify competency gaps in the Board, evaluate potential candidates as per the criteria laid above, ascertain their availability and make suitable recommendations to the Board. The objective is to ensure that the Company's Board is appropriate at all points of time to be able to take decisions commensurate with the size and scale of operations of the Company. The Committee also identifies suitable candidates in the event of a vacancy being created on the Board on account of retirement, resignation or demise of an existing Board member. Based on the recommendations of the Committee, the Board evaluates the candidate(s) and decides on the selection of the appropriate member. The Board then makes an invitation (verbal / written) to the new member to join the Board as a Director. On acceptance of the same, the new Director is appointed by the Board.

7 Compensation Structure:

7.1 Remuneration to Non-Executive Directors:

The Non-executive Directors of the company are paid remuneration by way of sitting fees only for attending the meetings of the Board of Directors and its Committees. The sitting fees paid to the Non-executive Directors for attending meetings of Board of Directors and Audit Committee of Board of Directors will be as per industrial norms and mutually agreed from time to time. Beside the sitting fees they are also entitled to reimbursement of expenses. The Non-executive Directors of the Company are not paid any other remuneration or commission. The sitting fees of the Non-executive Directors for attending meetings of Board of Directors and the Committees of Board of Directors may be modified or implemented from time to time only with the approval of the Board in due compliance of the provisions of Companies Act, 2013.

7.2 Remuneration to Executive Directors, Key Managerial Personnel(s) (KMPs) & Senior Management Personnel (s) (SMPs):

The Company has a credible and transparent framework in determining and accounting for the remuneration of the Managing Director / Whole Time Directors (MD/WTDs), Key Managerial Personnel(s) (KMPs) and Senior Management Personnel(s) (SMPs). Their remuneration shall be governed by the external competitive environment, track record, potential, individual performance and performance of the company as well as industry standards. The remuneration determined for MD/WTDs, KMPs and SMPs are subjected to the approval of the Board of Directors in due compliance of the provisions of Companies Act, 2013. The remuneration for the KMP and the SMP at the time of the appointment has to be approved by the Board but any subsequent increments shall be approved by the Managing Director of the Company as per the HR policy of the Company and ratified by the Board. As a policy, the Executive Directors are neither paid sitting fee nor any commission.

8 Role of Independent Directors:

8.1 The Committee shall, in consultation with the Independent Directors of the Company, prepare and submit this policy to the Board for its approval

8.2 The Independent Directors shall have power and authority to determine appropriate levels of remuneration of executive directors and Employees and have a prime role in appointing and where necessary recommend removal of executive directors and Employees.

8.3 The Independent Directors shall submit its recommendations / proposals / decisions to the Committee which the Committee shall consult and take to the Board of Directors.

9 Approval and publication:

9.1 This remuneration policy as framed by the Committee shall be recommended to the Board of Directors for its approval.

9.2 This policy shall be hosted on the Company's website.

9.3 The policy shall form part of Director's report to be issued by the Board of Directors in terms of Companies Act, 2013.

10 Supplementary provisions:

10.1 This Policy shall formally be implemented from the date on which they are adopted pursuant to a resolution of the Board of Directors.

10.2 Any matters not provided for in this Policy shall be handled in accordance with relevant State laws and regulations and the Company's Articles of Association. If this Policy conflict with any laws or regulations subsequently promulgated by the state or with the Company's Articles of Association as amended pursuant to lawful procedure, the relevant state laws and regulations and the Company's Articles of Association shall prevail, and this Policy shall be amended in a timely manner and submitted to the Board of Directors for review and adoption.

10.3 The right to interpret this Policy vests in the Board of Directors of the Company.

ANNEXURE-B

Business Responsibility Report

The Company believes that contributing back to the society is not only a RESPONSIBILITY but a COMMITMENT. The little value addition to the betterment of society is a part of the Company's mission, in line with its commitment to human health. Pursuant to regulation 34(2) (f) of SEBI (Listing obligation and Disclosure Requirements) Regulation, 2015, the Company has prepared Business Responsibility Report as under:

Section A: General Information about the Company

1.	Corporate Identity Number (CIN) of the Company	:	L99999MH1993PLC072892
2.	Name of the Company	:	Bajaj Healthcare Limited
3.	Registered address	:	602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39 A/1, Rd No.23, Wagle Ind. Estate Thane West Thane MH 400604.
4.	Website	:	www.bajajhealth.com
5.	E-mail id	:	investors@bajajhealth.com
6.	Financial Year reported	:	2019-20
7.	Sector(s) that the Company is engaged in (industrial activity code-wise)	:	Industrial Activity Code - 220 Manufacturing of Pharmaceuticals
8.	List three key products / services that the Company manufactures / provides (as in balance sheet)	:	Ascorbic Acid, CH Base and Its Derivatives, Citicoline Sodium
9.	Total number of locations where business activity is undertaken by the Company		
	(a) Number of International Locations (Provide details of major 5)	:	Nil
	(b) Number of National Locations	:	In Maharashtra- 2 Locations & In Gujarat-3 Location
10.	Markets served by the Company Local / State / National / International		In addition to serving the Indian Market, the Company export to around 51 countries worldwide

Section B: Financial Details of the Company

1.	Paid up Capital (₹)	:	13,79,92,000
2.	Total Turnover (₹)	:	4,13,18,74,499
3.	Total profit after after taxes (₹)	:	22,49,97,780
4.	Total spending on Corporate Social Responsibility (CSR) as a percentage of profit after tax	:	2.18%
5.	List of activities in which expenditure in 4 above has been Incurred	:	(a) Promoting education including special education and environment. (b) Eradicating poverty and malnutrition. (c) Promoting healthcare including preventive Healthcare

Section C: Other Details

1.	Does the Company have any Subsidiary Company/ Companies?	:	NO
2.	Do the Subsidiary Company/Companies participate in the BR Initiatives of the parent company? If yes, then indicate the number of such subsidiary company(s)	:	NO
3.	Do any other entity/entities (e.g. suppliers, distributors etc.) that the Company does business with, participate in the BR initiatives of the Company?	:	NO

Section D: BR Information

1. **Details of Director/Directors responsible for BR:**

(a) Details of the Director/Director responsible for implementation of the BR policy/policies:

1.	DIN Number	:	00225950
2.	Name	:	Mr. Sajankumar R. Bajaj
3.	Designation	:	Chairman & Managing Director

(b) Details of the BR head:

SR. NO.	PARTICULARS	DETAILS
1.	DIN Number	00225950
2.	Name	Mr. Sajankumar R. Bajaj
3.	Designation	Chairman & Managing Director
4.	Telephone No.	022-6617 7400
5.	E-mail ID	bajajhealth@bajajhealth.com

2. **Principle-wise (as per NVGs) BR Policy/policies:**

Sr. No.	Questions	P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9
1	Do you have a policy / policies for....	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Has the policy being formulated in consultation with the relevant stakeholders?	All the policies have been formulated in consultation with the Management of the Company and is approved by the Board								
3	Does the policy conform to any national / international standards?	The policies are broadly based on the National Voluntary Guidelines on Social, Environment and economical responsibility of business issued by the Ministry of Corporate Affairs, Government of India								
4	Has the policy being approved by the Board?	All the policies have been approved by the Board and have been signed by the Managing Director								
5	Does the company have a specified committee of the Board / Director / Official to oversee the implementation of the policy?	The Board has appointed Mr. Rupesh H. Nikam, Whole-time Director – Bajaj Healthcare Limited, to oversee the policy implementation								
6	Indicate the link for the policy to be viewed online?	Copies will be made available on receipt of written request from shareholders.								
7	Has the policy been formally communicated to all relevant internal and external stakeholders?	The policies have been formally communicated to internal stakeholders. The external stakeholders will be communicated in due course.								
8	Does the company have in-house structure to implement the policy / policies.	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Does the Company have a grievance redressal mechanism related to the policy / policies to address stakeholders' grievances related to the policy / policies?	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Has the company carried out independent audit / evaluation of the working of this policy by an internal or external agency?	It will be done in due course.								

3. **Governance related to BR**

(a) Indicate the frequency with which the Board of Directors, Committee of the Board or CEO to assess the BR performance of the Company.

- Annually

(b) Does the Company publish a BR or a Sustainability Report? What is the hyperlink for viewing this report? How frequently it is published?

- The Company does not publish BR / Sustainability Report. However, details are provided in the Management Discussion and Analysis Report forming part of Annual Report every year.

Section E: Principle-Wise Performance

Principal 1:

1. **Does the policy relating to ethics, bribery and corruption cover only the company? Yes / No. Does it extend to the Group / Joint Ventures / Suppliers / Contractors / NGOs / Others?**

A successful business is built on the foundation of good principles. The philosophy of the Bajaj Healthcare Limited on corporate governance has been adhere to the highest standard of ethical corporate behaviour and fairness to the stakeholders. The Company have institutionalised a healthy governance structure.

Codes of Conduct have been adopted for Directors, Independent Directors and Senior Management Personnel as well as for employee of the Company. As a testament of its robust corporate governance practices and ethical conduct of business, the Company instituted an initiative that encompasses three important policies viz. Code of Conduct, Whistle blower policy and Prevention of Workplace harassment including sexual harassment at workplace.

The Company's vision and values form the base of its policies and practices. Each role at every level of the employees, from the top to the bottom, is transparently defined and held accountable for its responsibilities. While the Company strive to add value to every stakeholder, including the planet and the people, there is no compromise on ethics and integrity.

The key principles of its corporate governance philosophy are:

- High levels of transparency
- Delegation of responsibility
- Consistent value systems
- Accountability.

2. **How many stakeholder complaints have been received in the past financial year and what percentage was satisfactorily resolved by the management?**

   The Company did not receive any complaint from stakeholders.

Principal 2:

1. **List up to 3 of your products or services whose design has incorporated social or environmental concerns, risks and / or opportunities.**

   (a) Ascorbic acid & amp; its salts a Vitamins

   (b) Chlorhexidine Gluconate a Disinfectant and Antiseptic

   (c) Vildagliptin an Anti-Diabetics drug

2. **For each such product, provide the following details in respect of resource use (energy, water, raw material etc.) per unit of product (optional):**

   (a) Reduction during sourcing / production / distribution achieved since the previous year throughout the value chain?

   The Company manufactures as well as distributes a varied range of generics and branded Formulations and active pharmaceutical ingredients at its state of art manufacturing facilities. Since consumption per unit depends on the product mix, there are no specific standards to ascertain reduction achieved at product level.

   (b) Reduction during usage by consumers (energy, water) has been achieved since the previous year?

   The Company's products do not have any broad-based impact on energy and water consumption by consumers.

3. **Does the company have procedures in place for sustainable sourcing (including transportation)?**

   (a) If yes, what percentage of your inputs was sourced sustainably? Also, provide details thereof, in about 50 words or so.

   Yes, the company has standard operating procedures in place for approving vendor and to evaluate sustainability of suppliers which are reviewed periodically. Material are procured from approved vendors both local as also international. The company quality assurance team conducts periodic audits of vendors, especially those who supply key materials.

   The Company has long standing business relations with regular vendors and enters annual freight contracts with leading transporters for movements of materials.

   The raw material and packaging purchased is tightly specified due to critical nature of our products and no compromise is permissible on specifications.

4. **Has the company taken any steps to procure goods and services from local & amp; small producers, including communities surrounding their place of work?**

   (a) If yes, what steps have been taken to improve their capacity and capability of local and small vendors?

   Yes, the company procures goods and avails services from local and small vendors, particularly those located around its manufacturing locations. As a result of procurements of goods from local vendors, the company saves on transportation as also inventory carrying cost.

   The Company sources packing materials and has awarded contracts like security, canteen, employee transport, housekeeping and other repairs and maintenance through local sources.

   As the Company deals in hazardous and non-hazardous substances, the purchases are mostly from organized sector. However, it does buy some engineering items from small producers and help them improve their product quality by improving their engineering skills.

   The Company also hire contractors from the areas neighbouring itsplant and improve their capability by imparting training in various fields like safety, hazard handling, compliances etc.

5. **Does the company have a mechanism to recycle products and waste? If yes what is the percentage of recycling of products and waste (separately as <5%, 5-10%, >10%). Also, provide details thereof, in about 50 words or so.**

   A mechanism for recycling and reuse of products is in place in the Company and it actively and continually promotes the concept of recovery, reuse and recycling.

   About 65% of the waste water generated in plants, is recovered, recycled and reused thereby reducing usage of fresh water. Besides, steam condensate is recovered and reused which has resulted in reduction in use of fresh water.

Treated waste water is also used for gardening inside the Company premises in place of fresh water.

Principal 3:

1. **Please indicate the Total number of employees.**
   Total number of employees on pay roll of Company are 715 and on temporary / contractual / casual basis are 696.
2. **Please indicate the Total number of employees hired on temporary / contractual / casual basis.**
   Total number of employees on temporary/contractual/ casual basis 696.
3. **Please indicate the Number of permanent women employees.**
   Total number of women employees are 65.
4. **Please indicate the Number of permanent employees with disabilities:** NIL
5. **Do you have an employee association that is recognized by management?** NO
6. **What percentage of your permanent employees is members of this recognized employee association?** NIL
7. **Please indicate the Number of complaints relating to child labour, forced labour, involuntary labour, sexual harassment in the last financial year and pending, as on the end of the financial year.**

No.	Category	No of complaints filed during the year	No of complaints pending as on end of the financial year
1	Child labour / forced labour / involuntary labour	NIL	NIL
2	Sexual harassment	NIL	NIL
3	Discriminatory employment	NIL	NIL

8. **What percentage of your under mentioned employees were given safety & skill up-gradation training in the last year?**
   (a) Permanent Employees – 100%
   (b) Permanent Women Employees – 100%
   (c) Casual/Temporary/Contractual Employees – 100%
   (d) Employees with Disabilities – N.A.

Principle 4

1. **Has the company mapped its internal and external stakeholders? Yes / No**
   Yes, the Company has mapped its stakeholders.
2. **Out of the above, has the company identified the disadvantaged, vulnerable & marginalized stakeholders.**
   The Company has identified the disadvantaged, vulnerable and marginalized stakeholders
3. **Are there any special initiatives taken by the company to engage with the disadvantaged, vulnerable and marginalized stakeholders.**
   The Company has distributed Mask, Sanitizer and food for poor during COVID-19 pandemic at Tarapaur, Maharashtra for around 1,200 person on daily basis. And Company has also donated isolation ward at Rajasthan during COVID-19 Pandemic.

Principle 5

1. **Does the policy of the company on human rights cover only the company or extend to the Group / Joint Ventures / Suppliers / Contractors / NGOs / Others?**
   In line with the Company's commitment to respect and protect human rights, the Company neither hires child labour, forced labour or involuntary labour nor discriminates between its employees. The Company's code of conduct and the human resource practices cover most of these aspects.
2. **How many stakeholder complaints have been received in the past financial year and what percent was satisfactorily resolved by the management?**
   The Company did not receive any complaint during the financial year in respect of violation of human rights.

Principle 6

1. **Does the policy related to Principle 6 cover only the company or extends to the Group / Joint Ventures / Suppliers / Contractors / NGOs / others.**
   The policy covers the Company and all contractors working within the Company premises.
2. **Does the company have strategies / initiatives to address global environmental issues such as climate change, global warming, etc? Y / N. If yes, please give hyperlink for webpage etc.**
   The Company always accords the topmost priority to conservation and optimum utilization of natural resources. As humans keep producing more for convenience and comfort, they are ironically progressing towards a time where clean air, fresh water, rich biodiversity and required natural resources are getting scarce.

   The Companyis aware of the emerging situation and investing in measures that mitigate this situation. Be it conservation measures or reducing its dependence on limited resources, it is not only reducing the burden on the environment, but also on its operational costs. The Company is in process of framing The Environment, Health, Safety and Sustainability policy

   Some of the green steps which are a must-do:

   - Ensure statutory compliance
   - Optimise natural resources
   - Effect continuous improvement in environment management
   - Innovate greener technologies and processes
   - Spread green awareness across internal and external stakeholders
3. **Does the company identify and assess potential environmental risks? Y / N**
   Yes, internal and external mechanisms are in place, whereby

all new facilities and products are risk assessed including environmental impact assessment and development of environmental management plans. The said environmental management plans are reviewed during internal meetings.

4. **Does the company have any project related to Clean Development Mechanism? If so, provide details thereof, in about 50 words or so. Also, if Yes, whether any environmental compliance report is filed?**
No, the company does not have any project related to Clean Development Mechanism.

5. **Has the company undertaken any other initiatives on – clean technology, energy efficiency, renewable energy, etc. Y / N. If yes, please give hyperlink for web page etc.**
Yes, the company has installed solar panels at one of its Manufacturing Plants at Baroda.

6. **Are the Emissions / Waste generated by the company within the permissible limits given by CPCB/SPCB for the financial year being reported?**
Yes, Emissions / Waste generated by the company are within the permissible limits.

7. **Number of show cause/ legal notices received from CPCB/ SPCB which are pending (i.e. not resolved to satisfaction) as on end of Financial Year.**
There are no unresolved show cause / legal notice pending from CPCB / SPCB.

Principle 7:

1. **Is your company a member of any trade and chamber or association? If Yes, Name only those major ones that your business deals with:**
The Company is a member of various trade bodies, task forces and forums, chambers and associations including the "Federation of Indian Chambers of Commerce and Industry" (FICCI)

2. **Have you advocated / lobbied through above associations for the advancement or improvement of public good?**
The Company has advocated at various forums about measures to be taken to address basic issues pertaining to improvement of public health and promote balanced as well as sustainable economic development. The Company supports the government in its efforts to harness the country's innovation capabilities and suggest measures to offer facilities and incentives viz. encourage investments in R&D.

Principle 8

1. **Does the company have specified programmes / initiatives / projects in pursuit of the policy related to Principle 8? If yes details thereof.**
The Company has adopted CSR Policy for specified project in:
   (a) Promoting education including special education and environment.
   (b) Eradicating poverty and malnutrition.
   (c) Promoting healthcare including preventive Healthcare

2. **Are the programmes / projects undertaken through in-house team / own foundation / external NGO / government structures / any other organization?**
Programmes are undertaken through in-house team, own foundation, any other foundation and any other organisation

3. **Have you done any impact assessment of your initiative?**
Company regularly conduct impact assessment by internal sources of programmes undertaken under Corporate Social Responsibility Policy.

4. **What is your company's direct contribution to community development projects- Amount in INR and the details of the projects undertaken?**
During the year, an amount of ₹ 49.05 lakhs was spent on various CSR Activity for Promoting education including special education and environment, Eradicating poverty and malnutrition and Promoting healthcare including preventive Healthcare.

5. **Have you taken steps to ensure that this community development initiative is successfully adopted by the community? Please explain in 50 words, or so.**
Most of the CSR initiatives undertaken by the Company are not imposed from the top but are designed with people's participation right from the village level. Consequently, only those activities, which are beneficial to the community are taken up.

Principle 9

1. **What percentage of customer complaints/consumer cases are pending as on the end of financial year.**
There are no customer complaints / Consumer cases are pending.

2. **Does the company display product information on the product label, over and above what is mandated as per local laws?**
Yes, the Company display product information on the product label, over and above what is mandated as per local laws

3. **Is there any case filed by any stakeholder against the company regarding unfair trade practices, irresponsible advertising and / or anti-competitive behaviour during the last five years and pending as on end of financial year.**
No, there are no case filed by any stakeholder against the company regarding unfair trade practices, irresponsible advertising and / or anti-competitive behaviour during the last five years and pending as on end of financial year.

4. **Did your company carry out any consumer survey / consumer satisfaction trends?**
The Company regularly carries out consumer surveys through feedback forms.

Report on Corporate Governance

1. Company Philosophy on Code of Corporate Governance:

The Companies Act, 2013 ('the Act') and the Securities & Exchange Board of India (Listing Obligations & Disclosure Requirements) Regulations, 2015 ('Listing Regulations') have strengthened the framework of Corporate Governance for India Inc.

The Company's Corporate Governance is a set of systems and practices to ensure that the affairs of the Company are being managed in a way which ensures accountability, transparency and fairness in all its transactions in the widest sense and meet its stakeholders' aspirations and societal expectations. The Company is committed to achieve highest standards of corporate governance. The Company has a well-defined structure for ensuring that business conduct is fair and ethical and has put in place mechanism for reporting illegal and unethical behavior.

2. Board of Directors:

2.1 Composition and categories of Directors:

The Company has broad based Board of Directors, constituted in compliance with the Act and Listing Regulations and in accordance with highest standards of Corporate Governance in its management, which ensures judicious mix of Directors that includes the Executive, Non-Executive and Independent Directors.

Details of the Composition of the Board of Directors as on the date of this report is stated below:

Sr. No	Name of Directors	Designation	Executive / Non Executive/Promoter	Independent / Non Independent
1	Mr. Sajankumar R. Bajaj	Chairman & Managing Director	Executive and Promoter	Non Independent
2	Ms. Namrata S. Bajaj	Whole Time Director	Executive	Non Independent
3	Mr. Anil C. Jain	Jt. Managing Director	Executive	Non Independent
4	Mr. Dhananjay S. Hatle	Whole Time Director	Executive	Non Independent
5	Mr. Rupesh H. Nikam	Whole Time Director	Executive	Non Independent
6	Mr. Pakshal A. Jain[1]	Whole Time Director	Executive	Non Independent
7	Mr. Hemant R. Karnik	Non-Executive Independent Director	Non Executive	Independent
8	Mr. Ram B. Banarse	Non-Executive Independent Director	Non Executive	Independent
9	Mr. Avinash Dalal[2]	Non-Executive Independent Director	Non Executive	Independent
10	Mr. Loukik D. Tipnis[3]	Non-Executive Independent Director	Non Executive	Independent
11	Mr. Luke B. Fernandez[4]	Additional Non-Executive Independent Director	Non Executive	Independent
12	Ms. Kejal N. Shah[5]	Additional Non-Executive Independent Director	Non Executive	Independent

[1] Mr. Pakshal A. Jain has been appointed as director w.e.f. 30th June, 2020.

[2] Mr. Avinash Dalal has been appointed as director w.e.f. 22nd April, 2019.

[3] Mr. Loukik D. Tipnis has been appointed as director w.e.f. 22nd April, 2019.

[4] Mr. Luke B. Fernandez has been appointed as director w.e.f. 30th June, 2020.

[5] Ms. Kejal N. Shah has been appointed as director w.e.f. 30th June, 2020.

Resignation of Independent Director

Mr. Vidyut Shah has resigned from the Directorship of the Company w.e.f. 12th June, 2020 due to his other professional commitments and has confirmed that there was no material reason other than mentioned above for his resignation.

The Board of Directors confirms that, in the opinion of the Board, newly appointed Independent Director as well as existing Independent Directors fulfill the conditions specified in SEBI (Listing Obligations Disclosure Requirement) Regulations, 2015 and are independent of the management.

2.2 Board Meetings, Attendance and other details:

During the financial year under review, 6 (Six) Board Meetings were held at the registered office on 11th April, 2019; 22nd April, 2019; 30th May 2019; 14th August, 2019; 14th November, 2019 and 13th February, 2020. The maximum time gap between any two consecutive Board Meetings does not exceed 120 days.

In compliance with Section 165(1) of the Act, and Regulation 25(1) of Listing Regulations, none of the Director of the Company is a Director on the Board of more than 20 Companies (including10 Public Limited Companies) or acts as an Independent Director in more than 7 Listed Companies. Further, none of the Director is a member of more than 10 Committees or act as Chairman of more than 5 Committees across all Companies in which they are Directors.

The attendance at the Board meetings held during the Financial Year under review and at the last Annual General Meeting, number of directorship, Memberships / Chairmanships of the Committees of public companies and their shareholding in the Company are as follows: -

Name of Directors	DIN	No. of Board Meetings attended / held in F.Y. 2019-20	Attendance at the last A.G.M.	No. of Directorship in Listed Entity	Committee position**		No. of Equity Shares
					Chairman	Member	
Mr. Sajankumar R. Bajaj	00225950	5/6	Y	1	Nil	Nil	48,14,000
Ms. Namrata S. Bajaj	05327071	5/6	Y	1	Nil	Nil	8,08,000
Mr. Anil C. Jain	00226137	6/6	Y	1	Nil	1	7,18,000
Mr. Dhananjay S. Hatle	00226390	6/6	Y	1	Nil	Nil	12,000
Mr. Rupesh H. Nikam	07007815	6/6	Y	1	Nil	1	Nil
Mr. Pakshal A. Jain(1)	08776385	0/0	N	1	Nil	Nil	Nil
Mr. Vidyut Shah(6)	02578165	6/6	Y	2	2	Nil	Nil
Mr. Hemant R. Karnik	07377151	6/6	N	1	1	1	Nil
Mr. Ram B. Banarse	07405486	5/6	Y	1	Nil	1	Nil
Mr. Avinash Dalal(2)	03574325	3/4	N	1	Nil	Nil	Nil
Mr. Loukik D. Tipnis(3)	08188583	4/4	N	2	1	1	Nil
Mr. Luke B. Fernandez(4)	01110174	0/0	N	1	1	Nil	Nil
Ms. Kejal N. Shah(5)	08608399	0/0	N	2	Nil	Nil	Nil

(1) Mr. Pakshal A. Jain has been appointed as director w.e.f. 30th June, 2020.

(2) Mr. Avinash Dalal has been appointed as director w.e.f. 22nd April, 2019.

(3) Mr. Loukik D. Tipnis has been appointed as director w.e.f. 22nd April, 2019.

(4) Mr. Luke B. Fernandez has been appointed as director w.e.f. 30th June, 2020.

(5) Ms. Kejal N Shah has been appointed as director w.e.f. 30th June, 2020.

(6) Mr. Vidyut Shah has been resigned from the Directorship of the Company w.e.f. 12th June, 2020.

Notes:

1. Excludes directorships in, Private Limited Companies, Foreign Companies and Section 8 Companies.
2. In accordance with Regulation 26(1)(b) of SEBI (Listing Regulation), Membership/ Chairpersonship of only the Audit Committee and Stakeholders Relationship Committee in all Indian Public Limited Companies have been considered.
3. Mr. Sajankumar R. Bajaj and Ms. Namrata S. Bajaj are related to each other. Mr. Anil C. Jain & Mr. Pakshal A. Jain are related to each other. No other directors are related inter-se.
4. The Company has not issued any convertible instruments.

2.3 Names of the Indian listed entities where the Directors of the Company hold Directorship and the category of directorship as on 31st March, 2020:

Name of Director(s)	Other Indian Listed entities in which they hold Directorship	Category of Directorship
Mr. Loukik D. Tipnis	Sky Gold Limited	Non-Executive Independent Director
Ms. Kejal N. Shah	Sky Gold Limited	Non-Executive Independent Director

2.4. Meeting of Independent Directors and performance evaluation of Non-Independent Board

As stipulated by the Code of Independent Directors pursuant to Companies Act, 2013 and the SEBI (Listing Regulations), a separate meeting of the Independent Directors of the Company was held on 13th February, 2020 to review the performance of Non-independent Directors (including the Chairman) and the entire Board. The Independent Directors also reviewed the quality, content and timeliness of the flow of information between the Management and the Board and its Committees which is necessary to effectively and reasonably perform and discharge their duties.

2.4. Director's Familiarization programme:

The Company undertakes and makes necessary provisions for an appropriate induction programme for new Directors and ongoing training for existing Directors. The details of familiarization programme of the independent Directors are available on the website of the Company: www.bajajhealth.com. The new directors are introduced to the Company's culture, through appropriate training programmes. Such kind of training programmes helps to develop relationship of the Directors with the Company and familiarise them with the Company processes. The management provides such information and training either at the meeting of Board of Directors or otherwise.

The induction process is designed to:-

- build an understanding of the Company processes and;
- fully equip the Directors to perform their role on the Board effectively;

Upon appointment, Directors receive a Letter of Appointment setting out in detail, the terms of appointment, duties, responsibilities and expected time commitments.

2.5 The following is the list of core skills/expertise/competencies identified by the Board of Directors, based on recommendations of the Nomination & Remuneration Committee, as required in the context of the Company's aforesaid business(es) for it to function effectively along with the names of Directors who have such skills / expertise / competence:

Sr. No.	Name of Director(s)	Sales & Marketing: Experience in sales and marketing management based on understanding of the consumer & consumer goods industry	International Business experience: Experience in leading businesses in different geographies / markets around the world	General management / Governance: Strategic thinking, decision making and protect interest of all stakeholders	Financial skills: Understanding the financial statements, financial controls, risk management, mergers and acquisition, etc	Technical, professional skills and knowledge including legal and regulatory aspects
1.	Mr. Sajankumar R. Bajaj	Y	Y	Y	Y	Y
2.	Mr. Anil C. Jain	Y	Y	Y	Y	Y
3	Mr. Dhananjay S. Hatle	Y	Y	Y	Y	Y
4	Ms. Namrata S. Bajaj	Y	Y	Y	Y	Y
5	Mr. Rupesh H. Nikam	Y	Y	Y	Y	Y
6	Mr. Hemant R. Karnik	N	Y	Y	Y	Y
7	Mr. Ram B. Banarse	Y	Y	Y	Y	Y
8	Mr. Avinash Dalal	Y	Y	Y	Y	Y
9	Mr. Vidyut Shah#	Y	Y	Y	Y	Y
10	Mr. Loukik D. Tipnis	N	N	Y	Y	Y

Mr. Vidyut Shah has resigned w.e.f. 12th June, 2020.

3. Committees of the Board:

The Committees of the Board are constituted as per the Act and SEBI (Listing Regulation)

3.1 Audit Committee:

The Audit Committee of the Company is constituted in line with provisions of Regulation 18 of Listing Regulations read with Section 177 of the Act and rules framed thereunder. All the members possess sound knowledge on accounts, audit, finance, taxation, internal controls etc. The previous AGM of the Company was held on 30th September, 2019 and was attended by the Chairman of the Audit Committee. The Company Secretary of the Company acts as the Secretary to the Committee.

3.1.1 Brief Terms of Reference

The terms of reference of Audit Committee broadly includes-

a) To oversee the Company's financial reporting process and the disclosure of its financial information to ensure that the financial statement is correct, sufficient and credible.

b) Recommending the appointment and removal of external auditor, fixation of audit fee and also approval for payment for any other services.

c) Reviewing with management the annual financial statements before submission to the Board

d) Review of compliance with provision of SEBI Insider Trading Regulations, 2015.

e) Review Compliance with Stock Exchange and legal requirements concerning financial statements.

f) Approval of related party transactions i.e. transactions of the Company of material nature, with promoters or the management, their subsidiaries or relatives, etc. that may have potential conflict with the interests of Company at large.

g) Reviewing with the management, External and Internal auditors the adequacy of Internal Control System.

h) Reviewing the findings of any internal investigations in the matters where there is suspected fraud or irregularity or failure of internal control systems of a material nature and reporting the matter to the Board.

i) Discussion with external auditors before the audit commences nature and scope of audit as well as post-audit discussion to ascertain any area of concern.

j) Reviewing the Company's financial and risk management policies.

k) To look into the reasons for substantial defaults in the payment to the depositors, debentures holders, shareholders (in case of no nonpayment of declared dividends) and creditors.

l) To approve the appointment of the Internal auditor after assessing the qualifications, experience, background, etc. of the candidate.

3.1.2 Composition and Attendance at the Meeting

The Audit Committee met 5 (Five) times during the year on 22nd April, 2019; 30th May, 2019; 14th August, 2019; 14th November, 2019 and 13th February, 2020.

The details on composition, names of the members, chairperson, category of Directors and no. of the meetings attended by the members during the FY 2019-20 are as follows: -

Sr. No.	Names of Member	Category of Directors	Designation	No. of Meeting Attended
1	Mr. Luke B. Fernandez#	Independent Director	Chairman	0/0
2	Mr. Hemant R. Karnik	Independent Director	Member	5/5
3	Mr. Rupesh H. Nikam	Executive Director	Member	5/5

Mr. Vidyut Shah resigned as Audit Committee Chairman w.e.f. 12th June, 2020 and Mr. Luke Fernendez has been appointed as Chairman w.e.f. 30th June, 2020.

3.2 Nomination and Remuneration Committee:

The Nomination and Remuneration Committee of the Company is constituted in time with the provisions of Regulation 19 of Listing Regulations read with Section 178 of the Act. The previous AGM of the Company was held on 30th September, 2019 and was attended by the then Chairman of the Nomination and Remuneration Committee, Mr. Vidyut Shah. The Company Secretary of the Company acts as the Secretary to the Committee.

3.2.1 Brief Terms of reference

The terms of reference of Nomination and Remuneration Committee broadly includes:

A. To help in determining the appropriate size, diversity and composition of the Board;

B. To recommend to the Board appointment/reappointment and removal of Directors;

C. To frame criteria for determining qualifications, positive attributes and independence of Directors;

D. To create an evaluation framework for Independent Directors and the Board;

E. To delegate its powers to any member of the Committee or the Compliance Officer.

3.2.3 Composition and Attendance at the Meeting

The Nomination and remuneration Committee met once during the year on 22nd April, 2019.

The composition, names of the members, chairperson, category of Directors and no. of the meeting attended by the members is as follows: -

Sr. No.	Names of Member	Category of Directors	Designation	No. of Meeting Attended
1	Mr. Ram Banarase	Independent Director	Chairman	1/1
2	Mr. Hemant R. Karnik	Independent Director	Member	1/1
3	Mr. Loukik D. Tipnis#	Independent Director	Member	0/0

Mr. Vidyut Shah resigned as the Member of the Committee w.e.f. 12th June, 2020 and Mr. Loukik D. Tipnis has been appointed as the Member of the Committee w.e.f. 30th June, 2020.

3.2.4 Remuneration Policy

The Remuneration Policy formulated in accordance with the Companies Act, 2013 and SEBI Listing Regulations and as recommended by Nomination and Remuneration Committee has been accepted by the Board of Directors and the same has been annexed to the report of the Directors and is also available on the Company's website www.bajajhealth.com

3.2.5 Performance evaluation criteria for independent directors

Pursuant to the provisions of the Companies Act, 2013 and the Listing Regulations, the Committee has laid down the manner in which formal annual evaluation of the performance of the Directors including Independent Directors and its Committees has to be made. An indicative list of factors on which evaluation was carried out includes participation and contribution by a director, commitment, effective deployment of knowledge and expertise, integrity and maintenance of confidentiality and independence of behavior and judgment.

3.2.6 Details of Remuneration paid to the Directors

Details of Remuneration paid to the Directors for the year ended 31st March, 2020 are as follows:

(Amount in ₹)

Name	Relationship with the other Directors	Remuneration (₹)	Commission (₹)	Sitting Fees (₹)	Total (₹)
Mr. Sajankumar R. Bajaj	Immediate relative to Ms. Namrata S. Bajaj	48,00,000	Nil	Nil	48,00,000
Mr. Anil C. Jain	Immediate relative to Mr. Pakshal A. Jain	46,00,000	Nil	Nil	46,00,000
Mr. Dhananjay S. Hatle	None	13,58,535	Nil	Nil	13,58,535
Ms. Namrata S. Bajaj	Immediate relative to Mr. Sajankumar R. Bajaj	10,15,000	Nil	Nil	10,15,000
Mr. Rupesh H. Nikam	None	16,15,440	Nil	Nil	16,15,440
Mr. Vidyut Shah[6]	None	Nil	Nil	1,20,000	1,20,000
Mr. Hemant R. Karnik	None	Nil	Nil	1,20,000	1,20,000
Mr. Ram B. Banarse	None	Nil	Nil	60,000	60,000
Mr. Avinash Dalal[1]	None	Nil	Nil	35,000	35,000
Mr. Loukik D. Tipnis[2]	None	Nil	Nil	45,000	45,000
Mr. Pakshal A. Jain[3]	Immediate relative to Mr. Anil C. Jain	Nil	Nil	Nil	Nil
Ms. Kejal Majethia[4]	None	Nil	Nil	Nil	Nil
Mr. Luke B. Fernandez[5]	None	Nil	Nil	Nil	Nil

[1] Mr. Avinash Dalal has been appointed as director w.e.f. 22nd April, 2019.

[2] Mr. Loukik D. Tipnis has been appointed as director w.e.f. 22nd April, 2019.

[3] Mr. Pakshal A. Jain has been appointed as director w.e.f. 30th June, 2020.

[4] Ms. Kejal N. Shah has been appointed as director w.e.f. 30th June, 2020.

[5] Mr. Luke B. Fernandez has been appointed as director w.e.f. 30th June, 2020.

[6] Mr. Vidyut Shah resigned from the Directorship of the Company w.e.f. 12th June, 2020.

Notes:

a. Sitting fees include payment of fees for attending Board / Committee Meetings.

b. The remuneration payments in the Company are made with an aim of rewarding performance, based on review of achievements. The remuneration levels are in consonance with the existing industry practices.

c. No provision of performance-linked variable pay for the FY 2019-20 is available to Managing Director, the Executive Director and the Whole-time Director. There are no provisions for notice period and payment of severance fees.

d. Payments to Non-Executive Directors are decided, based on multiple criteria of seniority / experience, number of years on the Board, Board / Committee meetings attended, Director's position on the Company's Board / Committees, other relevant factors and performance of the Company. There are no pecuniary relationship or transactions between your Company and its Non-Executive / Independent Directors for the financial year under review.

e. The Company has not granted any stock option to any of its Directors.

3.3 Stakeholders' Relationship Committee:

The Stakeholders' Relationship Committee is constituted in line with the provisions of Regulations 20 of Listing Regulations read with Section 178 of the Act. The previous AGM of the Company was held on 30th September, 2019 and was attended by the Chairman of the Stakeholders' Relationship Committee. The Company Secretary of the Company acts as the Secretary to the Committee.

3.3.1 Brief Terms of reference

The terms of reference of Stakeholders' Relationship Committee broadly includes:

I. Redressing of shareholders and investor complaints such as non-receipt of declared dividend, annual report, transfer of Equity Shares and issue of duplicate / split / consolidated share certificates;

II. Monitoring transfers, transmissions, dematerialization, re-materialization, splitting and consolidation of Equity Shares and other securities issued by our Company, including review of cases for refusal of transfer/ transmission of shares and debentures;

III. Reference to statutory and regulatory authorities regarding investor grievances;

IV. To otherwise ensure proper and timely attendance and redressal of investor queries and grievances

The Company's Registrar & Share Transfer Agents, M/s Link Intime India Private Limited are fully equipped to carry out the transfers of shares and redress Investor complaints received directly or through SEBI, Stock Exchanges, Ministry of Corporate Affairs, Registrar of Companies, etc.

3.3.2 Composition of the Committee

During the year under review, the Committee met on 13th February, 2020. The composition, names of the members, chairperson, category of Directors, and no. of the meetings attended by the members during the FY 19-20 are as follows:

Sr. No.	Names of Member	Designation	Category	No. of Meeting Attended
1	Mr. Hemant. R. Karnik	Chairman	Non-Executive, Independent	1/1
2	Mr. Anil C. Jain	Member	Executive, Non-Independent	1/1
3	Mr. Ram B. Banarase	Member	Non-Executive, Independent	1/1

3.3.3 Details in respect of Compliance Officer:

Mr. Aakashkumar Kesari, Company Secretary, acts as the Compliance Officer of the Company.

3.3.4 Details of Investors Complaints received during F.Y. 2019-20 are as follows:

Sr. No.	Nature of Complaints	Whether Received		No. of Complaints Redressed	Pending Complaints
1.	Non-Receipt of Shares lodged for transfer/transmission	Nil	Nil	Nil	Nil
2.	Non- Receipt of Dividend	Nil	Nil	Nil	Nil
3.	Non- Receipt of Annual Report	Nil	Nil	Nil	Nil

3.4 Corporate Social Responsibility (CSR) Committee:

The Corporate Social Responsibility (CSR) Committee comprises of Mr. Sajankumar R. Bajaj , as Chairman and Mr. Ram B. Banarse and Mr. Rupesh H. Nikam as Members of the Committee.

The composition, powers, role and terms of reference of the Committee are in accordance with the requirements mandated under Section 135 of the Companies Act, 2013 and are mentioned in Annexure IV - "Annual Report on CSR Activities" of the Directors' Report forming part of this Annual Report.

4) General Body Meetings:

4.1 Annual General Meeting

The details of Special Resolutions passed at the Annual General Meetings held in last 3 years along with the location and time of the AGMs are as follows:

The details of Annual General Meetings held during the last three years and special resolutions passed thereat are as follows:

AGM	Financial Year	Date & Time	Venue	Special Resolution Passed
24th AGM	31st March, 2017	Friday, 29th September, 2017 at 04.00 pm	602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39A/1 Road No. 23, Wagle Industrial Estate, Thane (West), Thane 400 604	• Revision in terms of remuneration of Mr. Sajankumar R. Bajaj (DIN: 00225950) Chairman & Managing Director of the Company. • Revision in terms of remuneration of Mr. Anil C. Jain (DIN: 00226137) Managing Director of the Company. • Revision in terms of remuneration of Mr. Dhananjay S. Hatle (DIN: 00226390) Whole Time Director of the Company. • Revision in terms of remuneration of Ms. Namrata S. Bajaj (DIN: 05327071) Whole Time Director of the Company. • Revision in terms of remuneration of Mr. Rupesh H. Nikam (DIN: 07007815) Whole Time Director & Chief Financial Officer of the Company
25th AGM	31st March, 2018	Friday, 28th September, 2018 at 04.00 pm	602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39A/1 Road No. 23, Wagle Industrial Estate, Thane (West), Thane 400 604	No
26th AGM	31st March, 2019	Monday, 30th September, 2019 at 04.00 pm	602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39A/1 Road No. 23, Wagle Industrial Estate, Thane (West), Thane 400 604	• Regularize Mr. Avinash Dalal (DIN: 03574325) as an Independent Director. • Regularize Mr. Loukik D. Tipnis (DIN: 08188583) as an Independent Director

4.2 Extraordinary General Meeting

No Extraordinary General Meeting was held during the financial years 2017-18; 2018-19 and 2019-20

4.3 Postal Ballot

During the year, no resolutions have been passed through postal ballot .

4.4. Whether any special resolution is proposed to be conducted through postal ballot:

Currently, there is no proposal to pass any Special resolution through Postal Ballot. Special resolutions by way of Postal Ballot, if required to be passed in the future, will be decided at the relevant time

5) Means of Communication

The Annual, half yearly and Quarterly results were submitted to the Stock Exchange and published in Newspapers in accordance with the Listing Regulations.

These results are simultaneously displayed on the website of the Company and uploaded on the website of BSE Ltd.

The Company also issues press releases from time to time. Press releases and presentations made to the institutional investors / analysts after the declaration of the results are submitted to BSE Ltd. as well as uploaded on the Company's website.

6) General Shareholder Information

6.1

Sr. No.	Salient items of interest Company Registration Details	Particulars	
i.	AGM Date, time and venue	Friday, 30th October, 2020, 1:00 PM Through Video Conferencing	
ii.	Financial year	The Financial Year of the Company is from 1st April, 2019 to 31st March, 2020.	
	Tentative Schedule for declaration of results during the financial year 2019-2020	First quarter:	30th June, 2020 - on or before 15th September, 2020
		Second quarter/Half Yearly	30th September, 2020 - on or before 14th November, 2020
		Third quarter/Nine months	31st December, 2020 - on or before 14th February, 2021
		Fourth quarter/Annual	on or before 30th May, 2021
iii.	Date of Book closure	Friday 23rd October, 2020 to Friday 30th October, 2020 (both days inclusive)	
iv.	Dividend Payment Date	N.A.	
v.	Registrar & Share Transfer Agent	Link Intime India Private Limited C 101, 247 Park, L B S Marg, Vikhroli West, Mumbai-400 083. Tel: +91-22-4918 6270; Fax: +91-22-4918 6060 Email: rnt.helpdesk@linkintime.co.in; Website: www.linkintime.co.in Contact Person: Mr. K. C. Ajitkumar SEBI Registration No.: INR000004058	
vi.	Share Transfer System	In respect of shares held in dematerialized mode, the transfer takes place instantaneously between the transferor, transferee, and the Depository Participant through electronic debit/credit of the accounts involved	
vii.	Dematerialization of shares and liquidity	The Company's shares are currently traded only in dematerialized form over BSE Limited. To facilitate trading in dematerialized form, the Company has tied up with NSDL and CDSL. Shareholders can open account with any of the depository participants registered with any of these depositories. As on 31st March, 2020, 93.70% (64,64,600 Equity Shares) of the Company's equity shares were held in dematerialized form. The equity shares held by the promoter & promoter group in the Company have been fully dematerialized.	
viii.	Address for correspondence	602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39A/1, Road No.23, Wagle Industrial Estate, Thane West, Thane - 400 604; Tel No.: +91-22-6617 7400.	

6.2 Unclaimed Dividend

During the financial year under review, the Company was not required to credit any amount to Investor Education and Protection Fund towards Unclaimed Dividend.

Pursuant to the provisions of Section 124 of the Act, dividend which remains unpaid or unclaimed for a period of seven years from the date of its transfer to unpaid dividend account is required to be transferred by the Company to Investor Education and Protection Fund (IEPF). Shareholders of the Company who have not received or encashed their dividend for the financial years, as mentioned below, are requested to claim the unpaid / unclaimed dividend from the Company before its transfer to the abovementioned Fund.

Sr. No	Year of Declaration of Dividend	Date of Declaration of Dividend	Unclaimed Amount (In ₹)	Due Date for transfer to IEPF Account
1	2017-18	29th September, 2018	1,600	28th September, 2025

6.3 Listing on Stock Exchanges

Equity Shares

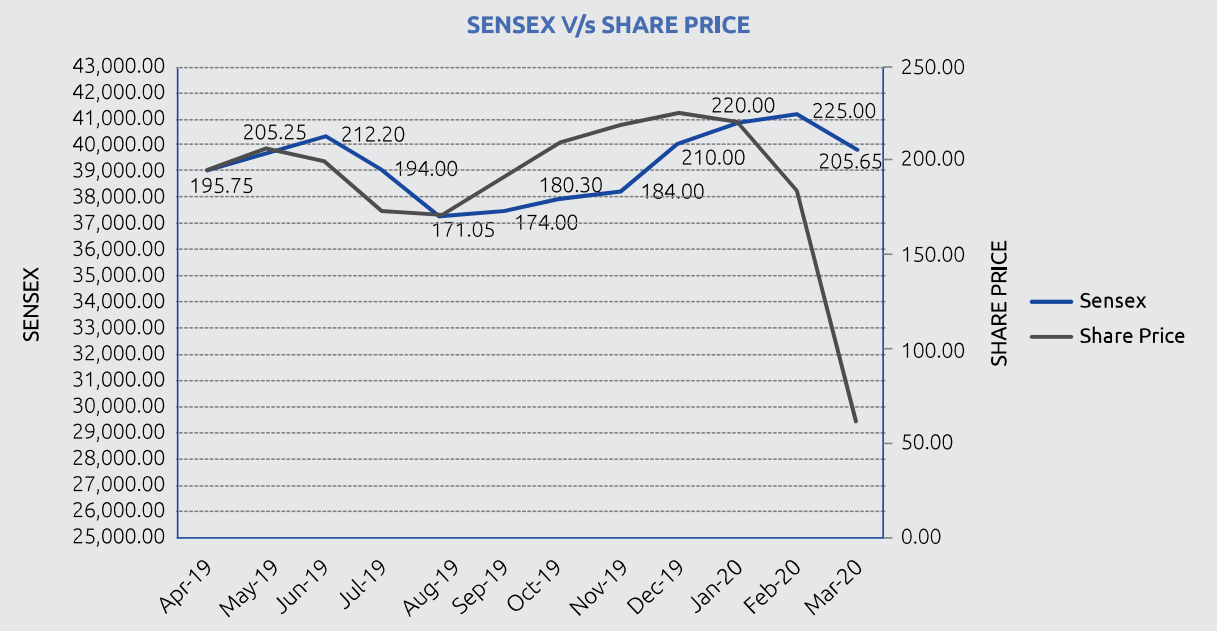
Name of the Stock Exchange	Security code/ Symbol	ISIN	Payment of Annual Listing fees for the FY 19-20 (Y/N)
BSE Limited	539872	INE411U01019	Y

6.4 Market Price Data:

High/Low during each month of 2019-20 on BSE limited

Market Price Data Month	Share prices of the Company for the Period April 2019 to March, 2020	
	HIGH	LOW
Apr-2019	195.75	197.75
May-2019	217.00	205.00
Jun-2019	215.00	200.00
Jul-2019	194.00	193.95
Aug-2019	180.00	171.05
Sep-2019	178.00	170.00
Oct-2019	181.95	172.00
Nov-2019	184.00	177.50
Dec-2019	222.45	210.00
Jan-2020	239.5	220.00
Feb-2020	235.00	225.00
Mar-2020	207.00	204.95

6.5 Share Price performance in comparison to BSE Sensex



6.6 Categories of Shareholding as on 31st March, 2020:

Categories	Number of Shares Shares	%
(A) Shareholding of Promoter and Promoter Group		
Promoters	92,82,000	67.26
Total Shareholding of Promoter & Promoter Group (A)	92,82,000	67.26
(B) Public Shareholding		
(i) Institutions		
Banks / FI	Nil	Nil
Central Govt.	Nil	Nil
Total Public Institutions (B) (i)	Nil	Nil
(ii) Non Institutions		
Individuals	10,67,143	7.74
NRI	4,944	0.04
Bodies Corporate	34,44,519	24.96
Overseas Corporate Bodies	Nil	Nil
Clearing Members	594	0.00
Total Public Non Institution (B) (ii)	45,17,200	32.74
Total Public Shareholding (B)=(B)(i)+(B)(ii)	45,17,200	32.74
Total Shareholding (A) + (B)	1,37,99,200	100

6.7 Top Ten equity shareholders of the Company as on 31st March, 2020 (other than Promoters)

Sr. No.	Name of Shareholders	No of equity Shares held	Percentage of holding
1	PROGYAN CONSTRUCTION AND ENGINEERS PRIVATE LIMITED	10,57,800	7.67
2	MAA SHARDA DISTRIBUTORS PVT LTD	8,70,000	6.31
3	SHRI RAVINDRA MEDIA VENTURES	5,40,600	3.92
4	ESCORP ASSET MANAGEMENT LIMITED	4,73,700	3.43
5	VINOD HARILAL JHAVERI	2,90,400	2.10
6	TIA ENTERPRISES PRIVATE LIMITED	2,73,600	1.72
7	SHASHANK PRAVINCHANDRA DOSHI	1,23,300	0.89
8	HETAL SHASHANK DOSHI	1,10,150	0.80
9	BIPIN CHABILDAS SHAH	1,03,200	0.75
10	MBM BEARINGS (RAJASTHAN) PRIVATE LIMITED	98,400	0.71

6.8 Distribution of Shareholding as on 31st March, 2020:

No. of equity Shares held	Shareholders		Total Shares	
	Number	% of Total	Shares	% of Total
Upto 100	879	85.257	5,330	0.039
101 to 200	14	1.358	2,218	0.016
201 to 500	14	1.358	4,858	0.035
501-1,000	43	4.171	32,947	0.239
1,001-5,000	40	3.880	85,660	0.621
5,001-10,000	8	3.880	61,602	0.441
10,001-1,00,000	16	1.552	5,47,835	3.970
1,00,001- above	17	1.649	1,30,58,750	94.634
Total	**1,031**	**100**	**1,37,99,200**	**100**

6.9 Reconciliation of Share Capital Audit:

As stipulated by Securities and Exchange Board of India (SEBI), a qualified practicing Company Secretary carries out the Share Capital Audit to reconcile the total admitted capital with National Securities Depository Limited (NSDL) and Central Depository Services (India) Limited (CDSL) and the total issued and listed capital. This audit is carried out every quarter and the report thereon is submitted to stock exchanges, NSDL and CDSL. No discrepancies were noticed during these audits.

6.10 Outstanding GDR/ ADR / Warrants or any convertible instruments, conversion date and impact on equity:

The Company has not issued any GDRs / ADRs / Warrants or any convertible instruments in the past and hence as on 31st March, 2020, the Company does not have any outstanding GDRs / ADRs / Warrants or any convertible instruments.

6.11 Plant Location

Unit – I
Plot No. N – 216, 217 & 128, MIDC, Tarapur, Boisar - 401 506, District Thane, Maharashtra

Unit – II
Plot No. 588, Savli – Karadhiya Road, Village Gothada, Savli, Vadodara - 391 776, Gujarat

Unit – III
R. S. No. – 1818, Manjusar – Savli Road, At & Post. - Manjusar, Savli, Vadodara - 391 775, Gujarat

Unit – IV
Plot No. 1717 & 1718, GIDC, Panoli, Ankleshwar, Bharuch - 394 116, Gujarat

Unit – V
Plot No. N –178, MIDC, Tarapur, Boisar - 401 506, District Thane, Maharashtra

Unit- VI
Plot No. E-62 & E-63, MIDC, Tarapur, Boisar - 401 505, District Thane, Maharashtra

6.12 Commodity price risk or foreign exchange risk and hedging activities:

The Company hedges its foreign currency exposure in respect of its imports, borrowings and export receivables as per its laid policies.

6.13 List of all credit ratings obtained by the entity along with any revisions thereto during the relevant financial year, for all debt instruments of such entity or any fixed deposit programme or any scheme or proposal of the listed entity involving mobilization of funds, whether in India or abroad.

The Company does not have any debt instruments and CRISIL Limited rated bank facilities of Bajaj Healthcare Limited as under:

Facilities	Rating for the year 2019-20	Rating for the year 2020-21
Loan term Bank Facilities	CRISIL BBB/Stable	CRISIL BBB/Positive
Short term Bank Facilities	CRISIL A3+	CRISIL A3+

7) Disclosures:

7.1 Related Party Transactions:

All transactions entered into with Related Parties as defined under the Act, and Regulation 23 of the SEBI (Listing Regulations) during the financial year were in the ordinary course of business and on an arm's length pricing basis and do not attract the provisions of Section 188 of the Companies Act, 2013. There were no materially significant transactions with related parties during the financial year which were in conflict with the interest of the Company.

The details of the transactions with related parties, if any, are placed before the Audit Committee from time to time.

The Board of Directors has formulated a policy on materiality of Related Party Transactions and also on dealing with Related Party Transactions. The same is also displayed on the Company's website www.bajajhealth.com

7.2. Strictures and Penalties

No strictures or penalties have been imposed on the Company by the Stock Exchanges or by the Securities and Exchange Board of India or by any statutory authority on any matters related to capital markets during the last three years.

7.3 Vigil Mechanism / Whistle Blower Policy:

Pursuant to Section 177(9) and sub section (10) of the Companies Act, 2013, and in terms of Regulation 22 of SEBI (Listing Regulation) read with Regulation 4(2)(d)(iv) of Securities and Exchange Board of India, the Company has in place a vigil mechanism for Directors and Employees and has adopted a Whistle Blower policy, to report genuine concerns about any wrongful conduct with respect to the Company or its business or affairs. This policy covers malpractices, misuse or abuse of authority, fraud, violation of company's policies or rules, manipulations, negligence causing danger to public health and safety, misappropriation of monies, and other matters or activity on account of which the interest of the Company is affected or likely to be affected and formally reported by whistle blowers.

The Policy provides that all Protected Disclosures can be addressed to the Chairman of the Audit Committee in all the cases and to Whole-time Director / Chairman in exceptional cases. All protected disclosures under this policy will be recorded and thoroughly investigated. If an investigation leads the Chairman of the Audit Committee to conclude that an improper or unethical act has been committed, the Chairman of the Audit Committee shall recommend to the management of the Company to take such disciplinary or corrective action as he may deem fit. The details of the vigil mechanism are also available on the Company's website www.bajajhealth.com

7.4. Status of compliance with mandatory requirements and Non-Mandatory Requirements:

The Company has complied with all mandatory requirements of Corporate Governance norms as specified in Regulation 17 to 27 and clause (b) to (i) of sub regulation (2) of Regulation 46 of SEBI (Listing Regulation), 2015, to the extent applicable to the company.

7.5 Code for prevention of Insider-Trading Practices:

As per the Securities and Exchange Board of India (Prohibition of Insider Trading) Regulations, 2015, the Company has adopted a Code of Conduct for prevention of Insider Trading.

The Company has instituted a comprehensive code of conduct for its directors, management and officers and the other connected persons with the Practices and Procedures for Fair Disclosure of Unpublished Price Sensitive Information, guidelines and procedures to be made while dealing with shares of the Company including the consequences of violations if any. The code clearly specifies, among other matters, that the Directors and specified employees of the Company can trade in the shares of the Company only during 'Trading Window Open Period'. The trading window is closed during the time of declaration of results, dividend and material events, etc. as per the Policy. Disclosure of shareholding is taken from all the directors and Designated Employees and other connected persons of the Company.

7.6 Compliance with Mandatory and Non-Mandatory Requirements

The Company has adopted following non-mandatory requirements of Listing Regulations:

Auditors Qualification:

The Company is in regime of unqualified/unmodified financial statements..

Reporting of Internal Auditor:
The Internal Auditor reports directly to the Audit Committee periodically to ensure independence of the Internal Audit function.

7.7 Details of utilization of funds
During the year under review, there were no Preferential Allotment or Qualified Institutional Placement as specified under Regulation 32(7A) of the Listing Regulations

7.8. Disclosures with respect to demat suspense account / unclaimed suspense account
During the year under review, the Company was not required to transfer any shares to demat suspense account/unclaimed suspense account.

7.9 Certification by Practicing Company Secretary
As per the amended Listing Regulations, the Company has obtained a certificate from the Company Secretary in practice that none of the Directors on the Board of the Company have been debarred or disqualified, from being appointed or continuing as Directors, by Securities and Exchange Board of India/Ministry or Corporate Affairs or any such authority and the same is annexed to this Report.

7.10 Disclosures in relation to the Sexual Harassment of Women at Workplace (Prevention, Prohibition and Redressal) Act, 2013:

a. number of complaints filed during the financial year : Nil
b. number of complaints disposed of during the financial year : Nil
c. number of complaints pending as on end of the financial year : Nil

7.11 Where the Board had not accepted any recommendation of any Committee of the Board which is mandatorily required, in the relevant Financial Year, the same to be disclosed along with reasons
During the year under review, the Board has accepted all the recommendation of all the Committees of the Board.

8) Compliance Certificate on Corporate Governance
Certificate from the statutory auditors confirming compliance with the conditions of Corporate Governance, as stipulated under SEBI (Listing Obligations and Disclosure Requirements) regulations, 2015, is attached and forms part of the Annual Report

9) Review of Directors Responsibility Statement
The Board in its Report has confirmed that annual accounts for the year ended 31st March 2020 have been prepared as per Indian Accounting Standard (Ind AS) and policies and that sufficient care has been taken for maintaining adequate accounting records.

10) CEO / CFO Certificate:
As required under Regulation 17 (8) of SEBI (LODR) Regulations, 2015, the Certificate for the FY 2019-20 signed by Mr. Rupesh H. Nikam, Chief Financial Officer forms part of the Annual Report.

11) Declaration Regarding Compliance by Board Members and Senior Management Personnel with the Company's Code of Conduct:
This is to confirm that the Company has adopted a Code of Conduct for its employees including the Managing Director and Executive Directors. In addition, the Company has adopted a Code of Conduct for its Non-Executive Directors and Independent Directors. The Company has in respect of the year ended 31st March, 2020, received from the Senior Management Team of the Company and the Members of the Board a declaration of compliance with the Code of Conduct as applicable to them.

For and on behalf of the Board of Directors
of **Bajaj Healthcare Limited**

Sd/-
Sajankumar R. Bajaj
Chairman & Managing Director
DIN: 00225950

Place: Thane
Dated: 14th September, 2020

INDEPENDENT AUDITOR'S CERTIFICATE REGARDING COMPLIANCE OF CONDITIONS OF CORPORATE GOVERNANCE:

To the Members of Bajaj Healthcare Limited

We have examined all the relevant records of Bajaj Healthcare Limited, for the purpose of certifying compliance of the conditions of the Corporate Governance under para C of Schedule V read with Regulation 34(3) of Chapter IV of SEBI (Listing Obligations and Disclosure Requirements) Regulations, 2015 for the year ended on 31st March, 2020.We have obtained all the information and explanations which to the best of our knowledge and belief were necessary for the purposes of certification.

The compliance of conditions of Corporate Governance is the responsibility of the Company's management. Our examination was limited to the procedure and implementation process adopted by the Company for ensuring the compliance of the conditions of the corporate governance.

This certificate is neither an assurance as to the future viability of the Company nor of the efficacy or effectiveness with which the management has conducted the affairs of the Company.

In our opinion and to the best of our information and according to the explanations given to us, we certify that the Company has complied with all the mandatory requirements of Corporate Governance as stipulated in the para C of Schedule V read with Regulation 34(3) of Chapter IV of SEBI (Listing Obligations and Disclosure Requirements) Regulation, 2015.

For **Paresh Rakesh & Associates,**
Chartered Accountants
Firm Registration Number: 119728W

Sd/-
Rakesh Chaturvedi
Partner
M No : 102075

Place: Mumbai
Date: 14th September, 2020

Compliance Certificate

(Pursuant to Regulation 17 (8) of SEBI (LODR) Regulations, 2015)

We, Mr. Rupesh H. Nikam, chief Financial Officer of Bajaj Healthcare Limited, hereby certify that:

We have reviewed the Audited financial statements and the cash flow statement for the Financial Year ended on 31st March, 2020 and that to the best of my knowledge and belief;

i. these statements do not contain any materially untrue statement or omit any material fact nor contain statements that might be misleading;

ii. these statements together present a true and fair view of the company's affairs and are in compliance with the applicable laws and regulations.

There are, to the best of my knowledge and belief, no transactions entered into by the company during the year, which are fraudulent, illegal or violative of the company's Code of Conduct;

We accept responsibility for establishing and maintaining internal controls for financial reporting and we have evaluated the effectiveness of internal control systems of the listed entity pertaining to financial reporting and we have disclosed to the auditors and the audit committee, deficiencies in the design or operation of such internal controls, if any, of which they are aware and the steps they have taken or propose to take to rectify these deficiencies; and

We have indicated to the auditors and the Audit committee, significant changes in accounting policies during the year and that the same have been disclosed in the notes to the financial statements.

Sd/-
Rupesh H. Nikam
Chief Financial Officer

Place : Thane
Date : 30th June, 2020

Certificate of Non-Disqualification of Directors

[Pursuant to Regulation 34(3) and Schedule V Para C Sub clause (10)(i) of
SEBI (Listing Obligations and Disclosure Requirements) Regulations, 2015]

To,
The Members of
BAJAJ HEALTHCARE LIMITED,
CIN: L99999MH1993PLC072892
602-606, Bhoomi Velocity Infotech Park,
Plot No. B-39, B-39A, B-39 A/1,
Rd No.23, Wagle Ind. Estate
Thane West 400604

I have examined the List of disqualified Directors published by the Ministry of Corporate Affairs ("MCA"); Declaration from all the Directors self-certifying their non-disqualification as required under section 164 of the Companies Act, 2013 ("Act"); and Disclosure of Directors' concern/interests as required under section 184 of the Act (hereinafter referred as "**the relevant documents**") of **Bajaj Healthcare Limited**, bearing Corporate Identification Number (CIN) - L99999MH1993PLC072892, having its registered office at 602-606, Bhoomi Velocity Infotech Park, Plot No. B-39, B-39A, B-39 A/1, Rd No.23, Wagle Ind. Estate Thane West 400604 (hereinafter referred as "**the Company**") for the purpose of issuing this Certificate, in accordance with Regulation 34(3) read with Schedule V Para-C Sub clause 10(i) of the SEBI (Listing Obligations and Disclosure Requirements) Regulations, 2015.

Based on my examination as well as on information and according to the verifications (including Directors Identification Number (DIN) status at the portal www.mca.gov.in) as considered necessary and explanations furnished provided by the officers, agents and authorised representatives of the Company, I hereby certify that none of the Directors of the Company stated below who are on the Board of the Company as on 31st March 2020, have been debarred or disqualified from being appointed or continuing to act as Directors of the Company by Securities and Exchange Board of India or the MCA or any such other statutory authority.

Sr. no.	Name of the Directors	DIN	Date of appointment*
1	Mr. Sajankumar Rameshwarlal Bajaj	00225950	1st April, 2002
2	Mr. Anil Champalal Jain	00226137	15th January, 2004
3	Mr. Dhananjay Sabaji Hatle	00226390	1st April, 2005
4	Mr. Vidyut Jayantilal Shah	02578165	8th January, 2016
5	Mr. Avinash Krishnalal Dalal	03574325	22nd April, 2019
6	Ms. Namrata Sajankumar Bajaj	05327071	11th January, 2013
7	Mr. Rupesh Hanumant Nikam	07007815	1st November, 2014
8	Mr. Hemant Rajaram Karnik	07377151	8th January, 2016
9	Mr. Ram Baliramji Banarse	07405486	14th January, 2016
10	Mr. Loukik Deepak Tipnis	08188583	22nd April, 2019

*the date of appointment is as per the MCA Portal

I further state that such compliance is neither an assurance as to the future viability of the Company nor of the efficiency or effectiveness with which the management has conducted the affairs of the Company.

This Certificate has been issued at the request of the Company to make disclosure in its Corporate Governance Report of the Financial Year ended 31st March 2020.

Haresh Sanghvi
Practicing Company Secretary
FCS No.: 2259/CoP No.: 3675
UDIN: F002259B000670619

Place: Mumbai
Date: 5th September, 2020

Independent Auditor's Report

To the Members of **Bajaj Healthcare Limited**
Report on the Financial Statements

Opinion

We have audited the accompanying financial statements of Bajaj Healthcare Limited ("the Company"), which comprise the Balance Sheet as at 31st March 2020, and the Statement of Profit and Loss and Cash Flow Statement for the year then ended, and notes to financial statements, including a summary of significant accounting policies and other explanatory information.

In our opinion and to the best of our information and according to the explanations given to us, the aforesaid financial statements give the information required by the Act in the manner so required and give a true and fair view in conformity with the accounting principles generally accepted in India, of the state of affairs of the Company as at 31st March 2020, its Profit and its Cash flows for the year ended on that date.

Basis for Opinion

We conducted our audit in accordance with the Standards on Auditing (SAs) specified under section 143(10) of the Companies Act, 2013. Our responsibilities under those Standards are further described in the Auditor's Responsibilities for the Audit of the Financial Statements section of our report. We are independent of the Company in accordance with the Code of Ethics issued by the Institute of Chartered Accountants of India together with the ethical requirements that are relevant to our audit of the financial statements under the provisions of the Companies Act, 2013 and the Rules thereunder, and we have fulfilled our other ethical responsibilities in accordance with these requirements and the Code of Ethics. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Key Audit Matters

Key audit matters are those matters that, in our professional judgment, were of most significance in our audit of the financial statements of the current period. These matters were addressed in the context of our audit of the financial statements as a whole, and in forming our opinion thereon, and we do not provide a separate opinion on these matters.

We have determined that there are no key audit matters to be communicated in our report.

Information Other than the Financial Statements and Auditor's Report Thereon

The Company's Board of Directors is responsible for the other information in Annual Report, which comprises the information included in the Management Discussion and Analysis, Board's Report including Annexures to Board's Report and Shareholder's Information but does not include the financial statements and our auditor's report thereon.

Our opinion on the financial statements does not cover such other information and we do not express any form of assurance conclusion thereon.

In connection with our audit of the financial statements, our responsibility is to read the other information identified above when it becomes available and, in doing so, consider whether the other information is materially inconsistent with the financial statements or our knowledge obtained in the audit, or otherwise appears to be materially misstated.

Management's Responsibility for the Financial Statements

The Company's Board of Directors is responsible for the matters stated in Section 134(5) of the Companies Act, 2013 ("the Act") with respect to the preparation of these financial statements that give a true and fair view of the financial position, financial performance and cash flows of the company in accordance with the accounting principles generally accepted in India, including the Accounting Standards specified under section 133 of the Act, read with rule 7 of the Companies (Accounts) Rules, 2014.

This responsibility also includes maintenance of adequate accounting records in accordance with the provision of the Act for safeguarding the assets of the Company and for preventing and detecting frauds and other irregularities; selection and application of the appropriate accounting policies; making judgements and estimates that are reasonable and prudent; and design, implementation and maintenance of adequate internal financial controls, that we are operating effectively for ensuring the accuracy and completeness of the accounting records, relevant to the preparation and fair presentation of the financial statements that give a true and fair view and are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, management is responsible for assessing the Company's ability to continue as a going concern, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless management either intends to liquidate the Company or to cease operations, or has no realistic alternative but to do so.

Those Board of Directors are also responsible for overseeing the company's financial reporting process.

Auditor's Responsibilities for the Audit of the Financial Statements

Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditor's report that includes our opinion. Reasonable assurance is a high level of assurance, but is not a guarantee that an audit conducted in accordance with SAs will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the

aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements.

As part of an audit in accordance with SAs, we exercise professional judgment and maintain professional skepticism throughout the audit. We also:

- Identify and assess the risks of material misstatement of the Financial Statements, whether due to fraud or error, design and perform audit procedures responsive to those risks, and obtain audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control.
- Obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on whether company has in place an adequate internal financial control system over financial reporting and the operating effectiveness of such controls.
- Evaluate the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by management.
- Conclude on the appropriateness of management's use of the going concern basis of accounting and, based on the audit evidence obtained, whether a material uncertainty exists related to events or conditions that may cast significant doubt on the Company's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the Financial Statements or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report. However, future events or conditions may cause the Company to cease to continue as a going concern.
- Evaluate the overall presentation, structure and content of the Financial Statements, including the disclosures, and whether the Financial Statements represent the underlying transactions and events in a manner that achieves fair presentation.

We communicate with those charged with governance regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that we identify during our audit.

We also provide those charged with governance with a statement that we have complied with relevant ethical requirements regarding independence, and to communicate with them all relationships and other matters that may reasonably be thought to bear on our independence, and where applicable, related safeguards.

Report on Other Legal and Regulatory Requirements

1. As required by the Companies (Auditor's Report) Order, 2016 ("the Order"), issued by the Central Government of India in terms of sub-section (11) of section 143 of the Companies Act, 2013, we give in the Annexure A statement on the matters specified in paragraphs 3 and 4 of the Order, to the extent applicable.

2. As required by Section 143(3) of the Act, we report that:

   a) We have sought and obtained all the information and explanations which to the best of our knowledge and belief were necessary for the purposes of our audit.

   b) In our opinion, proper books of account as required by law have been kept by the Company so far as appears from our examination of those books.

   c) The Balance Sheet, Statement of Profit and Loss and Cash Flow Statement dealt with by this report are in agreement with the books of account.

   d) In our opinion, the aforesaid financial statements comply with the accounting standards specified under section 133 of the Act, read with Rule 7 of the Companies (Accounts) Rules, 2014.

   e) On the basis of written representations received from the directors as on 31st March 2020 taken on record by the Board of Directors, none of the directors is disqualified as on 31st March 2020 from being appointed as a director in terms of section 164(2) of the Act.

   f) With respect to the adequacy of the internal financial controls over financial reporting of the Company and the operating effectiveness of such controls, refer to our separate Report in "Annexure B".

   g) In our opinion, the managerial remuneration for the year ended 31st March, 2020 has been paid/provided by the Company to its directors in accordance with the provisions of section 197 read with Schedule V to the Act;

h) With respect to the other matters to be included in the Auditor's Report in accordance with Rules 11 of the Companies (Audit and Auditors) Rules, 2014, in our opinion and to the best of our information and according to the explanations given to us:

i. The Company does not have any pending litigations except as mention in Note no. 31 which would impact on its financial position.

ii. The Company did not have any material foreseeable losses on long-term contracts including derivative contracts that require provision under any law or accounting standards for which there were any material foreseeable losses; and

iii. There were no amounts which were required to be transferred to the Investor Education and Protection Fund by the Company.

For **Paresh Rakesh & Associates**
Chartered Accountants
FRN: 119728W

Rakesh Chaturvedi
Partner
M. No: 102075
UDIN: 20102075AAAAEO6942

Date: 30th June, 2020
Place: Mumbai

"Annexure A" to Independent Auditors' Report referred to in Paragraph 1 under the heading of "Report on other legal and regulatory requirements" of our report of even date.

1. In respect of its Fixed Assets :

a) The Company has maintained proper records showing full particulars including quantitative details and situation of fixed assets on the basis of available information.

b) According to explanation provided to us the company has carried out physical verification of fixed assets, which in our opinion appears to be reasonable having regard to the size of the Company and the nature of its assets. No material discrepancies were noticed on such verification

c) According to the information, explanations and records given to us, Immovable properties owned by the Company, are held in the name of the Company as at the balance sheet date.

2. In respect of its Inventories :

a) According to the information's and explanation given to us, Physical verification of inventory has been conducted, at reasonable intervals by the management.

b) In our opinion and according to the information and explanations given to us, the procedures of physical verification of inventories followed by the management are reasonable and adequate in relation to the size of the Company and the nature of its business.

c). The Company has maintained proper records of inventories. As per records provided to us, there was no material discrepancies noticed on physical verification of inventories as compared to the book records, having regards to the size of the operations of the company

3. Since, the Company has not granted any Loans to parties covered in in the register maintained under Section 189 of the Companies Act, 2013, the clause (iii) of paragraph 3 of the Order is not applicable to the Company.

4. In respect of Investment made by the Company:

a) The Company has complied with the provisions of section 185

b) The Company has complied with the provisions of section 186.

5. According to the information and explanations given to us, the Company has not accepted any deposits within the meaning of provisions of sections 73 to 76 or any other relevant provisions of the Act and the rules framed there under. Therefore, the clause (v) of paragraph 3 of the Order is not applicable to the Company.

6. The Company has maintained the Accounts and Records pursuant to the rules made by the Central Government for the maintenance of cost records under section 148 of the Act. However, we have not carried out a detailed examination of the same.

7. (a). According to the records examined by us, the Company has regularly deposited, undisputed statutory dues including Direct Taxes, Indirect Taxes and any other statutory dues with appropriate authorities and there were no outstanding dues as at 31st March 2020 for a period of more than six months from the date they became payable.

(b) According to the information and explanations given to us, and according to the books and records as produced and examined by us following disputed amount of tax demanded which have not been deposited with concern authorities as on 31st March,2020.

Sr. No	Nature of Liability	Name of Statute	Amt (in ₹)	Period which the amount relates	Forum where the dispute pending
1	Excise Duty	Central Excise Act,1944	1,89,973/-	2007-08	CESTAT, Mumbai
2	Excise Duty	Central Excise Act, 1944	67,61,197/-	2007-08	CESTAT, Mumbai
3	Central Sales Tax	Central Sales Tax (Gujarat) Rules, 1970 and Central Sales Tax Act, 1956	23,07,325/-	2014-15	Deputy Commissioner of Commercial Tax (Appeals), Baroda
	Total		**92,58,495/-**		

8. In our opinion and according to the information and explanations given to us, the company has not defaulted in repayment of outstanding dues to any financial institutions or banks or any government during the year. Accordingly, paragraph 3 (viii) of the order is not applicable.

9. In our opinion and according to the information and explanations given to us, Term Loan availed during the year has been applied for the purpose for which they have been raised. The Company has not raised money by way of initial public offer or further public offer (including debt instruments).

10. Based on the audit procedures performed for the purpose of reporting the true and fair view of the financial statements and as per information and explanations given to us, no fraud by the Company or on the Company by its officers or employees has been noticed or reported during the year.

11. In our opinion and according to the information and explanations given to us, managerial remuneration has been paid or provided in accordance with the requisite approvals mandated by the provisions of section 197 read with schedule V to the Act.

12. In our opinion company is not a nidhi company. Therefore, the provisions of clause (xii) of paragraph 3 of the Order are not applicable to the company.

13. In our opinion and according to the information and explanations given to us, in respect of transactions with related parties :

a) All transactions with related parties are in compliance with sections 177 of the Act.

b) Company is in compliance with the section 188 of the Act and details have been disclosed in the financial statements as required by the applicable accounting standards.

14. In our opinion and according to the information and explanations given to us, the Company has not made any preferential allotment or private placement of Shares or fully or partly convertible debentures during the year and hence clause (xiv) of paragraph 3 of the Order is not applicable to the company.

15. In our opinion and according to the information and explanations given to us, the Company has not entered into any non-cash transaction with the directors or persons connected with him and covered under section 192 of the Act. Hence, clause (xv) of the paragraph 3 of the Order is not applicable to the Company.

16. In our opinion and according to the information and explanations given to us, The Company is not required to be registered under section 45-IA of the Reserve Bank of India Act, 1934.

For **Paresh Rakesh & Associates**
Chartered Accountants
FRN: 119728W

Rakesh Chaturvedi
Partner
M. No: 102075
UDIN: 20102075AAAAEO6942

Date: 30th June, 2020
Place: Mumbai

"Annexure B" to Independent Auditors' Report referred to in paragraph 2(f) under the heading "Report on other legal and regulatory requirements" of our report of even date.

Report on the Internal Financial Controls under Clause (i) of Sub-section 3 of Section 143 of the Companies Act, 2013 ("the Act")

We have audited the Internal Financial Control over financial reporting of Bajaj Healthcare Limited ("the company") as of 31st March 2020, in conjunction with our audit of the financial statements of the Company for the year then ended.

Management Responsibility for the Internal Financial Controls

The Company's management is responsible for establishing and maintaining internal financial controls based on the internal control over financial reporting criteria established by the Company considering the essential components of internal control stated in the Guidance Note on Audit of Internal Financial Controls over Financial Reporting issued by the Institute of Chartered Accountants of India (ICAI). These responsibilities include the design, implementation and maintenance of adequate internal financial controls that were operating effectively for ensuring the orderly and efficient conduct of its business, including adherence to company's policies, the safeguarding of its assets, the prevention and detection of frauds and errors, the accuracy and completeness of the accounting records, and the timely preparation of reliable financial information, as required under the Act.

Auditor's Responsibility

Our responsibility is to express an opinion on the Company's internal financial controls over financial reporting based on our audit. We conducted our audit in accordance with the Guidance Note on Audit of Internal Financial Controls over Financial Reporting (the "Guidance Note") and the Standards on Auditing, issued by ICAI and deemed to be prescribed under section 143(10) of the Act, to the extent applicable to an audit of internal financial controls, both applicable to an audit of Internal Financial Controls and, both issued by the ICAI. Those Standards and the Guidance Note require that we comply with ethical requirements and plan and perform the audit to obtain reasonable assurance about whether adequate internal financial controls over financial reporting was established and maintained and if such controls operated effectively in all material respects.

Our audit involves performing procedures to obtain audit evidence about the adequacy of the internal financial controls system over financial reporting and their operating effectiveness. Our audit of internal financial controls over financial reporting included obtaining an understanding of internal financial controls over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion on the Company's internal financial controls system over financial reporting.

Meaning of Internal Financial Controls Over Financial Reporting

A company's internal financial control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal financial control over financial reporting includes those policies and procedures that:

(1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company;

(2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorisations of management and directors of the company; and

(3) provide reasonable assurance regarding prevention or timely detection of unauthorised acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Inherent Limitations of Internal Financial Controls Over Financial Reporting

Because of the inherent limitations of internal financial controls over financial reporting, including the possibility of collusion or improper management override of controls, material misstatements due to error or fraud may occur and not be detected. Also, projections of any evaluation of the internal financial controls over financial reporting to future periods are subject to the risk that the internal financial control over financial reporting may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Opinion

In our opinion, considering nature of business, size of operations and organizational structure of the entity, the Company has, in all material respects, an adequate internal financial controls system over financial reporting and such internal financial controls over financial reporting were operating effectively as at 31st March 2020 based on the Internal Control over Financial reporting criteria established by the Company considering the essential components of Internal Control stated in the Guidance Note on Audit of Internal Financial Controls over Financial reporting issued by the ICAI.

For **Paresh Rakesh & Associates**
Chartered Accountants
FRN: 119728W

Rakesh Chaturvedi
Partner
M. No: 102075
UDIN: 20102075AAAAEO6942

Date: 30th June, 2020
Place: Mumbai

Balance Sheet

as at 31st March, 2020

Particulars	Note No	As at 31st March, 2020		As at 31st March, 2019	
I. EQUITY AND LIABILITIES					
(1) Shareholder's Funds					
(a) Share Capital	2	13,79,92,000		6,89,96,000	
(b) Reserves and Surplus	3	1,37,80,70,102	1,51,60,62,102	1,22,20,68,322	1,29,10,64,322
(2) Non-Current Liabilities					
(a) Long-term borrowings	4		23,57,81,574		17,39,26,957
(b) Long-term Provisions	5		2,08,90,929		1,42,42,436
(3) Current Liabilities					
(a) Trade payables	6	47,70,73,321		29,98,48,884	
(b) Short Term Borrowings	7	58,43,25,430		54,88,64,347	
(c) Other current liabilities	8	30,95,65,823		25,61,90,572	
(d) Short Term Provisions	9	9,16,92,624	1,46,26,57,198	6,84,47,225	1,17,33,51,028
(4) Deffered Tax Liability			2,20,61,677		1,58,90,765
Total			**3,25,74,53,480**		**2,66,84,75,509**
II. Assets					
(1) Non-current assets					
(a) Tangible Fixed Assets	10		1,34,72,47,672		1,28,49,68,935
(b) Capital work-in-progress	10		5,44,59,996		1,17,81,098
(2) Long Term Investments	11		5,00,30,625		30,625
(3) Current assets					
(a) Inventories	12	39,27,50,586		30,04,78,771	
(b) Trade receivables	13	1,00,13,23,857		78,12,68,737	
(c) Cash and cash equivalents	14	4,15,84,899		7,86,15,392	
(d) Other current assets	15	37,00,55,845	1,80,57,15,187	21,13,31,950	1,37,16,94,851
Total			**3,25,74,53,480**		**2,66,84,75,509**

Accounting Policies	1
Notes to Financial Statements	2 to 40

As per our report of even date attached
For Paresh
Rakesh & Associates
Chartered Accountants
FRN: 119728W

For and on behalf of the Board
For **Bajaj Healthcare Limited**

Sd/-	Sd/-	Sd/-	Sd/-	Sd/-
Rakesh Chaturvedi	**Aakash Keshari**	**Rupesh H. Nikam**	**S. K. R. Bajaj**	**Anil C. Jain**
Partner	Company Secretary	CFO and Director	Chairman and Managing Director	Joint Managing Director
M. No: 102075		DIN: 07007815	DIN: 00225950	DIN: 00226137

Place: Thane
Date: 30th June, 2020

Profit and Loss Statement

for Year ended 31st March, 2020

Particulars	Note No	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
Revenue from operations	16	4,10,00,83,914	3,70,17,37,304
Other Income	17	3,17,90,585	97,17,488
Total Revenue		**4,13,18,74,499**	**3,71,14,54,791**
Expenditure			
Cost of materials consumed	18	2,68,32,05,300	2,45,33,02,287
Other Direct Expenses	19	51,95,05,194	46,00,27,800
Changes in inventories	20	-5,08,75,545	-3,30,19,933
Employee Benefit Expenses	21	28,43,33,913	24,61,89,594
Financial costs	22	6,44,92,820	8,01,78,131
Depreciation and amortization expense	23	12,12,33,402	11,41,00,429
Other expenses	24	18,54,66,487	14,89,78,824
Total Expenses		**3,80,73,61,570**	**3,46,97,57,133**
Profit before Tax		32,45,12,929	24,16,97,658
Tax expense:			
(1) Current tax		9,10,00,000	6,75,00,000
(2) Deffered Tax		61,70,912	38,92,493
(3) Earlier Years		23,44,238	72,02,091
Profit/(Loss) for the period		**22,49,97,780**	**16,31,03,073**
Earning per equity share:	25		
(1) Basic		16.31	11.82
(2) Diluted		**16.31**	**11.82**

As per our report of even date attached

For Paresh
Rakesh & Associates
Chartered Accountants
FRN: 119728W

Sd/-
Rakesh Chaturvedi
Partner
M. No: 102075

For and on behalf of the Board
For **Bajaj Healthcare Limited**

Sd/-
Aakash Keshari
Company Secretary

Sd/-
Rupesh H. Nikam
CFO and Director
DIN: 07007815

Sd/-
S. K. R. Bajaj
Chairman and Managing Director
DIN: 00225950

Sd/-
Anil C. Jain
Joint Managing Director
DIN: 00226137

Place: Thane
Date: 30th June, 2020

Cash Flow Statement

for Year ended 31st March, 2020

Amt in ₹

Sr No	Particulars	2019-2020		2018-2019	
A)	**Cash Flow From Operating Activities**				
	Net Profit Before Tax		32,45,12,929		24,16,97,658
	Adjustment for:				
	Depreciation	12,12,33,402		11,41,00,429	
	(profit) / loss on sale of Assets	(2,71,482)		15,53,628	
	Interest & Finance Charges	6,44,92,820		8,01,78,131	
	Interest on FD	(30,88,473)		(24,92,111)	
	Provision for Employee Benefits	91,69,367		72,96,710	
	Dividend Income	(4,450)	19,15,31,184	(4,450)	20,06,32,337
	Operating Profit before Working Capital Changes		**51,60,44,113**		**44,23,29,995**
	Adjustment for:				
	(Increase) / Decrease in other current assets	(13,73,49,427)		1,13,71,597	
	(Increase) / Decrease in Sundry Debtors	(22,00,55,119)		2,25,76,234	
	(Increase) / Decrease in Inventories	(9,22,71,815)		3,61,17,224	
	(Increase) / Decrease in non-current and current liabilities	23,05,99,688	(21,90,76,673)	(13,04,64,837)	(6,03,99,783)
	Cash generated from operations		29,69,67,440		38,19,30,212
	Income Tax Paid		(9,12,18,705)		(13,02,43,527)
	Net Cash Flow from Operating activities		**20,57,48,734**		**25,16,86,685**
B)	**Cash Flow from Investing Activities**				
	Purchase of Fixed Assets	(18,42,14,856)		(15,00,59,452)	
	Increase / (Decrease) in Capital WIP	(4,26,78,898)		(79,06,305)	
	Sale of Fixed Assets	9,74,199		83,172	
	Interest on FD	30,88,473		24,92,111	
	Payment to Gratuity Fund	(27,75,475)		(31,82,855)	
	Insurance Claim Received	-		1,25,00,000	
	Investment in Preference Shares	(5,00,00,000)			
	Dividend Income	4,450		4,450	
	Net cash used in investment activities		**(27,56,02,107)**		**(13,02,56,269)**

Cash Flow Statement

for Year ended 31st March, 2020

Amt in ₹

Sr No	Particulars	2019-2020	2018-2019
C)	**Net Cash used in Investing activities**		
	Cash Flow from Financing Activities		
	Increase / (Decrease) From Long Term Borrowing	6,78,13,665	(3,60,37,658)
	Increase / (Decrease) Of Unsecured Long Term Borrowing	(59,59,048)	(47,86,800)
	Increase / (Decrease) of Short Term Borrowing From Bank	5,34,46,599	1,52,70,432
	Increase / (Decrease) Of Borrowing From Director & Inter corporates	(1,79,85,516)	(1,16,21,337)
	Interest Paid	(6,44,92,820)	(8,01,78,131)
	Dividend Paid	-	(68,99,600)
	Dividend Distribution Tax paid	-	(14,18,233)
	Net cash used in financing activities	3,28,22,880	(12,56,71,327)
	Net increase in Cash & Cash Equivalents (A+B+C)	**(3,70,30,492)**	**(42,40,911)**
	Cash and Cash equivalents as at 1st April, 2019	7,86,15,392	8,28,56,303
	Cash and Cash equivalents as at 31st March, 2020	4,15,84,899	7,86,15,392

As per our report of even date attached

For Paresh
Rakesh & Associates
Chartered Accountants
FRN: 119728W

Sd/-
Rakesh Chaturvedi
Partner
M. No: 102075

For and on behalf of the Board
For **Bajaj Healthcare Limited**

Sd/-
Aakash Keshari
Company Secretary

Sd/-
Rupesh H. Nikam
CFO and Director
DIN: 07007815

Sd/-
S. K. R. Bajaj
Chairman and Managing Director
DIN: 00225950

Sd/-
Anil C. Jain
Joint Managing Director
DIN: 00226137

Place: Thane
Date: 30th June, 2020

Notes to the Financial Statements

for the year ended 31st March, 2020

1] Significant Accounting Policies

A. Basis of Accounting

The financial statements are prepared under the historical cost convention on accrued basis and in accordance with applicable Accounting Standards and relevant presentational requirements of the Companies Act, 2013, unless and otherwise specifically stated.

B. Revenue Recognition & Sales

a) The Company recognizes sales at the point of dispatch of goods to the customers.

b) Revenue is recognized in the appropriate circumstances when there are no significant uncertainties as regards its realization.

c) Sales are stated at gross and include all taxes, but excludes interdivisional transfers (Net).

C. Fixed Assets

a) Fixed Assets are stated at cost of acquisition or construction (net of recoverable taxes wherever availed) less accumulated depreciation.

b) Fixed Assets wherever revalued are reinstated by creating differential Revaluation Reserve which is added to the Gross Block as on the date of revaluation.

c) In the case of fixed assets acquired for new projects / expansion, interest cost on borrowings, and other related expenses incurred up to the date of completion of project are capitalized.

d) Expenditure incurred towards fixed assets including advances paid towards the same are shown as capital work in progress till the completion of the assets.

D. Depreciation

Depreciation on all the fixed assets is provided on the W.D.V. method at the rates and in the manner prescribed under schedule II to the Companies Act, 2013 and on the basis of life of assets in accordance with the Schedule II Part C.

Depreciation is calculated on WDV or restated value and debited to Profit and Loss Account. Also an amount equivalent to the differential depreciation on the assets due to revaluation is transferred from Revaluation Reserve to the Balance of Profit and Loss Account in balance sheet.

E. Stock In Trade / Purchase

a) Finished Goods are valued at cost or net realizable value whichever is lower,

b) Raw materials Purchase and in transit are accounted at cost recorded net of recoverable taxes.

c) WIP are valued at cost of materials plus overheads.

d) Inventories are valued on FIFO Basis.

F. Current Tax & Deffered Tax

Income Tax is accounted for in accordance with Accounting Standard - 22 on Accounting for taxes on Income issued by the ICAI. Tax comprises of both the current and deferred. Current tax is measured at the amount expected to be paid/ recovered from the tax authorities using the applicable tax rates. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to timing differences between the taxable income and accounting income that are capable of reversal in one or more subsequent periods and are measured using relevant enacted tax rates.

G. Foreign Currency Transactions

a) Transactions denominated in foreign currencies are normally recorded at the exchange rate prevailing at the time of transaction.

b) Any income or expense on account of exchange difference either on settlement or on translation is recognized in the profit and loss account.

H. Government Grants

a) Government grants are accounted for where it is reasonably certain that the ultimate collection will be made.

b) Government grants related to G.S.T Refund claim for 100% EOU of Baroda Unit for all four quarters are shown under current assets.

I. Borrowing Costs

Borrowing costs which are directly attributable to acquisition, construction, or production of qualifying assets are capitalized as a part of cost of that asset. Other borrowing costs are recognized as an expense in the period in which they are incurred.

J. Investments

Long term investments are stated at cost, less provision for diminution in value other than temporary in nature.

K. Provisions & Contingent Liabilities

Provision is made in accounts if it becomes probable that an outflow of resources will be required to settle the obligation, in respect of which reliable estimate can be made. Contingent liabilities are not recognized till they crystallized, but are disclosed in the notes on account.

L. Employee Benefits and Expenses

Short Term Employee Benefits:

The undiscounted amount of short term employee benefits expected to be paid in exchange for the services rendered by employees are recognised as an expense during the period when the employees render the services.

Notes to the Financial Statements

for the year ended 31st March, 2020

Post-Employment Benefits:

Defined Contribution Plans:

A defined contribution plan is a post-employment benefit plan under which the Company pays specified monthly contributions towards Provident Fund. The Company's contribution is recognized as an expense in the Profit and Loss Statement during the period in which the employee renders the related service.

Defined Benefit Plans:

a) Expenses for defined-benefit gratuity plan are calculated as at the balance sheet date by an independent actuary in a manner that distributes expenses over the employee's working life. These commitments are valued at the present value of the expected future payments, with consideration for calculated future salary increases, using a discount rate corresponding to the interest rate estimated by the actuary having regard to the interest rate on government bonds with a remaining term that is almost equivalent to the average balance working period of employees. The fair values of the plan assets if any, are deducted in determining the net liability.

b) Actuarial losses or gains are recognized in the Statement of Profit and Loss in the year in which they arise.

M. Earning Per Share

a) Basic earnings per share are calculated by dividing the net profit or loss for the period attributable to equity shareholders by the weighted average number of equity shares, outstanding during the period.

For the purpose of calculating diluted earnings per share the net profit or loss for the period attributable to equity shareholder and the weighted average number of shares outstanding during the period are adjusted for the effect of all dilutive potential equity shares.

Notes to the Financial Statements

for the year ended 31st March, 2020

2. Share Capital

(Amount in ₹)

	As at 31st March, 2020	As at 31st March, 2019
Authorised Share Capital :		
1,40,00,000 (PY 1,00,00,000) Equity Shares of ₹ 10 each	14,00,00,000	14,00,00,000
	14,00,00,000	**14,00,00,000**
Issued Subscribed and Paid Up Capital :		
1,37,99,200 (PY 68,99,600) Equity Shares of ₹ 10 each fully paid up	13,79,92,000	6,89,96,000
Total	**13,79,92,000**	**6,89,96,000**

Reconciliation of number of shares outstanding is set out below:

(Amount in ₹)

	As at 31st March, 2020	As at 31st March, 2019
Equity Shares		
At the beginning of the period	68,99,600	68,99,600
Addition during the period	68,99,600	-
Outstanding at the end of the period	**1,37,99,200**	**68,99,600**

2.1 Details of shareholders holding more than 5% shares in the company:

Name of the shareholder	As at 31st March, 2020		As at 31st March, 2019	
	% Holding	No of Shares	% Holding	No of Shares
a. Equity Shares:				
Mrs. Babita Bajaj	5.45	7,52,000	5.45	3,76,000
Mr. Sajankumar R. Bajaj	34.89	48,14,000	34.89	24,07,000
S K R Bajaj HUF	7.83	10,80,000	7.83	5,40,000
Ms. Namrata Bajaj	5.86	8,08,000	5.86	4,04,000
Ms. Nihita S. Bajaj	5.86	8,08,000	5.86	4,04,000
Mr. Anil C. Jain	5.20	7,18,000	5.20	3,59,000
M/s. Maa Sharda Distributors Pvt. Ltd.	6.30	8,70,000	6.30	4,35,000
M/s. Progyan Construction and Engineers Pvt. Ltd.	7.67	10,57,800	7.67	5,28,900

2.2 The Equity Shares issued and paid up includes 45,00,000 shares issued as bonus Shares for consideration other than cash issued on 18th January 2016.

The Equity Shares issued and paid up includes 68,99,600 shares issued as bonus Shares for consideration other than cash issued on 11th April 2019

Notes to the Financial Statements

for the year ended 31st March, 2020

3. Reserves & Surplus

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Capital Reserve				
As per Last Balance Sheet	5,60,623		5,60,623	
Add/(Less): Changes during the Year	(5,60,623)	-	-	5,60,623
Revaluation Reserve				
As per Last Balance Sheet	40,22,43,679		40,84,42,782	
Less: Changes during the Year (Refer Note No. 3.1)	(63,93,043)	39,58,50,635	(61,99,103)	40,22,43,679
Shares Premium				
As per Last Balance Sheet	6,64,36,000		6,64,36,000	
Less:: Changes during the Year	(6,64,36,000)	-	-	6,64,36,000
Profit & Loss Account				
As per last Balance Sheet	75,28,28,021		59,16,93,677	
Depreciation on Revalued Figure	63,93,043		61,99,103	
Adjustment for Provision of Gratuity as per AS 15 (Net)	-		1,50,000	
Less: Provison for Dividend Declared for FY 2017-18	-		(68,99,600)	
Less: Tax on Distribution of Dividend	-		(14,18,233)	
Less: Utilisation of Bonus Share	(19,99,377)		-	
Add: Transferred from Profit and Loss Account	22,49,97,780		16,31,03,073	
		98,22,19,467		75,28,28,021
Total		**1,37,80,70,102**		**1,22,20,68,322**

3.1 Changes in Revaluation Reserve is on account of Additional Depreciation on Revalued Assets pursuant to Revaluation.

4. Long Term Borrowings

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Secured				
Term Loan from Bank	19,48,83,859		12,43,61,126	
Term Loan from NBFC	3,48,54,719	22,97,38,578	3,75,63,787	16,19,24,913
Unsecured Loans				
Inter Corporate Loans (For Related Party Transaction Refer Note no. 32)		60,42,996		1,20,02,044
Total		**23,57,81,574**		**17,39,26,957**

4.1 Repayment Schedule for Secured Term Loans

Year	FY 2021-22	FY 2022-23	FY 2023-24	2024-25 onwards
Amount (₹)	5,79,40,113	3,85,09,258	2,46,34,374	10,86,54,834

4.2 The details of Security for term loans are Provided in note no. 26

Notes to the Financial Statements

for the year ended 31st March, 2020

5. Long Term Provisions

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Provision for Employee benefits				
Present Value of Obligation as per AS 15	2,53,30,983		1,84,75,807	
Fair Value of Plan Asset as at the End	(1,33,81,773)	1,19,49,210	(1,01,78,905)	82,96,902
Provision for Leave Encashment		89,41,719		59,45,534
Total		**2,08,90,929**		**1,42,42,436,**

6. Trade Payables

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Micro Small & Medium Enterprises	-		-	
Others (Net)	47,70,73,321	47,70,73,321	29,98,48,884	29,98,48,884
Total		**47,70,73,321**		**29,98,48,884**

6.1 Amount due to Small Scale Industries exceeding rupees one lac each, outstanding for more than 30 days are not distinctly determinable in absence of any intimation received by the Company from any parties.

7. Short Term Borrowings

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Secured				
Working Capital Loan From Banks				
Cash Credit	4,05,72,484		-	
Pre shipment / Post shipment / Buyers Credit	53,97,66,541	58,03,39,024	52,68,92,426	52,68,92,426
Unsecured				
From Director	-		1,06,03,489	
Inter Corporate Deposits (For Related Party Transaction Refer Note no. 32)	39,86,405	39,86,405	1,13,68,432	2,19,71,922
Total		**58,43,25,430**		**54,88,64,347**

7.1 The details of Security for Working Capital Loans from banks are provided in note no. 26

Notes to the Financial Statements

for the year ended 31st March, 2020

8. Other Current Liabilities

(Amount in ₹)

	As at 31st March, 2020	As at 31st March, 2019
Current Maturity of Long Term Borrowings Banks (Secured)	8,57,04,844	8,12,80,586
Current Maturity of Long Term Borrowings from NBFC (Secured)	34,46,533	31,89,747
Sundry Creditors For Expenses	9,77,72,133	9,29,09,986
Sundry Creditors for Capital Goods	5,14,53,410	97,79,708
Advances Received from Customers	65,16,394	67,98,105
Statutory Dues Payable	36,79,841	29,12,996
Deposits From Selling Agents	14,51,601	14,51,601
Other Payables	5,95,41,067	5,78,67,843
Total	**30,95,65,823**	**25,61,90,572**

9. Short Term Provsions

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Present Value of Obligation as per AS 15	18,33,171		24,46,366	
Less: Fair Value of Plan Asset as at the End	(18,33,171)	-	(24,46,366)	-
Provision for Leave Encashment		6,92,624		9,47,225
Provision for Income Tax		9,10,00,000		6,75,00,000
Total		**9,16,92,624**		**6,84,47,225**

10. Depreciation as Per Companies Act
1st April, 2019 to 31st March, 2020

Fixed Assets	Gross Block 1st April, 2019	Addition during year	Deduction during year	Gross Block 31st March, 2020	Dep. up tp 1st April, 2019	Dep. for the Year	Deduction during year	Total Dep 31st March, 2020	Net Block 31st March, 2020	Net Block 31st March, 2019
Air Condition	71,95,439	1,07,804	-	73,03,243	59,78,900	5,88,920	-	65,67,820	7,35,422	12,16,538
Computer	2,23,51,869	27,96,804	-	2,51,48,673	1,87,03,900	29,65,720	-	2,16,69,620	34,79,053	36,47,969
Electrical Equipment	5,71,23,489	78,37,287	-	6,49,60,777	3,97,95,191	48,17,333	-	4,46,12,524	2,03,48,253	1,73,28,298
Factory & Office Equipment	92,98,797	1,73,765	-	94,72,563	82,87,968	4,10,880	-	86,98,848	7,73,715	10,10,829
Factory Building	54,20,34,935	1,31,42,977	-	55,51,77,912	25,69,58,661	2,77,02,346	-	28,46,61,006	27,05,16,905	28,50,76,274
Fire Fighting Equipment	7,09,411	-	-	7,09,411	3,65,595	89,787	-	4,55,382	2,54,029	3,43,816
Furniture & Fixture	2,69,50,657	5,65,094	-	2,75,15,751	1,93,98,462	20,01,379	-	2,13,99,841	61,15,909	75,52,194
Guest House Staff Quarters	2,58,71,017	-	-	2,58,71,017	66,65,537	9,42,759	-	76,08,296	1,82,62,721	1,92,05,480
Lab Equipment	6,05,57,383	89,98,890	-	6,95,56,273	3,26,27,467	82,74,834	-	4,09,02,301	2,86,53,972	2,79,29,916
Land (Leasehold)	4,54,74,421	-	-	4,54,74,421	-	-	-	-	4,54,74,421	4,54,74,421
Land (Freehold)	33,92,86,740	-	-	33,92,86,740	-	-	-	-	33,92,86,740	33,92,86,740
Motor Vehicle	2,84,98,589	61,18,949	34,35,827	3,11,81,711	1,81,94,006	33,39,276	27,33,110	1,88,00,172	1,23,81,538	1,03,04,582
Office Premises (Freehold)	6,65,25,065	-	-	6,65,25,065	92,46,486	27,89,467	-	1,20,35,953	5,44,89,112	5,72,78,579
Office Premises (Leasehold)	3,67,98,230	-	-	3,67,98,230	1,78,92,809	21,81,943	-	2,00,74,752	1,67,23,478	1,89,05,421
Plant & Machinery	95,36,69,093	14,44,73,285	-	1,09,81,42,378	50,32,61,213	6,51,28,758	-	56,83,89,970	52,97,52,404	45,04,07,878
Total	**2,22,23,45,134**	**18,42,14,856**	**34,35,827**	**2,40,31,24,163**	**93,73,76,197**	**12,12,33,402**	**27,33,110**	**1,05,58,76,486**	**1,34,72,47,672**	**1,28,49,68,935**
(Previous Year)	2,09,64,68,664	15,00,59,452	2,41,82,982	2,22,23,45,134	83,03,05,323	11,41,00,429	70,29,553	93,73,76,197	1,28,49,68,937	1,26,61,63,341
Capital W.i.p									5,44,59,996	1,17,81,098

10.1 In Financial Year 2014-15,the Assets of the Company compressing of Land and Buildings acquired or constructed by the Company prior to 01st April, 2014 were revalued and reinstated as on 31st March, 2015 to reflect the fair value of the assets by creating revaluation reserve account with equivalent value.

Notes to the Financial Statements

for the year ended 31st March, 2020

11. Long Term Investments

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Investment in 50,00,000 Preference Share of Face Value of ₹ 10/- each of Bajaj Sindhudurg Rice Mill Ltd	5,00,00,000		-	
500 (P.Y. 500) Shares of Tima Cooperative Society limited of ₹ 10/- Each	5,000		5,000	
2,500 (P.Y. 2,500) Equity Shares of Saraswat Co-op Bank of ₹ 10/- Each	25,000		25,000	
25 (P.Y. 25) Shares of Shamrao Vithal Co-op Bank of ₹ 25/- each	625	30,625	625	30,625
Total		**5,00,30,625**		**30,625**

12. Inventories

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
(As Valued and certified by Management)				
Raw Material	23,71,00,680		19,75,41,883	
Finished Goods	13,51,21,170		8,42,45,625	
Packing Material	87,54,215		63,65,788	
Stores and Spares	1,17,74,521	39,27,50,586	1,23,25,475	30,04,78,771
Total		**39,27,50,586**		**30,04,78,771**

13. Trade Receivables

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Unsecured - Considered Good				
Over 6 months	2,37,53,766		5,28,17,101	
Others	97,75,70,091	1,00,13,23,857	72,84,51,636	78,12,68,737
Total		**1,00,13,23,857**		**78,12,68,737**

14. Cash & Cash Equivalents

(Amount in ₹)

	As at 31st March, 2020	As at 31st March, 2019
Cash Balance on Hand		
Cash in Hand	8,36,588	4,37,865
Bank Balance with Scheduled Bank		
In Current Accounts	4,07,48,310	5,06,77,527
In Deposit Accounts	-	2,75,00,000
Total	**4,15,84,899**	**7,86,15,392**

Notes to the Financial Statements

for the year ended 31st March, 2020

15. Other Current Assets

(Amount in ₹)

	As at 31st March, 2020	As at 31st March, 2019
Advances Receivable in cash or kind or Value to be received	13,48,46,477	9,85,38,435
Fixed Deposit With Banks (Under Lien for Bank Guarantee)	1,84,10,193	1,79,70,810
Deposit With Public Authorities and Others	2,65,04,181	2,34,15,135
Advance to Suppliers	10,17,96,545	42,83,589
Advance Tax & Tax Deducted at Source	8,84,98,449	6,71,23,982
Total	**37,00,55,845**	**21,13,31,950**

16. Revenue from Operations

(Amount in ₹)

	As at 31st March, 2020		As at 31st March, 2019	
Local Sales				
Manufacturing Sales	2,66,59,04,448		2,48,45,29,234	
Add: Duties & Taxes on Sales	48,48,83,515	3,15,07,87,963	45,15,37,336	2,93,60,66,570
Export Sales				
Manufacturing Export Sales	92,67,22,103		74,80,70,580	
Duties and Taxes on Export Sale	-	92,67,22,103	-	74,80,70,580
Processing Charges		2,25,73,848		1,76,00,154
Total		**4,10,00,83,914**		**3,70,17,37,304**

17. Other Income

(Amount in ₹)

	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
Dividend Received	4,450	4,450
Interest on Fixed Deposit Received	30,88,473	24,92,111
Insurance and other Claim	1,75,40,443	43,75,518
Professional fees	70,95,930	-
Rent Income	21,93,000	15,30,000
Scrap Sale	15,96,807	12,51,931
Income of Duty Drawback	-	2,678
Profit on sale of Assets	2,71,482	60,799
Total	**3,17,90,585**	**97,17,488**

18. Cost of Material Consumed

(Amount in ₹)

	For the year ended on 31st March, 2020		For the year ended on 31st March, 2019	
Opening Stock	20,39,07,671		27,32,55,953	
Add: Purchases	2,24,02,69,009		1,93,23,95,747	
Less: Closing Stock	24,58,54,895	2,19,83,21,785	20,39,07,671	2,00,17,44,029
GST/ Excise Duty & Sales Tax		48,48,83,515		45,15,58,258
Total		**2,68,32,05,300**		**2,45,33,02,287**

Notes to the Financial Statements

for the year ended 31st March, 2020

19. Other Direct Expenses

(Amount in ₹)

	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
Effluent Treatment Chgs	3,45,67,337	3,24,37,976
Fuel charges	9,63,22,616	9,16,56,714
Furnance Oil / LDO	1,05,17,622	61,54,783
Freight Forwarding & Transport	8,21,47,802	8,18,10,699
Material Testing & Inspection Charges	1,57,81,709	1,18,95,032
Processing & Labour Charges	10,13,89,245	7,56,89,520
Power Charges	12,15,05,901	10,94,48,994
Repairs & Maintenance Plant & Mach.	2,80,13,581	2,30,07,329
Stores & Spares	1,52,15,624	1,68,64,773
Water Charges	1,40,43,758	1,10,61,982
Total	**51,95,05,194**	**46,00,27,800**

20. Changes in Inventories

(Amount in ₹)

	For the year ended on 31st March, 2020		For the year ended on 31st March, 2019	
Fininshed Goods				
Opening Stock	8,42,45,625		5,12,25,692	
Less: Closing Stock	13,51,21,170	(5,08,75,545)	8,42,45,625	(3,30,19,933)
Total		**(5,08,75,545)**		**(3,30,19,933)**

21. Employee Benefit Expenses

(Amount in ₹)

	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
Salary	24,48,25,148	21,73,73,285
Staff Welfare	1,33,41,494	1,07,92,525
Provision for Gratuity & Leave Encashment	1,02,92,030	72,96,710
Provident Funds and Other Contributions	1,58,75,241	1,07,27,074
Total	**28,43,33,913**	**24,61,89,594**

22. Finance Costs

(Amount in ₹)

	For the year ended on 31st March, 2020		For the year ended on 31st March, 2019	
Bank Charges		1,48,44,429		1,18,46,998
Processing Fees		15,16,596		2,00,700
Interest on Buyers Credit		1,03,72,434		1,58,69,805
Interest on C.C., L.C. & P.C. facilities		1,27,19,972		1,89,10,982
Interest on Unsecured Loan		28,82,267		74,58,194
Interest on Car Loan		3,41,181		4,33,227
Interest on Term Loan	2,63,97,097		2,76,37,945	
Less : Interest Capitalized	(45,81,156)	2,18,15,941	(21,79,719)	2,54,58,226
Total		**6,44,92,820**		**8,01,78,131**

Notes to the Financial Statements

for the year ended 31st March, 2020

23. Depreciation & Amortization of Expenses

(Amount in ₹)

	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
Depreciation	12,12,33,402	11,41,00,429
Total	**12,12,33,402**	**11,41,00,429**

24. Other Expenses

(Amount in ₹)

	For the year ended on 31st March, 2020		For the year ended on 31st March, 2019	
Advertisment & Presentation		47,33,945		14,02,212
Brokerage & Commission		69,39,842		1,50,90,104
Courier Charges & Telephone Expenses		22,31,458		25,02,602
Discount & Rebate		-		-
Donation		1,40,57,950		1,79,04,551
Loss Due to Foreign Exchange Rate Fluctuation		2,76,38,743		2,54,55,895
Hotel / Boarding / Lodge / Guest House Expense		7,74,086		16,24,025
Insurance		1,13,72,252		83,59,057
Interest on Excise, Service Tax & TDS		18,07,400		29,74,541
Legal & Professional Expenses		2,01,95,380		2,08,05,666
Loss on GST Fire Claim		-		5,79,100
Loss on Sale of Assets		-		16,14,428
Corporate Social Responsibility Expenses		44,49,056		55,30,887
Sundry Balance W/off		3,51,71,794		2,67,488
Membership & Subscription		7,57,486		4,47,217
Miscellaneous Expenses		15,09,810		15,38,846
Motor Vehicle & Fuel Expenses		11,39,601		12,04,839
Printing & Stationery		51,84,883		45,46,627
Repairs & Maintenance Building		85,13,709		90,43,354
Repairs & Maintenance Others		1,22,83,936		1,09,14,340
Rent Rates & Taxes		1,38,14,659		48,45,820
Security & Cleaning Charges		16,71,915		15,06,771
Seminar Expenses		9,24,614		1,16,590
Travelling & Conveyence Expenses		66,89,595		79,88,439
Travelling Expenses - Foreign		21,75,624		17,15,676
Audit Fees				
Statutory Audit Fees	4,00,000		3,50,000	
Tax Audit Fees	1,00,000	5,00,000	1,00,000	4,50,000
Sponsorship Expenses		9,28,751		5,49,751
Total		**18,54,66,487**		**14,89,78,824**

Notes to the Financial Statements

for the year ended 31st March, 2020

25. Earning Per Share

(Amount in ₹)

		For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
A.	Net Profit / Loss available for Equity shareholders (after tax)	22,49,97,780	16,31,03,073
B.	Weighted number of equity share outstanding during the year	1,37,99,200	1,37,99,200
C.	Basic earnings per share of ₹ 10/- each	16.31	11.83

26. A) The Security except as detailed in Clause B and Clause C below, created under a security trust (presently with IL&FS Trust Company Limited as trustee) shall rank pari-passu for multiple lenders, without any preference or priority of one lender over the other:

i. **For Term Loan**
Pari Passu Charge on Movable Fixed Assets and immovable properties and Second Pari Passu charge on current assets.

ii. **For Working Capital**
First Pari Passu Charge on Current assets and Pari Passu Charge on movable fixed Assets and immovable properties.

(Working Capital Limits Includes Packing Credit, Post Shipment Credit, Buyers Credit, Cash Credit, Letter of Credit)

B) Office Premises at Thane is exclusively Mortgaged / Hypothecated to Aditya Birla Finance Limited

C) Loan for Motor Vehicle are secured against respective Motor Vehicles for which Loan is obtained.

D) Further, All borrowings are, secured by personal guarantees of the directors Mr. S. K. R. Bajaj, Mr. Anil C. Jain.

27. In opinion of the Directors, Current Assets Loans and advances have the value at which they are stated in the Balance Sheet if realized in the ordinary course of business. All the outstanding liabilities other than those stated under contingent liabilities have been provided for.

28. The balance of Sundry Debtors, Creditors and Loans & Advances are subject to confirmations and reconciliation.

29. Since no specific intimation has been received from any of the suppliers regarding the status of their registration as Micro, Small, or Medium as defined under Micro, Small and Medium Enterprises Department (MSMED) Act, 2006 as at 31st March 2020, disclosure relating to amounts unpaid as at the year end, if any, have not been furnished. However, the Company has been regular in paying to the Vendors as per agreed terms and conditions and hence the management feels there are no requirements for any provision towards interest.

30. Deferred Tax Liabilities:

Deferred Tax Assets as on 31st March 2020 comprises of the following :

(Amount in ₹)

		As at 31st March, 2020	As at 31st March, 2019
	Timing difference on account of Depreciation on fixed asset	61,70,912	38,92,493
	Total	**61,70,912**	**38,92,493**

31. Contingent Liabilities:

- Letter of credits issued by Banks USD 25,46,598/- (Previous Year USD 17,95,331/-)
- Bank Guarantee issued by Bank amount of ₹ 184.10 lakhs (Previous Year ₹ 179.71 lakhs) to MGVCL, MPCB, Customs etc.
- Estimated amount of Capital Commitment for purchase plant and machinery ₹ 1,650 lakhs (Previous Year : ₹ 546.76 lakhs)

Notes to the Financial Statements

for the year ended 31st March, 2020

Claim Against company not acknowledged as debts:

- High Court of Justice Business and Property Courts of England and Wales in a business dispute has passed the order against the Company to pay GBP 646883.39 to a Debtor which shall however be subject deduction of outstanding receivable from such Debtor of USD 513946.20. Further, the Court has yet to pass the order quantifying the Interest payable on differential amount. The Company has estimated the net claim which could be payable to this Debtor at ₹ 2,16,11,165. (Plus Applicable interest as quantified).The Company is exploring the remedy against the order and its enforceability.
- Central Excise, Custom Duty, Central Sales Tax & GVAT Liabilities ₹ 457.84 Lakhs Plus Applicable Interest (Previous year ₹ 709.17 Lakhs). This represents the demands made by authorities which in opinion of company are not sustainable and appeals are pending with appropriate authority. The details of claim against company not acknowledged as debts are as under:

Sr. No	Nature of Liability	Name of Statute	Amount (in ₹)	Period which the amount relates	Forum where the dispute pending
A.	**Appeal filed by Company**				
1	Excise Duty	Central Excise Act,1944	1,89,973	2007-08	CESTAT, Mumbai
2	Excise Duty	Central Excise Act, 1944	67,61,197	2007-08	CESTAT, Mumbai
3	Central Sales Tax	Central Sales Tax (Gujarat) Rules, 1970 and Central Sales Tax Act, 1956	23,07,325	2014-15	Deputy Commissioner of Commercial Tax (Appeals), Baroda
B.	**Appeal filed by Department**				
4	Custom Duty	Central Excise Act, 1944 and Customs Act, 1962	3,65,25,427	Dec 2003 to Dec 2005	CESTAT, Mumbai
	Total		**4,57,83,922**		

32. Related Party Disclosures:

The following transactions have been done with the related parties as defined under the AS 18 issued by the ICAI.

Names of related parties with whom transactions have taken place during the year:

Key Management Personnel-Category I	Mr. S. K. R. Bajaj Mr. Anil C. Jain Mr. Dhananjay S. Hatle Ms. Namrata Bajaj Mr. Rupesh H. Nikam	- CMD - JMD - Director - Director - Director & CFO
Relative of key management personnel-Category II	Ms. Babita Bajaj Ms. Padma Jain Mr. Siddhesh Hatle Ms. Gayatri Hatle Mr. Pakshal A. Jain	
Enterprises owned or significantly influenced by key management personnel or their relatives-Category III	Bajaj Health &Nutritions Pvt Ltd Bansal Pharma Ltd Bajaj Sindhudurg Rice Mills Limited	
Enterprise owned or significantly influenced by group of individuals or their relatives who have control or significant influence over the Firm-Category IV	Nil	

Notes to the Financial Statements

for the year ended 31st March, 2020

Transactions with related parties during the year (Amt. in ₹)

Sr. No.	Particulars	Category I	Category II	Category III	Category IV
1	Remuneration	1,33,88,975/- (1,21,37,660/-)	Nil (475,00)	Nil (Nil)	Nil (Nil)
2	Rent Paid	Nil (Nil)	Nil (Nil)	Nil (12,000/-)	Nil (Nil)
3	Interest Paid (net of interest recd)	5,46,146/- (7,43,709)	Nil (Nil)	23,36,121/- (67,14,485/-)	Nil (Nil)
4	Sponsorship For Education	Nil (Nil)	8,98,805/- (4,19,751/-)	Nil (Nil)	Nil (Nil)
5	Balance outstanding as on 31st March, 2020 of Long Term Unsecured loan taken	Nil (Nil)	Nil (Nil)	60,42,996/- (1,20,02,044/-)	Nil (Nil)
6	Balance outstanding as on 31st March, 2020 of Short Term Unsecured loan taken	Nil (1,06,03,489/-)	Nil (Nil)	39,86,405/- (1,13,68,432/-)	Nil (Nil)
7	Advance For Purchase	Nil (Nil)	Nil (Nil)	2,62,00,000/- (Nil)	Nil (Nil)
8	Purchase of Assets	Nil (Nil)	Nil (Nil)	6,82,335/- (Nil)	Nil (Nil)
9	Investment in Preference Shares	Nil (Nil)	Nil (Nil)	5,00,00,000/- (Nil)	Nil (Nil)

Note: Amount shown in brackets represents the amount of previous year.

Long Term Borrowings Include:

Sr. No.	Name of the Party	Year	Opening	Closing
1	Bajaj Health & Nutrition Pvt Ltd	C Y	1,20,02,044/-	60,42,996/-
		P Y	(1,67,88,844/-)	(1,20,02,044/-)

Short Term Borrowings Include:

Sr. No.	Name of the Party	Year	Opening	Closing
1	Bajaj Health & Nutrition Pvt Ltd	C Y	1,02,60,745/-	22,63,735/-
		P Y	(2,97,37,857/-)	(1,02,60,745/-)
2	Bansal Pharma Limited	C Y	11,07,687/-	17,22,670/-
		P Y	(38,07,543/-)	(11,07,687/-)
3	Mr. S. K. R. Bajaj	C Y	98,71,558/-	Nil
		P Y	(Nil)	(98,71,558/-)
4	Mr. Anil C. Jain	C Y	7,31,931/-	Nil
		P Y	(Nil)	(7,31,931/-)
5	Ms. Namrata Bajaj	C Y	Nil	Nil
		P Y	(47,858/-)	(Nil)

Advance to Suppliers Include:

Sr. No.	Name of the Party	Year	Opening	Closing
1	Bajaj Sindhudurg Rice Mills Limited	C Y	-	2,62,00,000/-
		P Y	-	-

Investment in 7.5% Optionally Convertible Non-cumulative Preference Shares:

Sr. No.	Name of the Party	Year	Opening	Closing
1	Bajaj Sindhudurg Rice Mills Limited	C Y	-	5,00,00,000/-
		P Y	-	-

Note: Amount shown in brackets represents the amount of previous year.

Notes to the Financial Statements

for the year ended 31st March, 2020

Income and Expenditure:

i. Remuneration includes payment to Mr. S. K. R. Bajaj ₹ 48,00,000/- (P.Y. ₹ 48,00,000/-), Mr. Anil C. Jain ₹ 46,00,000/- (PY ₹ 36,00,000/-), to Mr. Dhananjay S. Hatle ₹ 13,58,535/- (PY ₹ 12,40,989/-), to Ms. Namrata Bajaj ₹ 10,15,000/- (PY ₹ 10,12,917/-), to Mr. Rupesh H. Nikam ₹ 16,15,440/- (PY ₹ 14,93,076), to Ms. Babita Bajaj ₹ Nil (PY ₹ 25,000/-), and to Ms. Padma Jain ₹ Nil (PY ₹ 22,500/-).

ii. Rent Paid Includes paid Bansal Pharma Ltd ₹ NIL (PY ₹ 12,000/-).

iii. Interest payment includes payment to Bansal Pharma Ltd ₹ 2,04,950/- PY (₹ 5,23,137/-), to Bajaj Health and Nutritions Pvt Ltd ₹ 21,31,171/- (PY ₹ 61,91,348/-), to Mr. S. K. R. Bajaj: ₹ 4,69,876/- (PY ₹ 7,29,719) and to Mr. Anil C. Jain ₹ 76,270/- (PY ₹ 13,990/-).

iv. Sponsorship payment for education includes payment made to Ms. Gayatri Hatle ₹ 1,21,633 (PY ₹ NIL/-); to Mr. Siddhesh Hatle ₹ 1,70,446/- (PY ₹ 1,36,551/-); to Mr. Pakshal A. Jain ₹ 3,15,225/- (PY ₹ 2,83,200/-), to Ms. Khushi Jain ₹ 2,91,500/- (PY ₹ NIL).

v. Purchase of assets includes purchase from Bajaj Sindhudurg Rice Mills Limited ₹ 6,82,335/- (PY ₹ NIL).

Note: Amount shown in brackets represents the amount of previous year.

33. Segment Information as per Accounting Standard 17:

Information about Primary Business Segments

Sr. No.	Particulars	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
A	**Segment Revenue (Excluding Intersegment Revenue)**		
	Bulk Drugs	3,85,36,52,790	3,61,55,31,066
	Formulations	24,64,31,124	8,62,06,237
	Total	**4,10,00,83,914**	**3,70,17,37,304**
	Segment Revenue (Intersegment Revenue)		
	Bulk Drugs	21,08,97,570	6,76,40,512
	Formulations	86,17,620	85,10,278
	Total	**21,95,15,190**	**7,61,50,790**
	Gross Segment Revenue (Including Intersegment Revenue)		
	Bulk Drugs	4,06,45,50,360	3,68,31,71,578
	Formulations	25,50,48,744	9,47,16,515
	Total	**4,31,95,99,104**	**3,77,78,88,093**
B	**II. Segment Results**		
	Profit / (Loss) Before Tax & Finance Cost		
	Bulk Drugs	59,57,64,138	49,56,60,636
	Formulations	(2,12,91,903)	(2,48,06,022)
	Total	**57,44,72,235**	**47,08,54,614**
	Less : Interest	6,44,92,820	8,01,78,131
	Other Unallocable Expenditure (Net)	18,54,66,487	14,89,78,824
	Total Profit Before Tax	**32,45,12,929**	**24,16,97,658**

Notes to the Financial Statements

for the year ended 31st March, 2020

Sr. No.	Particulars	For the year ended on 31st March, 2020	For the year ended on 31st March, 2019
C	**I. Segment Assets**		
	Bulk Drugs	2,89,92,26,655	2,50,99,64,992
	Formulations	30,81,96,200	15,84,79,892
	Others	5,00,30,625	30,625
	Total (I)	**3,25,74,53,480**	**2,66,84,75,509**
	II. Segment Liabilities		
	Bulk Drugs	1,54,89,68,432	1,24,66,13,596
	Formulations	5,84,70,336	3,31,64,389
	Others	13,39,52,606	9,76,33,201
	Total (II)	**1,74,13,91,374**	**1,37,74,11,187**
	III. Total Capital Employed (I –II)	**1,51,60,62,106**	**1,29,10,64,323**
	Total (II+III)	**3,25,74,53,480**	**2,66,84,75,509**

Information about Secondary Segments: Geographical

Particulars	India		Outside India		Total	
	2020	2019	2020	2019	2020	2019
Gross Sales *	31,733.62	29,536.67	9,267.22	7,480.71	41,000.84	37,017.38
Less: Taxes	4,848.84	4,515.37	-	-	4,848.84	4,515.37
Net Sales	26,884.78	25,021.30	9,267.22	7,480.71	36,152.00	32,502.01

* Gross Sales Includes Taxes on Intersegment Transfers.

- **Business Segment:**
  The Company has Disclosed Business Segment as the Primary Segment. Segments have been identified taking into account the nature of the products, the differing risks and returns, the organizational structure and internal reporting system.

  The Company's Operations predominantly relate to manufacture of Bulk Drugs business. Other Business Segments Comprises Formulation of medicines and sell it to end user.

- **Segment Revenue :**
  Segment Revenue & Segment Results include the respective amounts identifiable to each of the segments as also amounts allocated on reasonable basis.

34. Disclosure under Accounting Standard 15 (Employee Benefits):

Defined Contribution Plans

Contribution to Defined Contribution Plans, recognized as expense for the year is as under :

Particulars	2019-20	2018-19
Employer's Contribution to Provident and Pension Fund	1,28,55,442	99,26,630

Notes to the Financial Statements

for the year ended 31st March, 2020

Defined Benefit Plan

i. Reconciliation of opening and closing balances of Defined Benefit Obligation:

Particulars	2019-20	2018-19
Defined Benefit Obligation at beginning of the year	2,09,22,173	1,73,38,298
Interest Cost	16,14,439	13,34,100
Past Service Cost	-	-
Current Service Cost	32,36,934	26,54,803
Actuarial (Gain) / Loss	23,63,621	2,99,993
Benefits Paid	(9,73,013)	(7,05,021)
Defined Benefit Obligation at year end	2,71,64,154	2,09,22,173

ii. Reconciliation of opening and closing balances of fair value of Plan Assets:

Particulars	2019-20	2018-19
Fair value of Plan Assets at beginning of year	1,26,25,271	96,19,706
Fair value of Plan Assets at year end	1,52,14,944	1,26,25,271

iii. Reconciliation of fair value of Assets and Obligations:

Particulars	2019-20	2018-19
Fair value of Plan Assets	1,52,14,944	1,26,25,271
Present value of Obligation	2,71,64,154	2,09,22,173
Net Liability recognised in Balance Sheet	1,19,49,210	82,96,902

iv. Expenses recognized during the year:

Particulars	2019-20	2018-19
Current Service Cost	32,36,934	26,54,803
Interest Cost	16,14,439	13,34,100
Expected Return on Plan Assets	9,74,217	(7,40,191)
Actuarial (Gain) / Loss	25,50,627	3,62,453
Net Cost	64,27,783	36,11,165

v. Actuarial Assumptions:

Particulars	2019-20	2018-19
Discount Rate (%)	6.75	7.7 0
Expected Return on plan assets (%)	6.75	7.70
Rate of escalation in Salary (per annum) (%)	5.00	5.00

35. Expenditure in Foreign Currency:

Particulars	2019-20	2018-19
CIF Value of Import in	1,20,02,63,861	1,32,78,71,169
Other Expenses in	1,09,66,667	1,48,69,512

Notes to the Financial Statements

for the year ended 31st March, 2020

36. Income in Foreign Currency:

Particulars	2019-20	2018-19
FOB Value of exports in	94,65,58,475	78,88,33,740

37. Research and Development Expenditure:

i. All revenue expenditure on research and development are changed to the profit and Loss Account. Fixed Assets used for research and development are capitalized.

ii. The Company has obtained renewed approval for In-house R&D Facility from the Department of Scientific and Industrial Research (DSIR) vide letter No. TU/IV-RD/4031/2019 dated 01st May 2019 for the purpose of section 35(2AB) of the Income Tax Act, 1961 valid till 31st March 2022 subject to the condition underline therein.

iii. There under, the company has claimed a weighted deduction of 150% of the following expenditure incurred wholly and exclusively for the Research & Development Activity so approved.

Particulars	2019-20	2018-19
Revenue Expenditure:		
Salary Expenses of R&D Personnel	68.00	102.03
R&D Chemical Purchase	117.06	45.42
Stores & Spares & Consumables in R&D	6.01	-
Travelling & Other Exp.	1.04	0.18
Common Utilities Expenses	30.85	23.21
Capital Expenditure:		
Laboratory Equipment	18.03	61.55
Total	**241.00**	**232.39**

38. Figures are rounded off to nearest value of Rupees.

39. On 11th March, 2020, the World Health Organization (WHO) officially declared COVID-19, the disease caused by novel coronavirus, a pandemic. It continued to progress and evolve from the year end till the date of signing of the results of the Company. Due to its nature, it is challenging at this juncture, to predict the full extent and duration of its impact on financial performance and business. However, management is closely monitoring the evolution of this pandemic and has evaluated and re-assessed its impact on all major class of assets, liabilities, income and expenditures which are likely to have significant impact on the operations, profitability and continuity of the business.

Based on above, Management is of the view that till date there is no significant impact of COVID-19 which requires adjustment to the carrying value of its assets and liabilities and provide for losses. Management currently has an appropriate response plan in place. Management will continue to monitor and assess the ongoing development and respond accordingly.

40. Previous year's figures have been regrouped or rearranged wherever necessary.

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CIN: L99999MH1993PLC072892

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OLUMIANT safely and effectively. See full prescribing information for OLUMIANT.

OLUMIANT (baricitinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)**
- **If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)**
- **Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)**

----------INDICATIONS AND USAGE----------

OLUMIANT® is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. (1.1)

Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose of OLUMIANT is 2 mg once daily. (2.1)

OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs. (2.1)

Anemia: Avoid initiation or interrupt OLUMIANT in patients with hemoglobin less than 8 g/dL. (2.2, 2.3, 5.5)

Lymphopenia: Avoid initiation or interrupt OLUMIANT in patients with an Absolute Lymphocyte Count less than 500 cells/mm^3. (2.2, 2.3, 5.5)

Neutropenia: Avoid initiation or interrupt OLUMIANT in patients with an Absolute Neutrophil Count less than 1000 cells/mm^3. (2.2, 2.3, 5.5)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets (not scored): 2 mg (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Serious Infections: Avoid use of OLUMIANT in patients with active, serious infection, including localized infections. If a serious infection develops, interrupt OLUMIANT therapy until the infection is controlled. Do not give OLUMIANT to patients with active tuberculosis. (5.1)
- Thrombosis: Use with caution in patients who may be at increased risk. (5.3)
- Gastrointestinal Perforations: Use with caution in patients who may be at increased risk. (5.4)
- Laboratory Assessment: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. (5.5)
- Vaccinations: Avoid use of OLUMIANT with live vaccines. (5.6)

----------ADVERSE REACTIONS----------

Adverse reactions (greater than or equal to 1%) include: upper respiratory tract infections, nausea, herpes simplex, and herpes zoster. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

OLUMIANT is not recommended in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid). (2.5, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic Impairment: OLUMIANT is not recommended in patients with severe hepatic impairment. (2.4, 8.6)
- Renal Impairment: OLUMIANT is not recommended in patients with moderate or severe renal impairment. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with OLUMIANT are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt OLUMIANT until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before initiating OLUMIANT and during therapy. Treatment for latent infection should be considered prior to OLUMIANT use.**
- **Invasive fungal infections, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with OLUMIANT should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OLUMIANT including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with OLUMIANT *[see Warnings and Precautions (5.2)]*.

THROMBOSIS

Thrombosis, including deep venous thrombosis and pulmonary embolism, has been observed at an increased incidence in patients treated with OLUMIANT compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated. *[See Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

OLUMIANT® (baricitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Rheumatoid Arthritis

The recommended dose of OLUMIANT is 2 mg once daily.

OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs.

OLUMIANT is given orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.2 General Considerations for Administration

- OLUMIANT initiation is not recommended in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, absolute neutrophil count (ANC) less than 1000 cells/mm^3, or hemoglobin level less than 8 g/dL *[see Warnings and Precautions (5.5)]*.
- Avoid use of OLUMIANT in patients with active, serious infection, including localized infections *[see Warnings and Precautions (5.1)]*.

Prior to initiating OLUMIANT, test patients for latent tuberculosis (TB). If positive, consider treating for TB prior to OLUMIANT use *[see Warnings and Precautions (5.1)]*.

2.3 Dose Modifications Due to Serious Infections and Cytopenias

If a patient develops a serious infection, hold treatment with OLUMIANT until the infection is controlled.

Modify dosage in cases of lymphopenia, neutropenia or anemia (Tables 1, 2, and 3). For treatment initiation criteria *[see Dosage and Administration (2.2)]*.

Table 1: Dose Adjustments for Lymphopenia

Low Absolute Lymphocyte Count (ALC)	
Lab Value (cells/mm^3)	Recommendation
ALC greater than or equal to 500	Maintain dose
ALC less than 500	Interrupt OLUMIANT until ALC greater than or equal to 500

Table 2: Dose Adjustments for Neutropenia

Low Absolute Neutrophil Count (ANC)	
Lab Value (cells/mm^3)	Recommendation
ANC greater than or equal to 1000	Maintain dose
ANC less than 1000	Interrupt OLUMIANT until ANC greater than or equal to 1000

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value	
Lab Value (g/dL)	Recommendation
Greater than or equal to 8	Maintain dose
Less than 8	Interrupt OLUMIANT until hemoglobin greater than or equal to 8

2.4 Dose Modifications in Patients with Renal or Hepatic Impairment

- OLUMIANT is not recommended for use in patients with estimated GFR of less than 60 mL/min/1.73 m^2 *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.
- OLUMIANT is not recommended for use in patients with severe hepatic impairment.

2.5 Dose Modifications Due to Drug Interactions

OLUMIANT is not recommended for use in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors, such as probenecid *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

OLUMIANT for oral administration is available as debossed, film-coated, immediate-release tablets:

- 2 mg tablet contains a recessed area on each face of the tablet surface, is light pink, oblong, debossed with "Lilly" on one side and "2" on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving OLUMIANT. The most common serious infections reported with OLUMIANT included pneumonia, herpes zoster, and urinary tract infection *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus, and BK virus were reported with OLUMIANT. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of OLUMIANT in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OLUMIANT in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OLUMIANT. Interrupt OLUMIANT if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with OLUMIANT should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and OLUMIANT should be interrupted if the patient is not responding to therapy. Do not resume OLUMIANT until the infection is controlled.

Tuberculosis

Evaluate and test patients for latent or active infection prior to administration of OLUMIANT. Patients with latent tuberculosis (TB) should be treated with standard antimycobacterial therapy before initiating OLUMIANT.

OLUMIANT should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of OLUMIANT in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection. Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with OLUMIANT. If a patient develops herpes zoster, interrupt OLUMIANT treatment until the episode resolves.

The impact of OLUMIANT on chronic viral hepatitis reactivation is unknown. Patients with evidence of active hepatitis B or C infection were excluded from clinical trials. Patients who were positive for hepatitis C antibody but negative for hepatitis C virus RNA were permitted to enroll. Patients with positive hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were permitted to enroll; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. Should HBV DNA be detected, consult with a hepatologist. Perform screening for viral hepatitis in accordance with clinical guidelines before starting therapy with OLUMIANT.

5.2 Malignancy and Lymphoproliferative Disorders

Consider the risks and benefits of OLUMIANT treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing OLUMIANT in patients who develop a malignancy. Malignancies were observed in clinical studies of OLUMIANT *[see Adverse Reactions (6.1)]*.

Non-melanoma skin cancers

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with OLUMIANT. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

5.3 Thrombosis

Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with OLUMIANT compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with OLUMIANT. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. OLUMIANT should be used with caution in patients who may be at increased risk of thrombosis. If clinical features of DVT/PE or arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

5.4 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with OLUMIANT, although the role of JAK inhibition in these events is not known.

OLUMIANT should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

5.5 Laboratory Abnormalities

Neutropenia – Treatment with OLUMIANT was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3) compared to placebo. Avoid initiation or interrupt OLUMIANT treatment in patients with an ANC less than 1000 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on ANC *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

Lymphopenia – ALC less than 500 cells/mm^3 were reported in OLUMIANT clinical trials. Lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with OLUMIANT, but not placebo.

Avoid initiation or interrupt OLUMIANT treatment in patients with an ALC less than 500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on ALC results *[see Dosage and Administration (2.3)]*.

Anemia – Decreases in hemoglobin levels to less than 8 g/dL were reported in OLUMIANT clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with hemoglobin less than 8 g/dL. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on hemoglobin results *[see Dosage and Administration (2.3)]*.

Liver Enzyme Elevations – Treatment with OLUMIANT was associated with increased incidence of liver enzyme elevation compared to placebo. Increases to greater than or equal to 5x and greater than or equal to 10x upper limit of normal (ULN) were observed for both ALT and AST in patients in OLUMIANT clinical trials.

Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST

are observed and drug-induced liver injury is suspected, interrupt OLUMIANT until this diagnosis is excluded *[see Adverse Reactions (6.1)]*.

Lipid Elevations – Treatment with OLUMIANT was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Assessment of lipid parameters should be performed approximately 12 weeks following OLUMIANT initiation *[see Adverse Reactions (6.1)]*.

Manage patients according to clinical guidelines for the management of hyperlipidemia.

5.6 Vaccinations

Avoid use of live vaccines with OLUMIANT.

Update immunizations in agreement with current immunization guidelines prior to initiating OLUMIANT therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The following data include six randomized double-blind placebo-controlled studies (three Phase 2, three Phase 3) and a long-term extension study. All patients had moderately to severely active RA. Patients were randomized to placebo (1070 patients), OLUMIANT 2 mg (479 patients), or baricitinib 4 mg (997 patients).

Patients could be switched to baricitinib 4 mg from placebo or OLUMIANT 2 mg from as early as Week 12 depending on the study design. All patients initially randomized to placebo were switched to baricitinib 4 mg by Week 24.

During the 16-week treatment period, adverse events leading to discontinuation of treatment were reported by 35 patients (11.4 events per 100 patient-years) treated with placebo, 17 patients (12.1 events per 100 patient-years) with OLUMIANT 2 mg, and 40 patients (13.4 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, adverse events leading to discontinuation of treatment were reported by 31 patients (9.2 events per 100 patient-years) with OLUMIANT 2 mg, and 92 patients (10.2 events per 100 patient-years) treated with baricitinib 4 mg.

Overall Infections – During the 16-week treatment period, infections were reported by 253 patients (82.1 events per 100 patient-years) treated with placebo, 139 patients (99.1 events per 100 patient-years) treated with OLUMIANT 2 mg, and 298 patients (100.1 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, infections were reported by 200 patients (59.6 events per 100 patients-years) treated with OLUMIANT 2 mg, and 500 patients (55.3 events per 100 patient-years) treated with baricitinib 4 mg.

In the 0 to 52 week exposure population, the most commonly reported infections with OLUMIANT were viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, and bronchitis.

Serious Infections – During the 16-week treatment period, serious infections were reported in 13 patients (4.2 events per 100 patient-years) treated with placebo, 5 patients (3.6 events per 100 patient-years) treated with OLUMIANT 2 mg, and 11 patients (3.7 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, serious infections were reported in 14 patients (4.2 events per 100 patient-years) treated with OLUMIANT 2 mg and 32 patients (3.5 events per 100 patient-years) treated with baricitinib 4 mg.

In the 0 to 52 week exposure population, the most commonly reported serious infections with OLUMIANT were pneumonia, herpes zoster, and urinary tract infection *[see Warnings and Precautions (5.1)]*.

Tuberculosis – During the 16-week treatment period, no events of tuberculosis were reported.

During 0 to 52 week exposure, events of tuberculosis were reported in 0 patients treated with OLUMIANT 2 mg and 1 patient (0.1 per 100 patient-years) treated with baricitinib 4 mg *[see Warnings and Precautions (5.1)]*.

Cases of disseminated tuberculosis were also reported.

Opportunistic Infections (excluding tuberculosis) – During the 16-week treatment period, opportunistic infections were reported in 2 patients (0.6 per 100 patient-years) treated with placebo, 0 patients treated with OLUMIANT 2 mg and 2 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, opportunistic infections were reported in 1 patient (0.3 per 100 patient-years) treated with OLUMIANT 2 mg and 5 patients (0.6 per 100 patient-years) treated with baricitinib 4 mg *[see Warnings and Precautions (5.1)]*.

Malignancy – During the 16-week treatment period, malignancies excluding non-melanoma skin cancers (NMSC) were reported in 0 patients treated with placebo, 1 patient (0.7 per 100 patient-years) treated with OLUMIANT 2 mg, and 1 patient (0.3 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, malignancies excluding NMSC were reported in 2 patients (0.6 per 100 patient-years) treated with OLUMIANT 2 mg and 6 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg *[see Warnings and Precautions (5.2)]*.

Venous Thrombosis – During the 16-week treatment period, venous thromboses (deep vein thrombosis or pulmonary embolism) were reported in 0 patients treated with placebo, 0 patients treated with OLUMIANT 2 mg, and 5 patients (1.7 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, venous thromboses were reported in 2 patients (0.6 per 100 patient-years) treated with OLUMIANT 2 mg and 7 patients (0.8 per 100 patient-years) treated with baricitinib 4 mg.

Arterial Thrombosis – During the 16-week treatment period, arterial thromboses were reported in 1 patient treated with placebo (0.3 per 100 patient-years), 2 patients (1.4 per 100 patient-years) treated with OLUMIANT 2 mg, and 2 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, arterial thromboses were reported in 3 patients (0.9 per 100 patient-years) treated with OLUMIANT 2 mg and 3 patients (0.3 per 100 patient-years) treated with baricitinib 4 mg.

Laboratory Abnormalities

Neutropenia – During the 16-week treatment period, neutrophil counts below 1000 cells/mm^3 occurred in 0% of patients treated with placebo, 0.6% of patients treated with OLUMIANT 2 mg, and 0.3% of patients treated with baricitinib 4 mg. There were no neutrophil counts below 500 cells/mm^3 observed in any treatment group *[see Warnings and Precautions (5.1, 5.5)]*.

Platelet Elevations – During the 16-week treatment period, increases in platelet counts above 600,000 cells/mm^3 occurred in 1.1% of patients treated with placebo, 1.1% of patients treated with OLUMIANT 2 mg, and 2.0% of patients treated with baricitinib 4 mg. Mean platelet count increased by 3000 cells/mm^3 at 16 weeks in patients treated with placebo, by 15,000 cells/mm^3 at 16 weeks in patients treated with OLUMIANT 2 mg and by 23,000 cells/mm^3 in patients treated with baricitinib 4 mg.

Liver Enzyme Elevations – Events of increases in liver enzymes greater than or equal to 3x ULN were observed in patients treated with OLUMIANT *[see Warnings and Precautions (5.5)]*.

- During the 16-week treatment period, ALT elevations greater than or equal to 3x ULN occurred in 1.0% of patients treated with placebo, 1.7% of patients treated with OLUMIANT 2 mg, and 1.4% of patients treated with baricitinib 4 mg.
- During the 16-week treatment period, AST elevations greater than or equal to 3x ULN occurred in 0.8% of patients treated with placebo, 1.3% of patients treated with OLUMIANT 2 mg, and 0.8% of patients treated with baricitinib 4 mg.
- In a phase 3 study of DMARD naive patients, during the 24-week treatment period, ALT and AST elevations ≥3x ULN occurred in 1.9% and 0% of patients treated with methotrexate monotherapy, 1.9% and 1.3% of patients treated with baricitinib 4 mg monotherapy, and 4.7% and 1.9% of patients treated with baricitinib 4 mg plus methotrexate.

Lipid Elevations – In controlled clinical trials, OLUMIANT treatment was associated with dose-related increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and remained stable thereafter. During the 12-week treatment period, changes in lipid parameters are summarized below:

- Mean LDL cholesterol increased by 8 mg/dL in patients treated with OLUMIANT 2 mg and by 14 mg/dL in patients treated with baricitinib 4 mg.
- Mean HDL cholesterol increased by 7 mg/dL in patients treated with OLUMIANT 2 mg and by 9 mg/dL in patients treated with baricitinib 4 mg.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 7 mg/dL in patients treated with OLUMIANT 2 mg and by 15 mg/dL in patients treated with baricitinib 4 mg.

[See Warnings and Precautions (5.5)].

Creatine Phosphokinase (CPK) – OLUMIANT treatment was associated with increases in CPK within one week of starting OLUMIANT and plateauing after 8 to 12 weeks. At 16 weeks, the mean change in CPK for OLUMIANT 2 mg and baricitinib 4 mg was 37 IU/L and 52 IU/L, respectively.

Creatinine – In controlled clinical trials, dose-related increases in serum creatinine were observed with OLUMIANT treatment. At 52 weeks, the mean increase in serum creatinine was less than 0.1 mg/dL with baricitinib 4 mg. The clinical significance of the observed serum creatinine increases is unknown.

Other Adverse Reactions

Other adverse reactions are summarized in Table 4.

Table 4: Adverse Reactions occurring in greater than or equal to 1% of OLUMIANT 2 mg and Baricitinib 4 mg Treated Patients in Placebo-Controlled Trials

Events	Weeks 0-16		
	Placebo n=1070 (%)	OLUMIANT 2 mg n=479 (%)	Baricitinib 4 mg n=997 (%)
Upper respiratory tract infections[a]	11.7	16.3	14.7
Nausea	1.6	2.7	2.8
Herpes simplex[b]	0.7	0.8	1.8
Herpes zoster	0.4	1.0	1.4

[a] Includes acute sinusitis, acute tonsillitis, chronic tonsillitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinobronchitis, sinusitis, tonsillitis, tracheitis, and upper respiratory tract infection.

[b] Includes eczema herpeticum, genital herpes, herpes simplex, ophthalmic herpes simplex, and oral herpes.

Additional adverse drug reactions occurring in fewer than 1% of patients: acne.

7 DRUG INTERACTIONS

7.1 Strong OAT3 Inhibitors

Baricitinib exposure is increased when OLUMIANT is co-administered with strong OAT3 inhibitors (such as probenecid) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

7.2 Other JAK Inhibitors or Biologic DMARDs

OLUMIANT has not been studied in combination with other JAK inhibitors or with biologic DMARDs *[see Indications and Usage (1.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data on use of OLUMIANT in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. In animal embryo-fetal development studies, oral baricitinib administration to pregnant rats and rabbits at exposures equal to and greater than approximately 20 and 84 times the maximum recommended human dose (MRHD), respectively, resulted in reduced fetal body weights, increased embryolethality (rabbits only), and dose-related increases in skeletal malformations. No developmental toxicity was observed in pregnant rats and rabbits treated with oral baricitinib during organogenesis at approximately 5 and 13 times the exposure at the MRHD, respectively. In a pre- and post-natal development study in pregnant female rats, oral baricitinib administration at exposures approximately 43 times the MRHD resulted in reduction in pup viability (increased incidence of stillborn pups and early neonatal deaths), decreased fetal birth weight, reduced fetal body weight gain, decreased cytotoxic T cells on post-natal day (PND) 35 with evidence of recovery by PND 65, and developmental delays that might be attributable to decreased body weight gain. No developmental toxicity was observed at an exposure approximately 9 times the exposure at the MRHD [*see* Animal Data].

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryofetal development study in pregnant rats, dosed orally during the period of organogenesis from gestation days 6 to 17, baricitinib was teratogenic (skeletal malformations that consisted of bent limb bones and rib anomalies) at exposures equal to or greater than approximately 20 times the MRHD (on an AUC basis at maternal oral doses of 10 mg/kg/day and higher). No developmental toxicity was observed in rats at an exposure approximately 5 times the MRHD (on an AUC basis at a maternal oral dose of 2 mg/kg/day).

In an embryofetal development study in pregnant rabbits, dosed orally during the period of organogenesis from gestation days 7 to 20, embryolethality, decreased fetal body weights, and skeletal malformations (rib anomalies) were observed in the presence of maternal toxicity at an exposure approximately 84 times the MRHD (on an AUC basis at a maternal oral dose of 30 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both early and late resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 12 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In a pre- and post-natal development study in pregnant female rats dosed orally from gestation day 6 through lactation day 20, adverse findings observed in pups included decreased survival from birth to post-natal day 4 (due to increased stillbirths and early neonatal deaths), decreased birth weight, decreased body weight gain during the pre-weaning phase, increased incidence of malrotated forelimbs during the pre-weaning phase, and decreased cytotoxic T cells on PND 35 with recovery by PND 65 at exposures approximately 43 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Developmental delays (that may be secondary to decreased body weight gain) were observed in males and females at exposures approximately 43 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). These findings included decreased forelimb and hindlimb grip strengths, and delayed mean age of sexual maturity. No developmental toxicity was observed in rats at an exposure approximately 9 times the MRHD (on an AUC basis at a maternal oral dose of 5 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of OLUMIANT in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Baricitinib is present in the milk of lactating rats. Due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear. Because of the potential for serious adverse reactions in nursing infants, advise an OLUMIANT-treated woman not to breastfeed.

Data

A single oral dose of 25 mg/kg radiolabeled baricitinib was administered to lactating female Sprague-Dawley rats on post-partum day 13. Drug exposure was approximately 45-fold greater in milk than in plasma based on AUC_{0-t} values.

8.4 Pediatric Use

The safety and effectiveness of OLUMIANT in pediatric patients have not been established.

8.5 Geriatric Use

Of the 3100 patients treated in the four phase 3 studies, a total of 537 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

OLUMIANT is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. *[See Dosing and Administration (2.4)]*.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Renal function was found to significantly affect baricitinib exposure. OLUMIANT is not recommended for use in patients with estimated GFR of less than 60 mL/min/1.73 m^2 *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

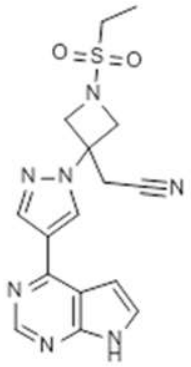
10 OVERDOSAGE

Single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in clinical trials without dose-limiting toxicity. Pharmacokinetic data of a single dose of 40 mg in healthy volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 24 hours.

In case of an overdose, it is recommended that the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

11 DESCRIPTION

OLUMIANT (baricitinib) is a Janus kinase (JAK) inhibitor with the chemical name {1-(ethylsulfonyl)-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile. Baricitinib has an empirical formula of $C_{16}H_{17}N_7O_2S$ and a molecular weight of 371.42. Baricitinib has the following structural formula:



OLUMIANT tablets contain a recessed area on each face of the tablet surface and are available for oral administration as debossed, film-coated, immediate-release tablets. The 2 mg tablet is light pink, oblong, debossed with "Lilly" on one side and "2" on the other.

Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Baricitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In cell-free isolated enzyme assays, baricitinib had greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3. In human leukocytes, baricitinib inhibited cytokine induced STAT phosphorylation mediated by JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, or JAK2/TYK2 with comparable potencies. However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

12.2 Pharmacodynamics

Baricitinib inhibition of IL-6 induced STAT3 phosphorylation – Baricitinib administration resulted in a dose dependent inhibition of IL-6 induced STAT3 phosphorylation in whole blood from healthy subjects with maximal inhibition observed approximately 1 hour after dosing, which returned to near baseline by 24 hours. Similar levels of inhibition were observed using either IL-6 or TPO as the stimulus.

Immunoglobulins – Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment with OLUMIANT, and remained stable through at least 52 weeks. For most patients, changes in immunoglobulins occurred within the normal reference range.

C-reactive protein – In patients with rheumatoid arthritis, decreases in serum C-reactive protein (CRP) were observed as early as one week after starting treatment with OLUMIANT and were maintained throughout dosing.

Cardiac Electrophysiology – At a dose 10 times the maximum recommended dose, baricitinib does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Following oral administration of OLUMIANT, peak plasma concentrations are reached approximately at 1 hour. A dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The pharmacokinetics of baricitinib do not change over time. Steady-state concentrations are achieved in 2 to 3 days with minimal accumulation after once-daily administration.

Absorption – The absolute bioavailability of baricitinib is approximately 80%. An assessment of food effects in healthy subjects showed that a high-fat meal decreased the mean AUC and C_{max} of baricitinib by approximately 11% and 18%, respectively, and delayed the t_{max} by 0.5 hours. Administration with meals is not associated with a clinically relevant effect on exposure. In clinical studies, OLUMIANT was administered without regard to meals.

Distribution – After intravenous administration, the volume of distribution is 76 L, indicating distribution of baricitinib into tissues. Baricitinib is approximately 50% bound to plasma proteins and 45% bound to serum proteins. Baricitinib is a substrate of the Pgp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug distribution.

Elimination – The total body clearance of baricitinib is 8.9 L/h in patients with RA. Elimination half-life in patients with rheumatoid arthritis is approximately 12 hours.

Metabolism – Approximately 6% of the orally administered baricitinib dose is identified as metabolites (three from urine and one from feces), with CYP3A4 identified as the main metabolizing enzyme. No metabolites of baricitinib were quantifiable in plasma.

Excretion – Renal elimination is the principal clearance mechanism for baricitinib through filtration and active secretion as baricitinib is identified as a substrate of OAT3, Pgp, BCRP and MATE2-K from *in vitro* studies. In a clinical pharmacology study, approximately 75% of the administered dose was eliminated in the urine, while about 20% of the dose was eliminated in the feces. Baricitinib was excreted predominately as unchanged drug in urine (69%) and feces (15%).

Specific Populations

Effects of Body Weight, Gender, Race, and Age

Body weight, gender, race, ethnicity, and age did not have a clinically relevant effect on the PK (AUC and C_{max}) of baricitinib (Figure 1). The mean effects of intrinsic factors on PK parameters (AUC and C_{max}) were generally within the inter-subject PK variability of baricitinib. The inter-subject variabilities (% coefficients of variation) in AUC and C_{max} of baricitinib are approximately 41% and 22%, respectively. *[See Use in Specific Populations (8.5)]*.

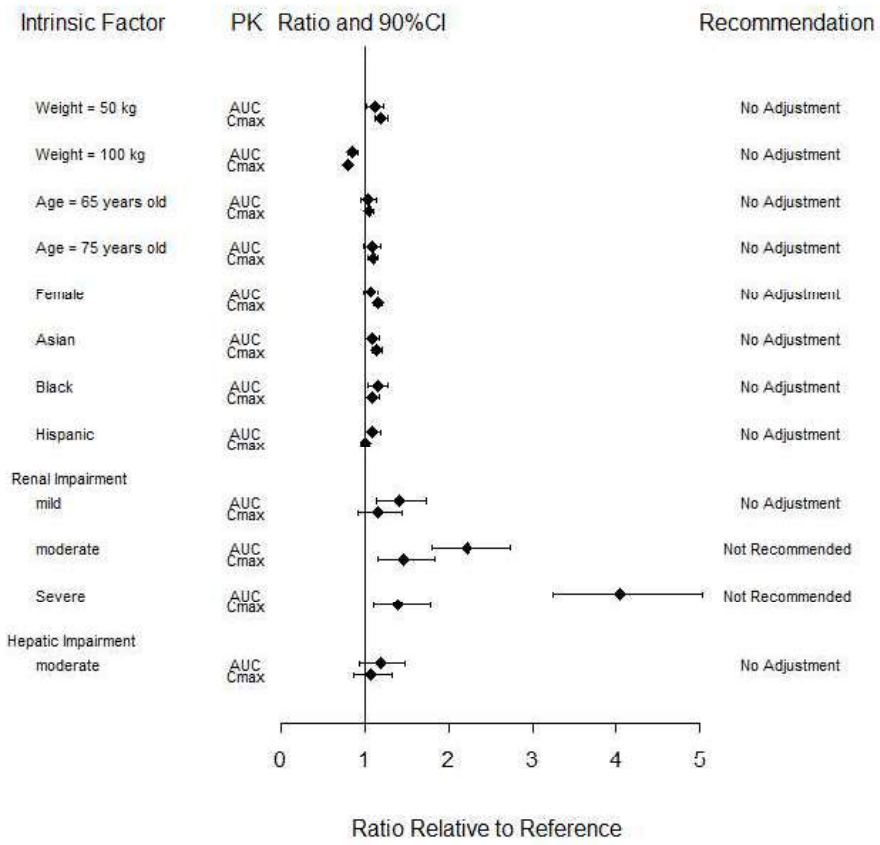
Renal Impairment

Baricitinib systemic exposure in AUC was increased by 1.41-, 2.22-, 4.05- and 2.41-fold for mild, moderate, severe, and ESRD (with hemodialysis) renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in C_{max} were 1.16-, 1.46-, 1.40- and 0.88-fold, respectively (Figure 1) *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment

Baricitinib systemic exposure and C_{max} increased by 1.19- and 1.08-fold for the moderate hepatic impairment group, respectively, compared to subjects with normal hepatic function (Figure 1) *[see Use in Specific Populations (8.6)]*.

Figure 1: Impact of Intrinsic Factors on Baricitinib Pharmacokinetics[a,b]



[a] Reference values for weight, age, gender, and race comparisons are 70 kg, 54 years, male, and white, respectively; reference groups for renal and hepatic impairment are subjects with normal renal and hepatic function, respectively.

[b] Effects of renal and hepatic impairment on baricitinib exposure were summarized from dedicated renal and hepatic impairment studies, respectively. Effects of other intrinsic factors on baricitinib exposure were summarized from population PK analysis.

Drug Interactions

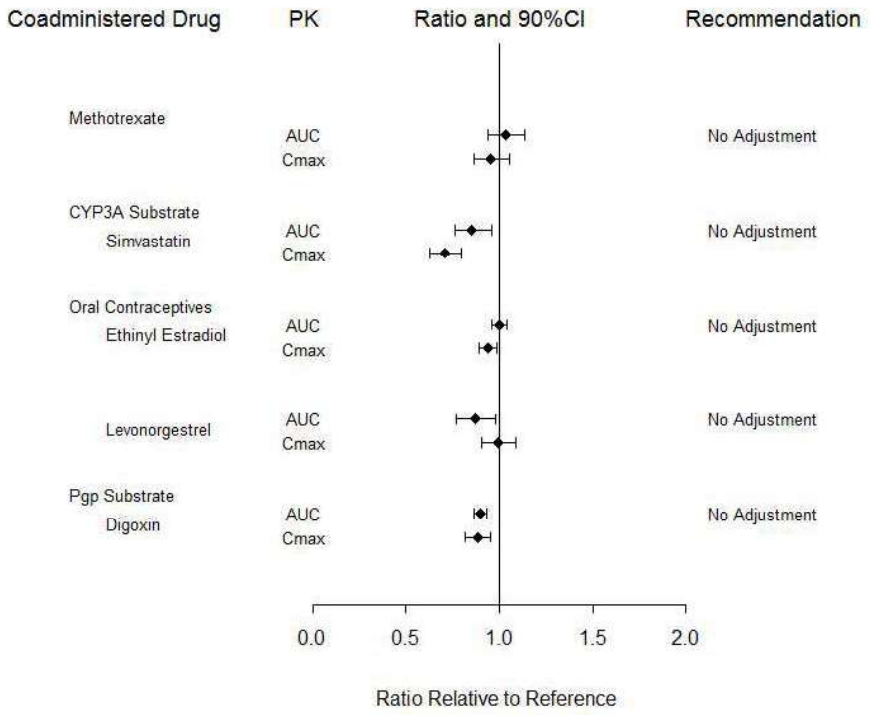
Potential for Baricitinib to Influence the PK of Other Drugs

In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies, there were no clinically meaningful changes in the pharmacokinetics (PK) of simvastatin, ethinyl estradiol, or levonorgestrel (CYP3A substrates) when co-administered with baricitinib.

In vitro studies suggest that baricitinib is not an inhibitor of the transporters, P-glycoprotein (Pgp) or Organic Anion Transporting Polypeptide (OATP) 1B1. *In vitro* data indicate baricitinib does inhibit organic anionic transporter (OAT) 1, OAT2, OAT3, organic cationic transporter (OCT) 1, OCT2, OATP1B3, Breast Cancer Resistance Protein (BCRP) and Multidrug and Toxic Extrusion Protein (MATE) 1 and MATE2-K, but clinically meaningful changes in the pharmacokinetics of drugs that are substrates for these transporters are unlikely. In clinical pharmacology studies there were no clinically meaningful effects on the PK of digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib.

Exposure changes of drugs following co-administration with baricitinib are shown in Figure 2.

Figure 2: Impact of Baricitinib on the Pharmacokinetics of Other Drugs[a]



[a] Reference group is administration of concomitant drug alone.

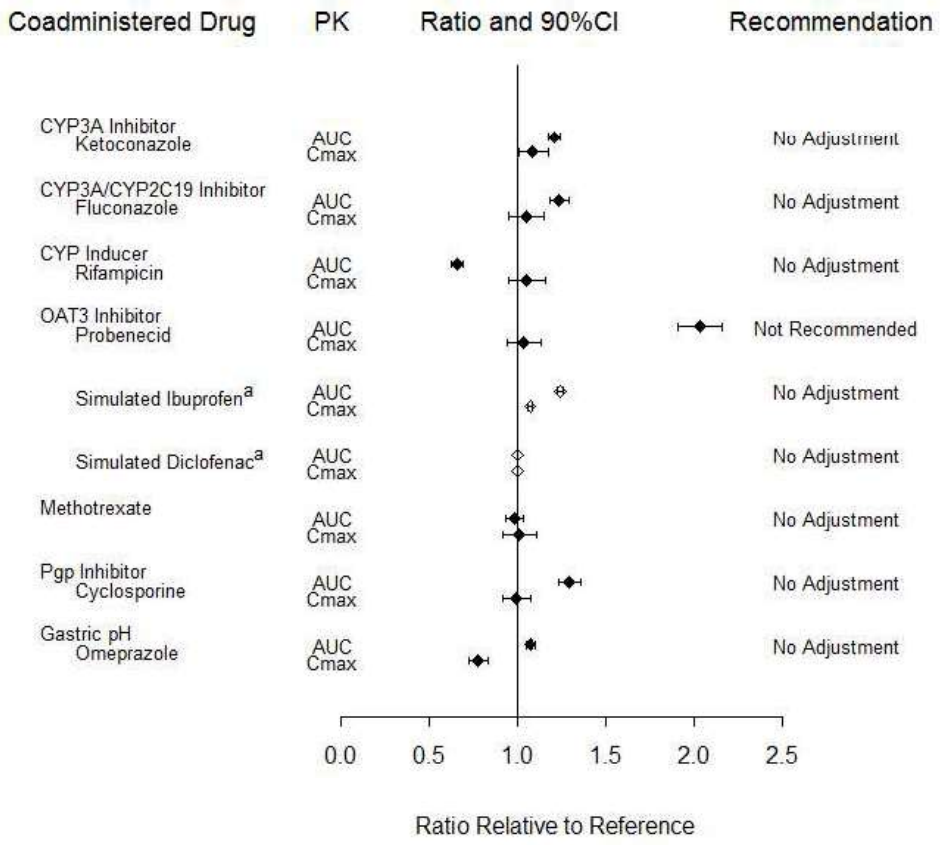
Potential for Other Drugs to Influence the PK of Baricitinib

In vitro studies suggest that baricitinib is a CYP3A4 substrate. In clinical pharmacology studies there was no effect on the PK of baricitinib when co-administered with ketoconazole (CYP3A inhibitor). There were no clinically meaningful changes in the PK of baricitinib when co-administered with fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (CYP3A inducer).

In vitro studies suggest that baricitinib is a substrate for OAT3, Pgp, BCRP and MATE2-K. In a clinical study, probenecid administration (strong OAT3 inhibitor) resulted in an approximately 2-fold increase in baricitinib $AUC_{0-\infty}$ with no effect on C_{max} and t_{max} *[see Dosage and Administration (2.5) and Drug Interactions (7.1)]*. However, simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on the PK of baricitinib. In clinical pharmacology studies there was no clinically meaningful effect on the PK of baricitinib when co-administered with cyclosporine (Pgp and BCRP inhibitor). Co-administration with methotrexate (substrate of several transporters) did not have a clinically meaningful effect on the PK of baricitinib.

Exposure changes of baricitinib following co-administration with CYP inhibitors or inducers, transporter inhibitors, as well as methotrexate and the proton pump inhibitor, omeprazole, are shown in Figure 3.

Figure 3: Impact of Other Drugs on the Pharmacokinetics of Baricitinib[b]



[a] Values are based on simulated studies.
[b] Reference group is administration of baricitinib alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of baricitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received baricitinib for 91 to 94 weeks at oral doses up to 8 or 25 mg/kg/day, respectively (approximately 12 and 55 times the MRHD on an AUC basis). No evidence of tumorigenicity was observed in Tg.rasH2 mice that received baricitinib for 26 weeks at oral doses up to 300 and 150 mg/kg/day in male and female mice, respectively.

Baricitinib tested negative in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Fertility (achievement of pregnancy) was reduced in male and female rats that received baricitinib at oral doses of 50 and 100 mg/kg/day respectively (approximately 113 and 169 times the MRHD in males and females, respectively, on an AUC basis) based upon findings that 7 of 19 (36.8%) drug-treated females with evidence of mating were not gravid compared to 1 of 19 (5.3%) control females. It could not be determined from the study design if these findings were attributable to toxicities in one sex or both. Fertility was unaffected in male and female rats at oral doses of 15 mg/kg and 25 mg/kg, respectively (approximately 25 and 48 times the MRHD on an AUC basis). However, maintenance of pregnancy was adversely affected at these doses based upon findings of increased post-implantation losses (early resorptions) and decreased numbers of mean viable embryos per litter. The number of viable embryos was unaffected in female rats that received baricitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 8 times the MRHD on an AUC basis). Reproductive performance was unaffected in male and female rats that received baricitinib at oral doses up to 50 and 100 mg/kg/day respectively (approximately 113 and 169 times the MRHD in males and females, respectively, on an AUC basis).

14 CLINICAL STUDIES

The OLUMIANT clinical development program included two dose-ranging trials and four confirmatory phase 3 trials. Although other doses have been studied, the recommended dose of OLUMIANT is 2 mg once daily.

Dose-Ranging Studies

The dose-ranging studies I (NCT01185353) and II (NCT01469013) included a 12-week randomized comparison of baricitinib 1, 2, 4, and 8 mg versus placebo in 301 and 145 patients, respectively.

The results from the dose-ranging studies are shown in Table 5. In dose-ranging Study I, the observed ACR response was similar for baricitinib 1 and 2 mg daily and for baricitinib 4 and 8 mg daily, with the highest response for baricitinib 8 mg daily. In dose-ranging Study II, there was not a clear trend of dose response, with similar response rates for 1 mg and 4 mg and 2 mg and 8 mg.

Table 5: Proportion of Patients with ACR20 Response at Week 12 in Dose-Ranging Studies

	% ACR20 Responders				
Dose-Ranging Study	**Placebo**	**Baricitinib 1 mg daily**	**Baricitinib 2 mg daily**	**Baricitinib 4 mg daily**	**Baricitinib 8 mg daily**
I (N=301)	41	57	54	75	78
II (N=145)	31	67	83	67	88

Confirmatory Studies

The efficacy and safety of OLUMIANT 2 mg once daily was assessed in two confirmatory phase 3 trials. These trials were randomized, double-blind, multicenter studies in patients with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism 2010 criteria. Patients over 18 years of age were eligible if at least 6 tender and 6 swollen joints were present at baseline. The two studies (Studies III and IV) evaluated OLUMIANT 2 mg and baricitinib 4 mg.

Study III (NCT01721057) was a 24-week trial in 684 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to conventional DMARDs (cDMARDs). Patients received OLUMIANT 2 mg or 4 mg once daily or placebo added to existing background cDMARD treatment. From Week 16, non-responding patients could be rescued to receive baricitinib 4 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Study IV (NCT01721044) was a 24-week trial in 527 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to 1 or more TNF inhibitor therapies with or without other biologic DMARDs (TNFi-IR). Patients received OLUMIANT 2 mg or baricitinib 4 mg once daily or placebo added to background cDMARD treatment. From Week 16, non-responding patients could be rescued to receive baricitinib 4 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Clinical Response

The percentages of OLUMIANT-treated patients achieving ACR20, ACR50, and ACR70 responses, and Disease Activity Score (DAS28-CRP) <2.6 in Studies III and IV are shown in Table 6.

Patients treated with OLUMIANT had higher rates of ACR response and DAS28-CRP <2.6 versus placebo-treated patients at Week 12 (Studies III and IV) (Table 6).

In Study IV, higher ACR20 response rates (Figure 4) were observed as early as 1 week with OLUMIANT 2 mg versus placebo.

In Study IV, the proportions of patients achieving DAS28-CRP <2.6 who had at least 3 active joints at the end of Week 24 were 18.2% and 10.5%, in the placebo and OLUMIANT 2 mg arms, respectively.

Table 6: Clinical Response[a]

	Percent of Patients			
	cDMARD-IR		**TNFi-IR**	
	Study III		**Study IV**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/day + cDMARDs** Δ **(95% CI)[b]**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/day + cDMARDs** Δ **(95% CI)[b]**
N	**228**	**229**	**176**	**174**
ACR 20				
Week 12 %	39	66 27 (18, 35)	27	49 22 (12, 32)
Week 24 %	42	61 19 (10, 28)	27	45 18 (8, 27)
ACR 50				

Week 12 %	13	34 21 (13, 28)	8	20 12 (5, 19)
Week 24 %	21	41 20 (12, 28)	13	23 10 (2, 18)
ACR 70				
Week 12 %	3	18 15 (9, 20)	2	13 11 (5, 16)
Week 24 %	8	25 17 (11, 24)	3	13 10 (4, 16)
DAS28-CRP<2.6				
Week 12 %	9	26 (10, 24)	4	11 (2, 12)
Week 24 %	11	31 (13, 27)	6	11 (-1, 11)

[a] Patients who were rescued or discontinued treatment were considered as non-responders in the analyses.
[b] 95% confidence interval for the difference (Δ) in response rate between OLUMIANT treatment and placebo (Study III, Study IV).

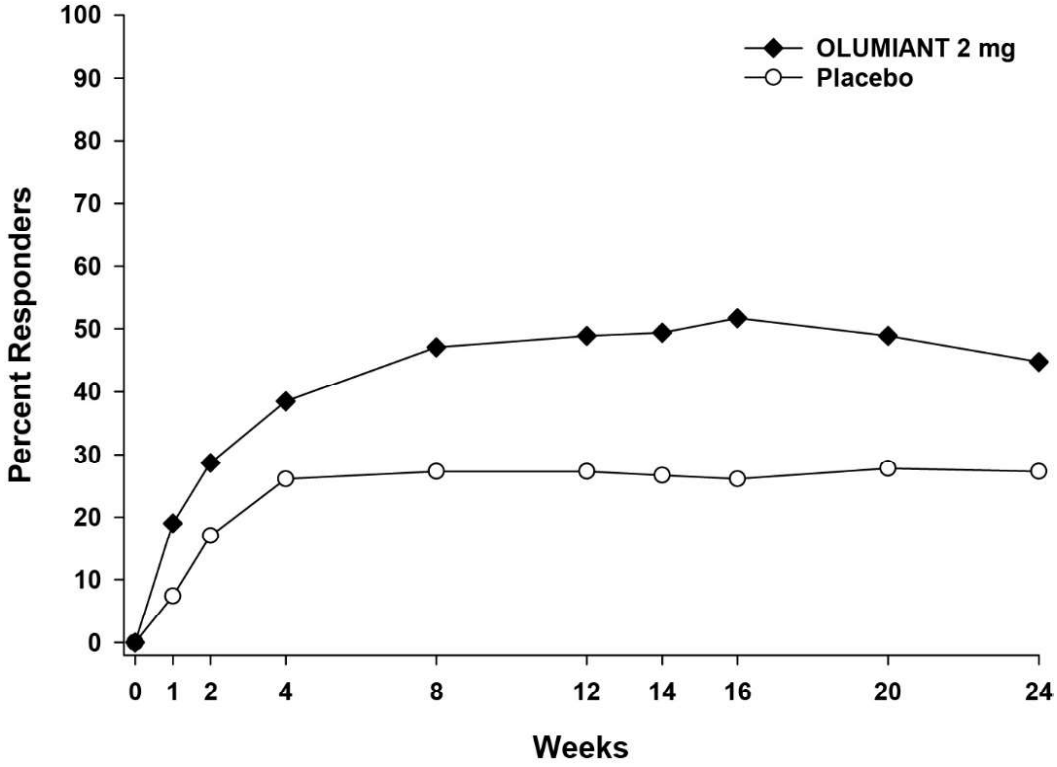
The effects of OLUMIANT treatment on the components of the ACR response criteria for Studies III and IV are shown in Table 7.

Table 7: Components of ACR Response at Week 12 in Studies III and IV[a]

	cDMARD-IR		**TNFi-IR**	
	Study III		**Study IV**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/day + cDMARDs**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/day + cDMARDs**
N	**228**	**229**	**176**	**174**
Number of Tender Joints (0-68)				
Baseline	24 (15)	24 (14)	28 (16)	31 (16)
Week 12	15 (14)	11 (13)	20 (16)	19 (18)
Number of Swollen Joints (0-66)				
Baseline	13 (7)	14 (9)	17 (11)	19 (12)
Week 12	8 (8)	5 (6)	12 (10)	10 (12)
Pain[b]				
Baseline	57 (23)	60 (21)	65 (19)	62 (22)
Week 12	43 (24)	34 (25)	55 (25)	46 (28)
Patient Global Assessment[b]				
Baseline	60 (21)	62 (20)	66 (19)	67 (19)
Week 12	44 (23)	36 (25)	56 (25)	46 (26)
Physician Global Assessment[b]				
Baseline	62 (17)	64 (17)	67 (19)	67 (17)
Week 12	41 (24)	33 (22)	50 (26)	36 (24)
Disability Index (HAQ-DI)[c]				
Baseline	1.50 (0.60)	1.51 (0.62)	1.78 (0.57)	1.71 (0.55)
Week 12	1.17 (0.62)	0.96 (0.69)	1.59 (0.68)	1.31 (0.72)
hsCRP (mg/L)				
Baseline	17.7 (20.4)	18.2 (21.5)	20.6 (25.3)	19.9 (22.5)
Week 12	17.2 (19.3)	8.6 (14.6)	19.9 (23.0)	13.5 (20.1)

[a] Data shown are mean (standard deviation).
[b] Visual analog scale: 0=best, 100=worst.
[c] Health Assessment Questionnaire–Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Figure 4: Percent of Patients Achieving ACR20



Physical Function Response

Improvement in physical function was measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). Patients receiving OLUMIANT 2 mg demonstrated greater improvement from baseline in physical functioning compared to placebo at Week 24. The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 24 was -0.24 (-0.35, -0.14) in Study III and -0.23 (-0.35, -0.12) in Study IV.

Other Health Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In Studies III and IV, compared to placebo, patients treated with OLUMIANT 2 mg demonstrated greater improvement from baseline in the physical component summary (PCS) score and the physical function, role physical, bodily pain, vitality, and general health domains at Week 12, with no consistent improvements in the mental component summary (MCS) scores or the role emotional, mental health, and social functioning domains.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

OLUMIANT for oral administration is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface.

OLUMIANT Tablets	2 mg
Color	Light Pink
Shape	Oblong
Identification	Lilly 2
NDC Code:	

Bottle of 30	0002-4182-30

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Patient Counseling

Advise patients of the potential benefits and risks of OLUMIANT.

Infections

Inform patients that they may be more likely to develop infections when taking OLUMIANT. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that the risk of herpes zoster is increased in patients treated with OLUMIANT and some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies and Lymphoproliferative Disorders

Inform patients that OLUMIANT may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking OLUMIANT. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions (5.2)]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with OLUMIANT. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.3)]*.

Laboratory Abnormalities

Inform patients that OLUMIANT may affect certain lab tests, and that blood tests are required before and during OLUMIANT treatment *[see Warnings and Precautions (5.5)]*.

Lactation

Advise a woman not to breastfeed during treatment with OLUMIANT *[see Use in Specific Populations (8.2)]*.

Literature issued Month dd, yyyy

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www.olumiant.com

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BAR-A10.0-NL0000-USPI-YYYYMMDD

MEDICATION GUIDE
OLUMIANT® (O-loo-me-ant)
(baricitinib)
tablets, for oral use

What is the most important information I should know about OLUMIANT?
OLUMIANT may cause serious side effects, including:

1. **Serious infections.**
   OLUMIANT is a medicine that affects your immune system. OLUMIANT can lower the ability of your immune system to fight infections. Some people have had serious infections while taking OLUMIANT, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.
   - Your healthcare provider should test you for TB before starting treatment with OLUMIANT.
   - Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with OLUMIANT.

   You should not start taking OLUMIANT if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles.
   Before starting OLUMIANT, tell your healthcare provider if you:
   - are being treated for an infection.
   - have an infection that does not go away or that keeps coming back.
   - have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
   - have TB or have been in close contact with someone with TB.
   - have had hepatitis B or C.
   - live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use OLUMIANT. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
   - think you have an infection or have symptoms of an infection such as:
     - fever, sweating, or chills
     - shortness of breath
     - warm, red, or painful skin or sores on your body
     - feeling tired
     - muscle aches
     - blood in your phlegm
     - diarrhea or stomach pain
     - cough
     - weight loss
     - burning when you urinate or urinating more often than normal

   After starting OLUMIANT, call your healthcare provider right away if you have any symptoms of an infection. OLUMIANT can make you more likely to get infections or make worse any infection that you have.
2. **Cancer and immune system problems.**
   OLUMIANT may increase your risk of certain cancers by changing the way your immune system works.
   - Lymphoma and other cancers including skin cancers can happen in people taking OLUMIANT. Tell your healthcare provider if you have ever had any type of cancer.
3. **Blood Clots.**
   Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) can happen in some people taking OLUMIANT. This may be life-threatening and cause death.
   - Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
   - Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with OLUMIANT, including: swelling, pain or tenderness in the leg, sudden unexplained chest pain, or shortness of breath.
4. **Tears (perforation) in the stomach or intestines.**
   - Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking OLUMIANT can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
   - Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.
5. **Changes in certain laboratory test results.**
   Your healthcare provider should do blood tests before you start taking OLUMIANT and while you take OLUMIANT to check for the following:
   - **low lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
   - **low neutrophil counts.** Neutrophils are white blood cells that help the body fight off infections.
   - **low red blood cell counts.** This may mean that you have anemia, which may make you feel weak and tired.

   Your healthcare provider should routinely check certain liver tests.
   You should not receive OLUMIANT if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.
   Your healthcare provider may stop your OLUMIANT treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels approximately 12 weeks after you start taking OLUMIANT, and as needed after that. Normal cholesterol levels are important to good heart health.

See "**What are the possible side effects of OLUMIANT?**" for more information about side effects.

What is OLUMIANT?

- OLUMIANT is a prescription medicine used to treat adult patients with moderately to severely active rheumatoid arthritis after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used, and did not work well enough or could not be tolerated.
- It is not known if OLUMIANT is safe and effective in children.

Before taking OLUMIANT, tell your healthcare provider about all your medical conditions, including if you:

- See "**What is the most important information I should know about OLUMIANT?**"
- have an infection.
- have kidney problems.
- have liver problems.
- have low red or white blood cell counts.
- have recently received or are scheduled to receive a vaccine. People who take OLUMIANT should not receive live vaccines.
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- are pregnant or plan to become pregnant. It is not known if OLUMIANT will harm an unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if OLUMIANT passes into your breast milk. You and your healthcare provider should decide if you will take OLUMIANT or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. OLUMIANT and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a medicine called probenecid.
- any other medicines to treat your rheumatoid arthritis. For example, you should not take tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab pegol (Cimzia®), golimumab (Simponi®), tofacitinib (Xeljanz®, Xeljanz® XR), sarilumab (Kevzara®), azathioprine or cyclosporine while you are taking OLUMIANT. Taking OLUMIANT with these medicines may increase your risk of infection.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take OLUMIANT?

- Take OLUMIANT exactly as your healthcare provider tells you to take it.
- Take OLUMIANT 1 time a day with or without food.

What are the possible side effects of OLUMIANT?

OLUMIANT can cause serious side effects including:

- See "**What is the most important information I should know about OLUMIANT?**"

Common side effects of OLUMIANT include (these are not all of the possible side effects of OLUMIANT):

- upper respiratory tract infections (common cold, sinus infections)
- nausea
- cold sores
- shingles

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OLUMIANT?

Store OLUMIANT at room temperature between 68°F to 77°F (20°C to 25°C).

Keep OLUMIANT and all medicines out of the reach of children.

General Information about the safe and effective use of OLUMIANT.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OLUMIANT for a condition for which it was not prescribed. Do not give OLUMIANT to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about OLUMIANT that is written for health professionals.

What are the ingredients in OLUMIANT?

Active ingredient: baricitinib

Inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

OLUMIANT is a registered trademark of Eli Lilly and Company.

Marketed by: Lilly USA, LLC Indianapolis, IN 46285, USA

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For more information, call 1-800-545-5979 or go to the following website: www.olumiant.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 05/2018

BAR-A3.0-0000-MG-YYYYMMDD

Baricitinib as potential treatment for 2019-nCoV acute respiratory disease

Given the scale and rapid spread of the 2019 novel coronavirus (2019-nCoV) acute respiratory disease, there is an immediate need for medicines that can help before a vaccine can be produced. Results of rapid sequencing of 2019-nCoV, coupled with molecular modelling based on the genomes of related virus proteins,[1] have suggested a few compounds that are likely to be effective, including the anti-HIV lopinavir plus ritonavir combination.

BenevolentAI's knowledge graph is a large repository of structured medical information, including numerous connections extracted from scientific literature by machine learning.[2] Together with customisations bespoke to 2019-nCoV, we used BenevolentAI to search for approved drugs that could help, focusing on those that might block the viral infection process. We identified baricitinib, which is predicted to reduce the ability of the virus to infect lung cells.

Most viruses enter cells through receptor-mediated endocytosis. The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells (figure). These AT2 cells are particularly prone to viral infection.[3] One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles.[4]

Of 378 AAK1 inhibitors in the knowledge graph, 47 have been approved for medical use and six inhibited AAK1 with high affinity. These included a number of oncology drugs such as sunitinib and erlotinib, both of which have been shown to inhibit viral infection of cells through the inhibition of AAK1.[5] However, these compounds bring serious side-effects, and our data infer high doses to inhibit AAK1 effectively. We do not consider these drugs would be a safe therapy for a population of sick and infected people.

By contrast, one of the six high-affinity AAK1-binding drugs was the janus kinase inhibitor baricitinib, which also binds the cyclin G-associated kinase, another regulator of endocytosis.[6] Because the plasma concentration of baricitinib on therapeutic dosing (either as 2 mg or 4 mg once daily) is sufficient to inhibit AAK1, we suggest it could be trialled, using an appropriate patient population with 2019-nCoV acute respiratory disease, to reduce both the viral entry and the inflammation in patients, using endpoints such as the MuLBSTA score, an early warning model for predicting mortality in viral pneumonia.[7]

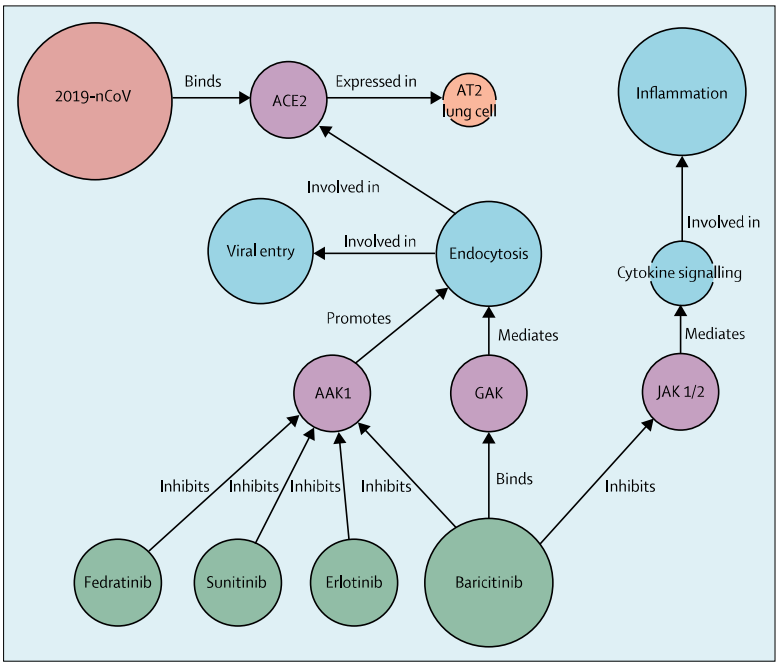


Figure: **The BenevolentAI knowledge graph**
The BenevolentAI knowledge graph integrates biomedical data from structured and unstructured sources. It is queried by a fleet of algorithms to identify new relationships to suggest new ways of tackling disease. 2019-nCoV=2019 novel coronavirus. AAK1=AP2-associated protein kinase 1. GAK=cyclin G-associated kinase. JAK1/2=janus kinase 1/2.

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAI, and has consulted with Lansdowne partners, Vitruvian, and Social Impact Capital; he now sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. All other authors are employees of BenevolentAI. Events in relation to the 2019-nCoV outbreak are evolving rapidly, and we make our initial thoughts available in this Correspondence in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.

*Peter Richardson, Ivan Griffin, Catherine Tucker, Dan Smith, Olly Oechsle, Anne Phelan, Michael Rawling, Edward Savory, *Justin Stebbing*
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ANNEXURE-6

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COVID-19: combining antiviral and anti-inflammatory treatments

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Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms.[1,2] In our previous Correspondence to *The Lancet*,[3] we described how BenevolentAI's proprietary artificial intelligence (AI)-derived knowledge graph,[4] queried by a suite of algorithms, enabled identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). We identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells (appendix). The drug targets are members of the numb-associated kinase (NAK) family—including AAK1 and GAK—the inhibition of which has been shown to reduce viral infection in vitro.[5,6] Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis. We suggested that this drug could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing.

See Online for appendix

To take this work further in a short timescale, a necessity when dealing with a new human pathogen, we re-examined the affinity and selectivity of all the approved drugs in our knowledge graph to identify those with both antiviral and anti-inflammatory properties. Such drugs are predicted to be of particular importance in the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality. Comparison of the properties of the three best candidates are shown in the table. Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK–STAT signalling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19.[7] Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.[7] The most significant side-effect seen over 4214 patient-years in the clinical trial programmes used for European Medicines Agency registration was a small increase in upper respiratory tract infections (similar to that observed with methotrexate), but the incidence of serious infections (eg, herpes zoster) over 52 weeks' dosing was small (3·2 per 100 patient-years), and similar to placebo.[7] Use of this agent in patients with COVID-19 over 7–14 days, for example, suggests side-effects would be trivial.

Other AI-algorithm-predicted NAK inhibitors include a combination of the oncology drugs sunitinib and

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	400
Affinity and efficacy: K_d or IC_{50}, nM*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

See regulatory approval documents for further information on these drugs. K_d=dissociation constant. IC_{50}=half-maximal inhibitory concentration. C_{max}=maximum serum concentration. *All values are IC_{50} except the cell free values for AAK1, GAK, and BIKE; "cell free" values indicate inhibitory activity against purified protein in biochemical assay; "cell" values indicate enzyme-inhibitory activity inside a cell. †In the absence of direct measurements of drug inhibition in cells, the predicted cell affinity and efficacy values are derived from the ratio of each compound for their primary target; for example, for baricitinib, IC_{50} AAK1[cell] = (IC_{50}AK1[cell] / IC_{50}AK1[cell free]) × IC_{50}AAK1[cell free]. ‡At a 10 mg dose.

Table: **Properties of three antiviral and anti-inflammatory candidate drugs**

erlotinib, shown to reduce the infectivity of a wide range of viruses, including hepatitis C virus, dengue virus, Ebola virus, and respiratory syncytial virus.[5,6] However, sunitinib and erlotinib would be difficult for patients to tolerate at the doses required to inhibit AAK1 and GAK. By contrast, at therapeutic doses used for the treatment of patients with rheumatoid arthritis, the free plasma concentrations of baricitinib are predicted to be sufficient to inhibit AAK1, and potentially GAK, in cell-based assays.

The predicted inhibition of clathrin-mediated endocytosis by baricitinib is unlikely to be observed with other anti-arthritic drugs or JAK inhibitors. Our analysis of the closely related JAK inhibitors ruxolitinib and fedratinib (table) illustrates that the predicted unbound plasma exposure required to inhibit the enzymes needed for clathrin-mediated endocytosis greatly exceeds the currently tolerated exposures used therapeutically. These drugs are, therefore, unlikely to reduce viral infectivity at tolerated doses, although they might reduce the host inflammatory response through JAK inhibition. Intriguingly, another JAK inhibitor, tofacitinib, shows no detectable inhibition of AAK1. The high affinity of baricitinib for NAKs, its anti-inflammatory properties, and its ability to ameliorate associated chronic inflammation in interferonopathies,[8] together with its advantageous pharmacokinetic properties, appear to make it a special case among the approved drugs.

In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. Furthermore, there is the potential for combining baricitinib with the direct-acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug-metabolising enzymes. Combinations of baricitinib with these direct-acting antivirals could reduce viral infectivity, viral replication, and the aberrant host inflammatory response. This work demonstrates that the use of an AI-driven knowledge graph can facilitate rapid drug development.

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAI, and consults with Lansdowne partners and Vitruvian; he now sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. All other authors are employees of BenevolentAI. Events in relation to the COVID-19 outbreak are evolving rapidly, and we make our initial thoughts available in this Comment in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.

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ANNEXURE-7

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Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

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ABSTRACT

BACKGROUND

Severe coronavirus disease 2019 (Covid-19) is associated with dysregulated inflammation. The effects of combination treatment with baricitinib, a Janus kinase inhibitor, plus remdesivir are not known.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15.

RESULTS

A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; P=0.03), as were new infections (5.9% vs. 11.2%; difference, −5.3 percentage points; 95% CI, −8.7 to −1.9; P=0.003).

CONCLUSIONS

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04401579.)

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*A complete list of members of the ACTT-2 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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In May 2020, the first stage of the Adaptive Covid-19 Treatment Trial (ACTT-1), a randomized, double-blind, placebo-controlled trial, showed that remdesivir is an effective treatment for hospitalized adult patients with coronavirus disease 2019 (Covid-19) pneumonia.[1] Despite the benefits of remdesivir, substantial morbidity and mortality due to Covid-19 remain. Emerging data suggest that disease severity may be due in part to a dysregulated inflammatory response.[2] It is postulated that mitigating the immune response and preventing a hyperinflammatory state may further improve clinical outcomes. Baricitinib, an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2, was predicted with the use of artificial intelligence algorithms to be a potential therapeutic against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3,4] Baricitinib inhibits the intracellular signaling pathway of cytokines known to be elevated in severe Covid-19, including interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor; acts against SARS-CoV-2 through the impairment of AP2-associated protein kinase 1 and the prevention of SARS-CoV-2 cellular entry and infectivity; and improves lymphocyte counts in patients with Covid-19.[3,5-8] In three case series of patients with Covid-19, baricitinib treatment was associated with both an improvement in oxygenation and a reduction in select inflammatory markers.[9-11] Randomized, controlled trials are needed to further understand the role of immunomodulation in patients with Covid-19.[12] After the successful completion of ACTT-1, we designed the next iteration of ACTT (ACTT-2) to evaluate whether the combination of baricitinib plus remdesivir was superior to remdesivir alone.

METHODS

DESIGN

The ACTT-2 protocol was designed and written by a working group of the ACTT investigators and the sponsor (the National Institute of Allergy and Infectious Diseases), with input from the manufacturer of baricitinib, Eli Lilly. Investigators and staff at participating sites gathered the data, which were then analyzed by statisticians at the statistical and data center (Emmes) and the sponsor. The authors wrote the manuscript, and, on behalf of the ACTT-2 Study Group, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Enrollment into this double-blind, placebo-controlled trial began on May 8, 2020, and ended on July 1, 2020. There were 67 trial sites in 8 countries: the United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), the United Kingdom (1), and Denmark (1). Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir and baricitinib or remdesivir and placebo. Randomization was stratified according to trial site and disease severity at enrollment (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients received remdesivir intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. Baricitinib was administered as a 4-mg daily dose (either orally [two 2-mg tablets] or through a nasogastric tube) for 14 days or until hospital discharge. Patients with an estimated glomerular filtration rate of less than 60 ml per minute received baricitinib at a dose of 2 mg once daily. A matching oral placebo was administered according to the same schedule as the active drug. All the patients received standard supportive care at the trial site hospital. Venous thromboembolism prophylaxis was recommended for all the patients without a major contraindication. If a hospital had a written policy for Covid-19 treatments, patients could receive those treatments. In the absence of a written policy, other experimental treatment and off-label use of marketed medications intended as specific treatment for Covid-19 were prohibited. This included glucocorticoids, which were permitted only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome.

The trial protocol was approved by the institutional review board at each site (or a centralized institutional review board as applicable) and was overseen by an independent data and safety monitoring board. Written informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. Full de-

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tails of the trial design, conduct, oversight, and analyses are provided in the protocol and statistical analysis plan (available at NEJM.org).

PROCEDURES

All patients were evaluated daily during their hospitalization, from day 1 through day 29. (See the full description of procedures in the Supplementary Appendix.) The trial team was unaware of the trial-group assignments until after all data queries were resolved and the database was locked. The first draft of the manuscript was written by the first author, and then all the authors contributed to the subsequent versions. No one who is not an author contributed to the writing of the manuscript.

OUTCOMES AND STATISTICAL ANALYSIS

The primary outcome measure was the time to recovery, with the day of recovery defined as the first day, during the 28 days after enrollment, on which a patient attained category 1, 2, or 3 on the eight-category ordinal scale. The competing event of death was handled in a manner similar to the Fine–Gray competing-risk approach.[13] The categories are the same as those used in ACTT-1[1] and are listed in Table S1 in the Supplementary Appendix. The primary analysis was a stratified log-rank test of the time to recovery with remdesivir plus baricitinib as compared with remdesivir plus placebo, stratified according to baseline disease severity (i.e., score on the ordinal scale of 4 or 5 vs. 6 or 7 at enrollment).

The key secondary outcome measure was clinical status at day 15, based on the eight-category ordinal scale. Other secondary outcome measures included the time to improvement by one or two categories from the ordinal score at baseline; clinical status, as assessed on the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; mean change in the ordinal score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; time to discharge or to a National Early Warning Score of 2 or less (on a scale from 0 to 20, with higher scores indicating greater clinical risk) that was maintained for 24 hours, whichever occurred first; change in the National Early Warning Score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; number of days of receipt of supplemental oxygen, noninvasive ventilation or high-flow oxygen, and invasive ventilation or extracorporeal membrane oxygenation (ECMO) up to day 29 (if these were being used at baseline); the incidence and duration of new use of oxygen, new use of noninvasive ventilation or high-flow oxygen, and new use of invasive ventilation or ECMO; duration of hospitalization up to day 29 (patients who remained hospitalized at day 29 had a value of 28 days); and mortality at 14 and 28 days after enrollment. Secondary safety outcomes included grade 3 and 4 adverse events and serious adverse events that occurred through day 29, discontinuation or temporary suspension of trial-product administration for any reason, and changes in assessed laboratory values over time. There was a single primary hypothesis test. For secondary outcomes, no adjustments for multiplicity were made.

Prespecified subgroups were defined according to sex, disease severity (as defined for stratification and by an ordinal score of 4, 5, 6, and 7 at enrollment), age (18 to 39 years, 40 to 64 years, or ≥65 years), race, ethnic group, duration of symptoms before randomization (measured as ≤10 days or >10 days, in quartiles, and as the median), site location, and presence of coexisting conditions.

RESULTS

PATIENTS

Of 1067 patients assessed for eligibility, 1033 underwent randomization; 515 were assigned to the combination group, and 518 to the control group (Fig. 1). The intention-to-treat population included 706 patients with moderate disease (ordinal score of 4 or 5 [not receiving ventilation]) and 327 with severe disease (ordinal score of 6 or 7 [receiving noninvasive or invasive ventilation]). Of those assigned to the combination group, 507 (98.4%) received treatment as assigned. Of those assigned to the control group, 509 (98.3%) received treatment as assigned. A total of 498 patients in the combination group and 495 in the control group completed the trial through day 29, recovered, or died. The mean age of the patients was 55.4 years, and 63.1% were male (Table 1). Overall, 48.0% of the patients were White, 15.1% were Black, 9.8% were Asian, and 1.0% were American Indian or Alaska Native; 51.4% were Hispanic or Latino (Table 1). The characteristics of the U.S. patients are shown in Table S4.

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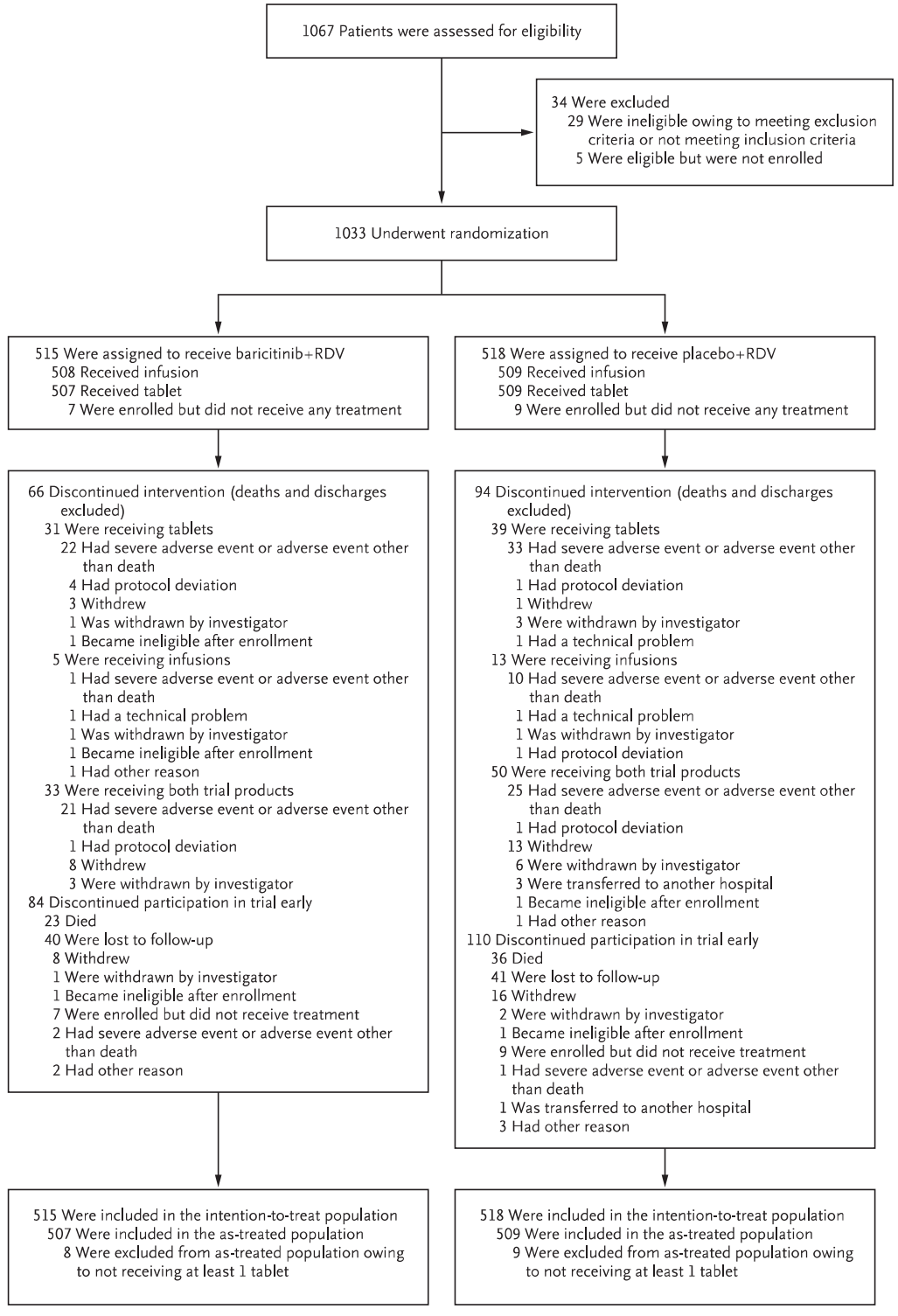


Figure 1. Enrollment and Randomization.
RDV denotes remdesivir.

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=1033)	Baricitinib+RDV (N=515)	Placebo+RDV (N=518)
Age			
Mean — yr	55.4±15.7	55.0±15.4	55.8±16.0
Distribution — no. (%)			
<40 yr	173 (16.7)	87 (16.9)	86 (16.6)
40–64 yr	555 (53.7)	281 (54.6)	274 (52.9)
≥65 yr	305 (29.5)	147 (28.5)	158 (30.5)
Sex — no. (%)			
Female	381 (36.9)	196 (38.1)	185 (35.7)
Male	652 (63.1)	319 (61.9)	333 (64.3)
Race — no. (%)†			
Asian	101 (9.8)	49 (9.5)	52 (10.0)
Black	156 (15.1)	77 (15.0)	79 (15.3)
White	496 (48.0)	251 (48.7)	245 (47.3)
Other or unknown	280 (27.1)	138 (26.8)	142 (27.4)
Ethnic group — no. (%)†			
Hispanic or Latino	531 (51.4)	263 (51.1)	268 (51.7)
Not Hispanic or Latino	486 (47.0)	246 (47.8)	240 (46.3)
Not reported or unknown	16 (1.5)	6 (1.2)	10 (1.9)
Body-mass index‡	32.2±8.3	32.2±8.2	32.3±8.4
Median time (IQR) from symptom onset to randomization — days	8 (5–10)	8 (5–10)	8 (5–11)
Disease severity — no. (%)			
Moderate	706 (68.3)	358 (69.5)	348 (67.2)
Severe	327 (31.7)	157 (30.5)	170 (32.8)
Coexisting conditions — no./total no. (%)			
None	155/994 (15.6)	64/496 (12.9)	91/498 (18.3)
One	270/994 (27.2)	148/496 (29.8)	122/498 (24.5)
Two or more	569/994 (57.2)	284/496 (57.3)	285/498 (57.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)
Geographic region — no. (%)			
Asia	67 (6.5)	33 (6.4)	34 (6.6)
Europe	13 (1.3)	6 (1.2)	7 (1.4)
North America	953 (92.3)	476 (92.4)	477 (92.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, ECMO extracorporeal membrane oxygenation, IQR interquartile range, and RDV remdesivir.
† Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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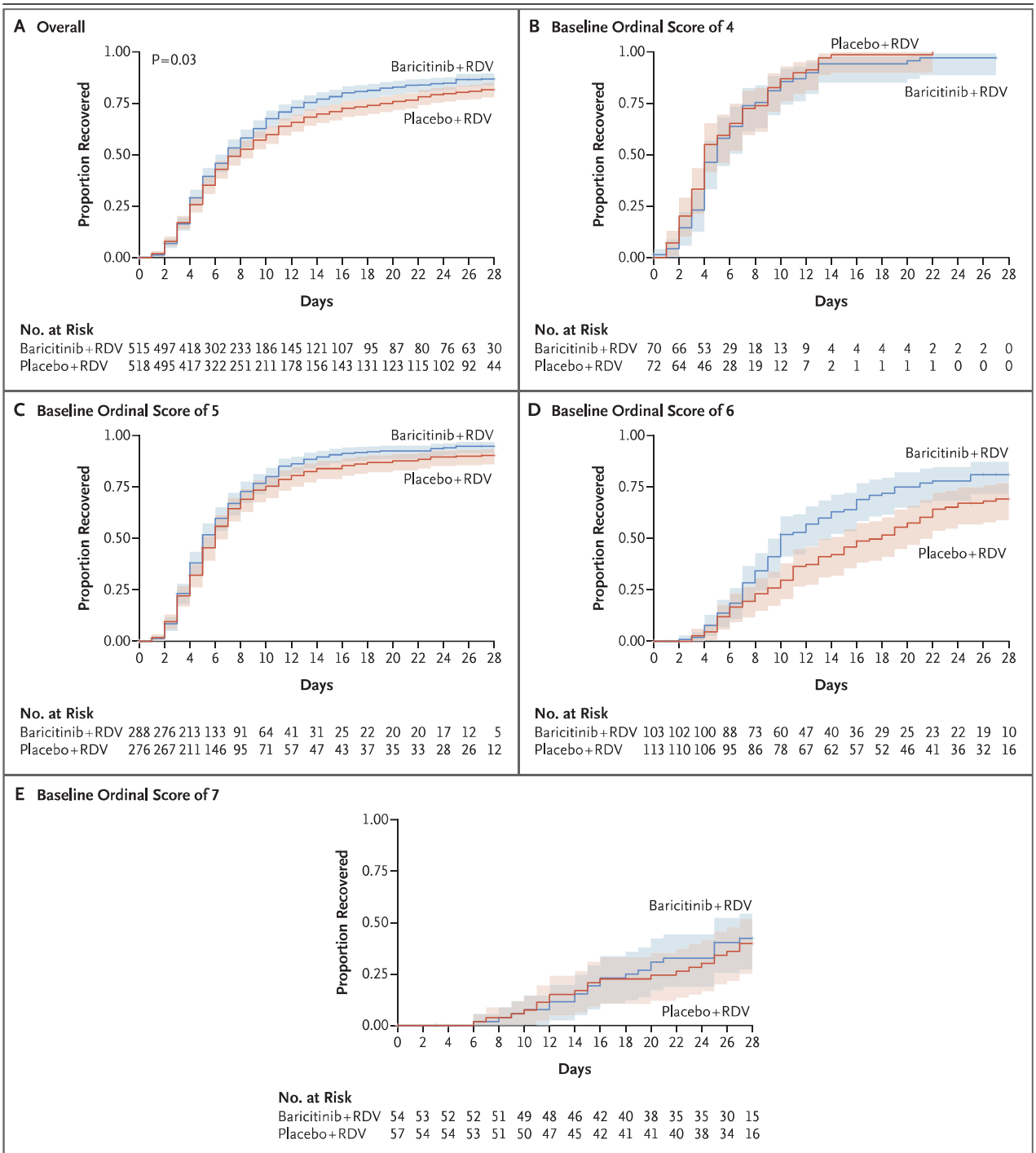


Figure 2. Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

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PRIMARY OUTCOME

Patients who received combination treatment with baricitinib plus remdesivir recovered a median of 1 day faster than patients who received remdesivir and placebo (median, 7 days vs. 8 days; rate ratio for recovery, 1.16; 95% confidence interval [CI], 1.01 to 1.32; P=0.03 by log-rank test stratified according to actual baseline severity) (Fig. 2 and Table 2). When analyzed according to the severity entered at the time of randomization (moderate vs. severe), the hazard ratio was 1.15 (95% CI, 1.00 to 1.31; P=0.047) (Table S6). The median time to recovery among patients receiving noninvasive ventilation or high-flow oxygen (baseline ordinal score of 6) was 10 days in the combination group and 18 days in the control group (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). Among patients with a baseline score of 4 (no oxygen) and 5 (supplemental oxygen), the rate ratio for recovery was 0.88 (95% CI, 0.63 to 1.23) and 1.17 (95% CI, 0.98 to 1.39), respectively. For those receiving mechanical ventilation or ECMO at enrollment (baseline ordinal score of 7), the rate ratio for recovery was 1.08 (95% CI, 0.59 to 1.97) (Table 2 and Fig. 3). The rate ratio for recovery among the 223 patients who received glucocorticoids for clinical indications during the trial was 1.06 (95% CI, 0.75 to 1.48). A sensitivity analysis with a random effect for hospital site yielded similar results (conditional random-effects estimate of rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.33; restricted maximum likelihood–based random-effects estimate of variance, 0.0305) (Table S13).

KEY SECONDARY OUTCOME

The odds of improvement in clinical status at day 15 as assessed with the ordinal scale were greater in the combination group than in the control group (odds ratio for improvement, 1.3; 95% CI, 1.0 to 1.6). Patients with a baseline ordinal score of 6 who received combination treatment were most likely to have clinical improvement at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6) (Table 2 and Fig. S1).

MORTALITY

The Kaplan–Meier estimates of mortality at day 28 after randomization were 5.1% (95% CI, 3.5 to 7.6) in the combination group and 7.8% (95% CI, 5.7 to 10.6) in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). The greatest numerical differences in mortality between patients in the combination group and those in the control group were observed among those with a baseline ordinal score of 5 (1.9% vs. 4.7%; hazard ratio, 0.40; 95% CI, 0.14 to 1.14) or 6 (7.5% vs. 12.9%; hazard ratio, 0.55; 95% CI, 0.22 to 1.38). The Kaplan–Meier estimates of mortality at 14 days after randomization were 1.6% in the combination group and 3.0% in the control group (hazard ratio, 0.54; 95% CI, 0.23 to 1.28) (Table 2 and Fig. S2).

ADDITIONAL SECONDARY OUTCOMES

The median time to an improvement by one category on the ordinal scale was 6 days in the combination group and 8 days in the control group (rate ratio, 1.21; 95% CI, 1.06 to 1.39), and the median time to discharge or a National Early Warning Score of 2 or less for 24 hours was 6 days and 7 days in the respective groups (rate ratio, 1.24; 95% CI, 1.07 to 1.44) (Table 3). The incidence of new use of oxygen was lower in the combination group than in the control group (22.9% vs. 40.3%; difference, –17.4 percentage points; 95% CI, –31.6 to –2.1), as was the incidence of new use of mechanical ventilation or ECMO (10.0% vs. 15.2%; difference, –5.2 percentage points; 95% CI, –9.5 to –0.9). The median number of days of receipt of mechanical ventilation or ECMO among the 128 patients in whom these interventions were started after enrollment or who died with no observed new use was 16 days in the combination group and 27 days in the control group (difference, –11.0; 95% CI, –17.7 to –4.3). The incidence of progression to death or noninvasive or invasive ventilation was lower in the combination group than in the control group (22.5% vs. 28.4%; rate ratio, 0.77; 95% CI, 0.60 to 0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs. 17.2%; rate ratio, 0.69; 95% CI, 0.50 to 0.95).

SAFETY OUTCOMES

Grade 3 or 4 adverse events occurred in 207 patients (40.7%) in the combination group and 238 (46.8%) in the control group (Table S11). A total of 25 grade 3 or 4 adverse events were judged by the principal investigators to be related to com-

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Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

Outcome	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Baricitinib (N=515)	Placebo (N=518)	Baricitinib (N=70)	Placebo (N=72)	Baricitinib (N=288)	Placebo (N=276)	Baricitinib (N=103)	Placebo (N=113)	Baricitinib (N=54)	Placebo (N=57)
Recovery										
No. of recoveries	433	406	67	69	262	243	82	73	22	21
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)	5 (4–6)	4 (4–6)	5 (5–6)	6 (5–6)	10 (9–13)	18 (13–21)	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])		0.88 (0.63–1.23)		1.17 (0.98–1.39)		1.51 (1.10–2.08)		1.08 (0.59–1.97)	
Mortality over first 14 days‡										
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)		NE		0.73 (0.16–3.26)		0.21 (0.02–1.80)		0.69 (0.19–2.44)	
No. of deaths by day 14	8	15	0	0	3	4	1	5	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)	0 (NE–NE)	0 (NE–NE)	1.1 (0.4–3.4)	1.5 (0.6–3.9)	1.0 (0.1–6.7)	4.6 (2.0–10.8)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡										
Hazard ratio (95% CI)	0.65 (0.39–1.09)		NE		0.40 (0.14–1.14)		0.55 (0.22–1.38)		1.00 (0.45–2.22)	
No. of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)	0 (NE–NE)	0 (NE–NE)	1.9 (0.8–4.4)	4.7 (2.7–8.1)	7.5 (3.6–15.2)	12.9 (7.7–21.3)	23.1 (13.8–37.1)	22.6 (13.5–36.4)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	177 (34.4)	165 (31.9)	33 (47.1)	44 (61.1)	114 (39.6)	101 (36.6)	27 (26.2)	17 (15.0)	3 (5.6)	3 (5.3)
2	177 (34.4)	163 (31.5)	25 (35.7)	20 (27.8)	120 (41.7)	115 (41.7)	30 (29.1)	24 (21.2)	2 (3.7)	4 (7.0)
3	8 (1.6)	3 (0.6)	5 (7.1)	2 (2.8)	2 (0.7)	1 (0.4)	0	0	1 (1.9)	0
4	31 (6.0)	18 (3.5)	7 (10.0)	6 (8.3)	14 (4.9)	7 (2.5)	7 (6.8)	3 (2.7)	3 (5.6)	2 (3.5)
5	43 (8.3)	50 (9.7)	0	0	18 (6.2)	27 (9.8)	15 (14.6)	20 (17.7)	10 (18.5)	3 (5.3)
6	20 (3.9)	19 (3.7)	0	0	9 (3.1)	1 (0.4)	7 (6.8)	16 (14.2)	4 (7.4)	2 (3.5)
7	48 (9.3)	83 (16.0)	0	0	8 (2.8)	19 (6.9)	15 (14.6)	28 (24.8)	25 (46.3)	36 (63.2)
8	11 (2.1)	17 (3.3)	0	0	3 (1.0)	5 (1.8)	2 (1.9)	5 (4.4)	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.3 (1.0–1.6)		0.6 (0.3–1.1)		1.2 (0.9–1.6)		2.2 (1.4–3.6)		1.7 (0.8–3.4)	

* Patients in both groups received RDV in addition to either baricitinib or placebo. Neither the P value nor any confidence intervals have not been adjusted for multiple comparisons. Percentages may not total 100 because of rounding. NE denotes not possible to estimate.

† Rate ratios for recovery and hazard ratios were calculated from the stratified Cox model. The P value for the primary outcome was calculated with the stratified log-rank test (overall model stratified according to actual disease severity). Rate ratios for recovery greater than 1 indicate a benefit with baricitinib plus RDV; hazard ratios less than 1 indicate a benefit with baricitinib plus RDV.

‡ Mortality over the first 14 days includes data from all patients who were still alive through 14 days after enrollment, with data censored on day 14, as if 14 days was the maximum follow-up time. Mortality over the entire trial period uses the totality of the trial data and censors data from patients who completed follow-up alive at 28 days after enrollment.

§ The ordinal score at day 15 (±2-day visit window) is the patient's worst score on the ordinal scale during the previous day. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, receiving noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or ECMO; and 8, death. Five deaths (three in patients receiving baricitinib plus RDV and two in patients receiving placebo plus RDV) occurred within the day 15 visit window but after 14 days — these deaths are included in the outcome of the ordinal score at day 15 but not in the outcome of mortality over the first 14 days. Odds ratios were calculated with the use of a proportional odds model (overall model adjusted for actual disease severity). Odds ratios greater than 1 indicate a benefit with baricitinib plus RDV.

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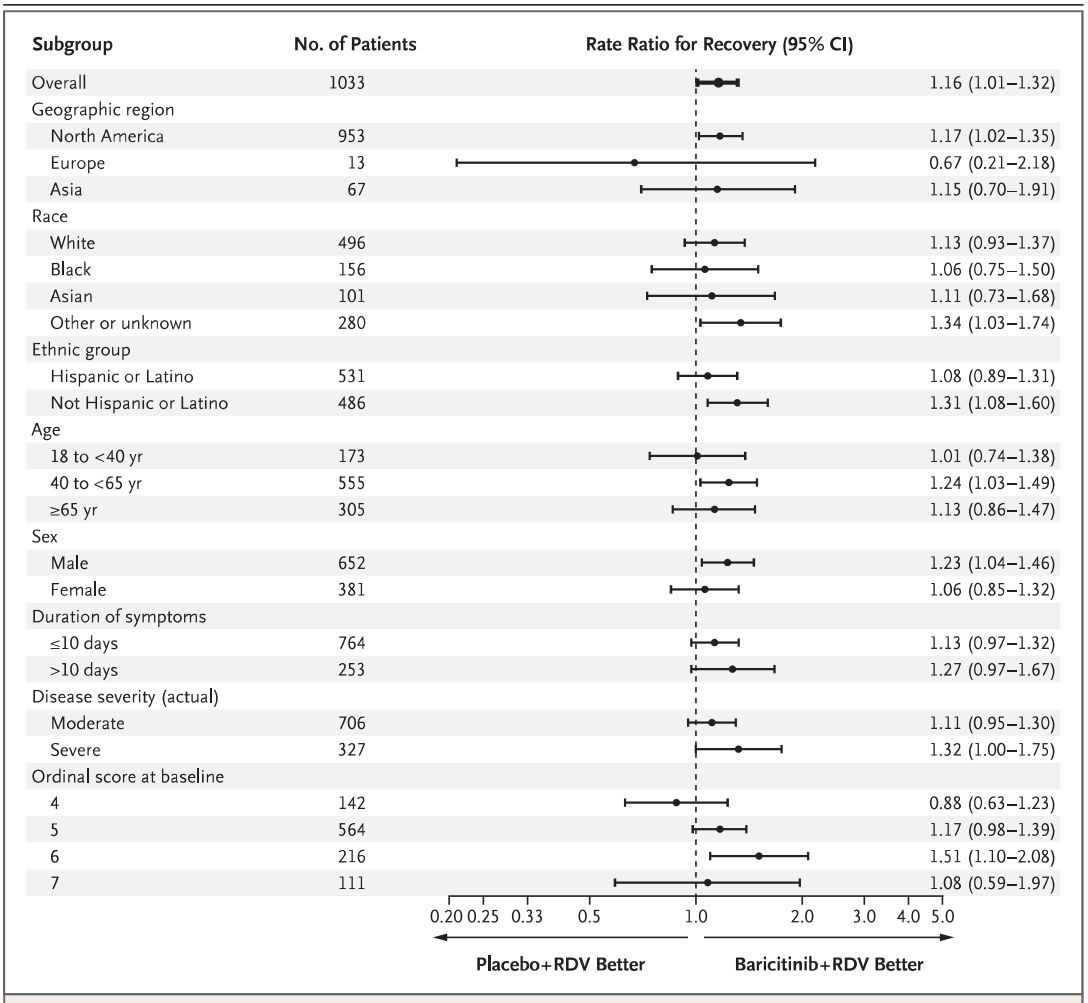


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

bination treatment and 28 to control (Table S10). The most common grade 3 or 4 adverse events occurring in at least 5% of all patients were hyperglycemia, anemia, decreased lymphocyte count, and acute kidney injury (Table S10). The incidence of these adverse events was similar in the two treatment groups. The percentage of patients who were reported to have a serious or nonserious adverse event of venous thromboembolism was similar in the combination group and the control group (21 patients [4.1%] and 16 patients [3.1%], respectively; difference, 1.0 percentage points; 95% CI, −1.3 to 3.3).

Serious adverse events occurred in 81 patients (16.0%) in the combination group, and six of these events were thought to be related to the trial product (Table S7). Serious adverse events occurred in 107 patients (21.0%) in the control group, and five of these events were thought to be related to the trial product. The between-group difference was −5.0 percentage points (95% CI, −9.8 to −0.3; P = 0.03). The incidences of all serious adverse events, all adverse events, serious adverse events with fatal outcome, and adverse events leading to discontinuation of the trial product were each lower in the combination group than in the control group. Overall, the incidence of serious or nonserious adverse events

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Table 3. Additional Secondary Outcomes.

Outcome	Baricitinib+RDV	Placebo+RDV	Rate Ratio (95% CI)
Median time to event (95% CI) — days			
Improvement by one category on ordinal scale	6.0 (5.0 to 7.0)	8.0 (7.0 to 9.0)	1.21 (1.06 to 1.39)
Improvement by two categories on ordinal scale	12.0 (12.0 to 13.0)	13.0 (NE)	1.20 (1.05 to 1.38)
Discharge or National Early Warning Score ≤2 for 24 hr*	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.24 (1.07 to 1.44)
Death or progression to noninvasive or invasive mechanical ventilation	NE	NE	0.77 (0.60 to 0.98)
Death or progression to invasive mechanical ventilation	NE	NE	0.69 (0.50 to 0.95)
New use of oxygen	NE	NE (3.0 to NE)	0.53 (0.29 to 0.98)
New use of invasive mechanical ventilation or ECMO	NE	NE	0.64 (0.44 to 0.93)
Use of noninvasive ventilation or high-flow oxygen	NE	NE	0.82 (0.60 to 1.13)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days			
With imputation of data for those who died†	8 (5 to 15)	8 (5 to 20)	0.0 (–1.1 to 1.1)
Among those who did not die	8 (5 to 13)	8 (5 to 15)	0.0 (–1.0 to 1.0)
Patients rehospitalized — % (95% CI)	3 (2 to 5)	2 (1 to 4)	1.0 (–1.1 to 3.1)‡
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)			
With imputation of data for those who died†	10 (4 to 27)	12 (4 to 28)	–2.0 (–5.2 to 1.2)
Among those who did not die	9 (4 to 24)	10 (4 to 28)	–1.0 (–3.8 to 1.8)
New use of oxygen during trial			
No. of patients/total no.	16/70	29/72	
Percent of patients (95% CI)	23 (15 to 34)	40 (30 to 52)	–17.4 (–31.6 to –2.1)‡
Median days receiving oxygen (IQR)	3 (2 to 4)	3 (2 to 6)	0.0 (–2.2 to 2.2)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	4 (3 to 9)	5 (2 to 12)	–1.0 (–2.9 to 0.9)
Among those who did not die	4 (3 to 6)	4 (2 to 9)	0.0 (–1.7 to 1.7)
New use of noninvasive ventilation or high-flow oxygen during trial			
No. of patients/total no.	70/358	82/348	
Percent of patients (95% CI)	20 (16 to 24)	24 (19 to 28)	–4.0 (–10.1 to 2.1)‡
Median days of use during trial (IQR)†§	6 (3 to 15)	5 (2 to 11)	1.0 (–1.6 to 3.6)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	20 (9 to 28)	25 (11 to 28)	–5.0 (–12.9 to 2.9)
Among those who did not die	13 (7 to 24)	16 (6 to 28)	–2.0 (–11.4 to 7.4)
New use of mechanical ventilation or ECMO during trial			
No. of patients/total no.	46/461	70/461	
Percent of patients (95% CI)	10 (8 to 13)	15 (12 to 19)	–5.2 (–9.5 to –0.9)‡
Median days of use during trial†§	16 (8 to 28)	27 (12 to 28)	–11.0 (–17.7 to –4.3)

* The National Early Warning Score includes six physiological measures; total scores range from 0 to 20, with higher scores indicating greater clinical risk. Only patients with a score of more than 2 at baseline were included in this analysis.
† The value for patients who died was imputed as 28 days.
‡ Differences between percentages are given in percentage points.
§ This analysis includes imputation of data for patients who died with no observed new use.

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of new infection was lower in the combination group (30 patients [5.9%]) than in the control group (57 patients [11.2%]) (difference, −5.3 percentage points; 95% CI, −8.7 to −1.9; P=0.003). Patients who received glucocorticoids after randomization had a higher incidence of serious or nonserious new infection than those who did not (56 of 223 patients [25.1%] vs. 44 of 793 patients [5.5%]).

DISCUSSION

The results of this randomized, double-blind, placebo-controlled trial show that combination treatment with the antiinflammatory drug baricitinib and the antiviral drug remdesivir was safe and superior to remdesivir alone for the treatment of hospitalized patients with Covid-19 pneumonia. The beneficial effects of the combination treatment were seen both in the primary outcome, with a 1-day shorter time to recovery, and in the key secondary outcome, with a greater improvement in clinical status as assessed on the ordinal scale. Although ACTT-2 was not powered to detect a difference in mortality between the two groups, both the survival rate and the time-to-death analyses favored combination treatment. These clinical benefits were observed across different age groups, sexes, ethnic groups, and races and were independent of symptom duration or disease severity at enrollment. The large proportion of Hispanic or Latino patients who were enrolled in the trial reflects the disproportionate effect of the pandemic on racial and ethnic minorities with respect to high incidences of hospitalization.[14]

The observed benefit of combination treatment was most evident in patients with a baseline ordinal score of 5 (supplemental oxygen) or 6 (high-flow oxygen or noninvasive ventilation), among whom the median time to recovery was, respectively, 1 and 8 days sooner with combination treatment than with placebo. Patients with a baseline ordinal score of 6 who received combination treatment were twice as likely as those in the control group to have improved clinical status at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6). The faster recovery in patients who received baricitinib plus remdesivir suggests that the combination treatment may have an effect in lowering the hospital-associated risk of nosocomial infections, thrombosis, and errors in hospital drug administration. Moreover, faster recovery also decreases the burden on the health care system, potentially increasing capacity, which is of critical importance during a surge of cases.

In addition, the combination treatment showed clinical benefits directly relevant to patient care, such as a difference of −17.4 percentage points in new use of oxygen (22.9% vs. 40.3%) and a difference of −5.2 percentage points in new use of mechanical ventilation or ECMO (10.0% vs. 15.2%). In fact, the odds of progression to death or invasive ventilation were 31% lower in the combination group than in the control group (hazard ratio, 0.69; 95% CI, 0.50 to 0.95), and patients in the combination group had 11 fewer days receiving new mechanical ventilation than those in the control group.

Despite concerns about immunosuppression, secondary infections, and thrombosis with use of JAK inhibitors, the addition of baricitinib was not associated with a significantly higher incidence of adverse events or thromboembolic events. In fact, patients receiving baricitinib plus remdesivir had a significantly lower incidence of adverse events, adverse events leading to discontinuation of the trial drug, serious adverse events, serious adverse events with a fatal outcome, and infection-related adverse events than patients who received remdesivir alone. The consistently lower incidence of adverse events with baricitinib may be related to its action in reducing inflammatory-mediated lung injury and improving lymphocyte counts, its antiviral properties, or its associated shorter recovery time and faster clinical improvement, all of which could have reduced the risk of nosocomial infection. Another ongoing trial may provide more information regarding the effects of baricitinib (ClinicalTrials.gov number, NCT04421027). In summary, our results and the characteristics of baricitinib, including the fact that it is an oral drug with few drug–drug interactions and a good safety profile, lend itself to use in low-to-middle-income countries.

The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial evaluated dexamethasone in patients with Covid-19[15] and showed a significant benefit in survival, most pronounced in patients receiving mechanical ventilation, and a 1-day shorter hospital stay. Baricitinib and dexa-

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methasone have important biologic differences, and ACTT-2 and the RECOVERY trial have design differences. Dexamethasone has a long half-life, acts on glucocorticoid receptors, and reduces inflammation through a broad-pathway approach that has been associated with immunosuppression, hospital-acquired infections, gastrointestinal bleeding, hyperglycemia, and neuromuscular weakness, even with short courses.[16] Baricitinib has a short half-life, acts on targeted critical pathways to reduce inflammation while minimizing biologic redundancy with less immunosuppression, and may have antiviral activity.[3] The two trials had different designs and cannot be compared directly. The high mortality in the control group of the RECOVERY trial and the low mortality in the control group of ACTT-2 suggest that these trials might not be generalizable to the same patient population. Only a randomized, double-blind, placebo-controlled, head-to-head comparison of baricitinib plus remdesivir with dexamethasone plus remdesivir will allow the efficacy and safety differences between these two approaches to be fully understood.

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status, notably among patients receiving high-flow oxygen or noninvasive mechanical ventilation. The combination was associated with fewer serious adverse events.

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APPENDIX

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Clinical Infectious Diseases

ANNEXURE-8

EDITORIAL COMMENTARY

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The Emergence of Baricitinib: A Story of Tortoises Versus Hares

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(See the Brief Reort by Titanji et al on pages 1247–50.)

Keywords. COVID-19; SARS-CoV-2; baricitinib; anti-viral; cytokine storm; trial.

Baricitinib is a once daily orally administered JAK1/2 inhibitor, which inhibits the signaling of many cytokines and has been approved for the treatment of moderate to severe rheumatoid arthritis (RA) based on long-term randomized dosing against both placebo and standard of care [1], notably tumor necrosis factor (TNF)-alpha blockade. Its use for the treatment of coronavirus disease 2019 (COVID-19) was originally suggested after a search of the extensive BenevolentAI knowledge graph for approved drugs that could be used in this pandemic [2]. An advantage of approved drugs is that they have a known safety profile and can therefore be rapidly approved in fast moving pandemics. The artificial intelligence algorithms predicted that baricitinib would inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of cells [2], (an effect later confirmed in human liver spheroids) [3], combined with its better-known anti-inflammatory properties. The doses required were predicted to be the same as used for the treatment of RA. At these doses, interleukin 6 (IL-6) levels were reduced both in COVID19 patients as well as dose dependently in RA patients in a previous phase 2b randomized RA trial, the first time this was shown in humans [4]. What was more intriguing was its inhibition of members of the numb associated kinase family, thought in turn to translate to reduced AP-2 mediated viral propagation early in the infectious cycle, suggesting antiviral activity; this was shown in liver spheroid models, which express detectable albeit low levels of the ACE2 receptor.

In hospitalized patients it is anticipated that residual virus that propagates itself in airway epithelial tissues maintains and amplifies the exaggerated inflammatory response typical of COVID-19. Consequently, the combined potential antiviral and anti-inflammatory effects of this dually acting drug could be ideal for halting the progression of the disease in hospitalized patients, when taken for a limited duration. At the University of Southern California now, a randomized placebo-controlled phase 2 study with remdesivir with/without baricitinib is ongoing to test the efficacy to prevent mechanical ventilation including significant biomarker research.

In this issue of *Clinical Infectious Diseases*, Titanji et al describe the outcome of 15 moderate-to-critically ill patients with COVID-19 treated with baricitinib and hydroxychloroquine. This therapy was associated with a reduction in inflammatory markers including fever, C reactive protein (CRP), improvement of oxygen requirements, and recovery in 12 of the 15 (80%) patients studied. Although it is possible that the antiviral and anti-inflammatory effects of hydroxychloroquine contributed to this positive outcome, this would seem unlikely according to the recently reported National Institutes of Health (NIH) randomized trials) [5], among many other studies. This new paper in the journal extends the previous published reports of baricitinib treatment in mild-to-moderate COVID19 patients and provides further evidence that baricitinib could be a potential treatment for unwell hospitalized patients with this disease, independent of severity. Indeed, in mild-to-moderate patients, baricitinib therapy was also associated with a reduction in the requirement for intensive care unit (ICU) care when compared with matched case controls [6, 7]. In each series baricitinib treatment has been associated with a reduction in inflammation and recovery from the disease in the vast majority of patients, consistent with the present report, but we do not know if this is simply an association or represents a causative effect of the drug. In this new paper, 3 patients died, 2 of which had very high plasma IL-6 levels prior to starting baricitinib therapy consistent with previous data that high IL-6 is a predictor of mortality in COVD19 infections [8, 9]. These useful results retrospectively justified the testing of the anti-IL6/

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IL6R antibodies Kevzara (sarilumab) and Actemra (tocilizumab) in severely unwell patients, although randomized studies are yet to show benefits.

Baricitinib treatment over prolonged periods in RA patients has been associated with increased infections and thromboembolism, but the short duration of treatment in COVID-19 patients may mitigate against such side effects. In this report it is difficult to say whether one incident of pulmonary embolism and methicillin-resistant *Staphylococcus aureus* (MRSA) infection were due to the complications of COVID-19 or baricitinib, but the much larger numbers of patients in the yet to report randomized studies should clarify this. One would be advised to remain vigilant of such signals reflecting thromboembolic or infection risk in randomized controlled trials testing a variety of immunomodulatory therapies in COVID-19 patients, either alone or in combination, especially in view of associations between clots and SARS-CoV-2 infection [10]. Specifically, severe endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes, widespread vascular thrombosis with microangiopathy, and occlusion of alveolar capillaries including significant new vessel growth through a mechanism of intussusceptive angiogenesis has been described [11].

The first report of a significant reduction in COVID-19 mortality in any randomized study recently came from the RECOVERY trial in the United Kingdom showing that low dose dexamethasone had a significant effect in reducing mortality when given with standard of care (21.6% vs 24.6% of the patients dying within 28 days) [12]; this effect was greatest in ventilated patients (a 30% reduction in mortality) and slightly less in those provided with noninvasive supplemental oxygen (a 20% reduction) [12]. It is tempting to speculate that a similar or greater reduction in mortality could be expected with baricitinib in randomized trials, especially because baricitinib is now reported to be associated with recovery from COVID-19 in different series of patients. It may even be possible to combine the baricitinib with dexamethasone, at least in critically ill patients, although once again it would of course be important to assess the risk of infection when administering these 2 potent anti-inflammatory agents together.

As acknowledged by Titanji et al, and reiterated by us, randomized trials are required for us to be certain if baricitinib is an effective and safe therapy for COVID-19 patients [3]. This report, and others like it, have supported the selection of baricitinib in a number of studies including the ACTT2 randomized trial, where it is being tested in combination with remdesivir, and a further placebo-controlled phase 3 trial recently commenced. It is anticipated that these trials should provide a robust estimate of the efficacy of baricitinib in COVID-19 and would be complementary to each other. These initial case series warrant further confirmation from the ongoing larger, randomized and controlled trials. Thus far, these data sets also validate use of artificial intelligence at a time of a biomedical crisis, to help speed drug development. The use of an oral medicine taken once daily for a short duration should also lend itself to low- and middle-income countries.

Note

Potential conflicts of interest. P. J. R. is an employee of BenevolentAI and has received honoraria for giving a lecture to Lilly with J. S. And J. S. has sat on SABs for Vaccitech, Heat Biologics, Eli Lilly, Replete, Alveo, Certis Oncology Solutions, Greenmantle and BenevolentAI, has consulted with Lansdowne partners and Vitruvian. He sits on the Board of Directors for BB Biotech Healthcare Trust. H.-J. L. has no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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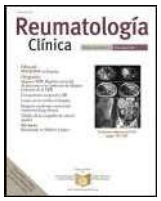
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Original article

Experience With the Use of Baricitinib and Tocilizumab Monotherapy or Combined, in Patients With Interstitial Pneumonia Secondary to Coronavirus COVID19: A Real-World Study

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ABSTRACT

Objective: To describe the experience of treatment with baricitinib (BARI) and/or tocilizumab (TCZ), in monotherapy or combined, in patients admitted for interstitial pneumonia secondary to COVID19, and for 30 days after discharge.
Methods: Medical records of patients admitted with COVID19 and IP with $PaO_2/FiO_2 < 300$, treated with BARI and/or TCZ, and compared with patients who did not, were retrospectively reviewed.
Results: Sixty patients were included; 43 (72%) are males, mean age 67 (SD: 14) years (<50 years: 17%; 51–70: 30%; >70: 53%), with 8.5 (SD: 1) days of symptoms. Sixteen (27%) patients required ICU (94% in <70 years). Fifteen (25%) patients died, 67% in >70 years; 11 (18%) patients died in the first 15 days of admission and 4 (7%) between days 16 to 30. Twenty-three (38%) patients received BARI, 12 (52%) monotherapy (Group 1), during 6 (SD: 2.6) days on average, none required ICU and 2 (17%) died. Thirty-one (52%) patients received TCZ, 20 (33%) as monotherapy (Group 2), 16 (52%) patients required ICU and 4 (20%) died. In the 11 (18%) patients who received BARI (2.8 [SD: 2.5] days average) and TCZ combined (Group 3), 3 (27%) required ICU and died. There were no severe side effects in BARI or TCZ patients. In the 17 (28%) patients who received neither BARI nor TCZ (Group 4), none required ICU and 6 (35%) died. Mean (SD) PaO_2/FiO_2 at admission between groups was respectively: 167 (82.3), 221 (114.9), 236 (82.3), 276 (83.2).
Conclusion: Treatment with BARI and TCZ did not cause serious side effects. They could be considered early in patients with NI secondary to COVID19 and impaired PaO2/PaFi.

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Experiencia con el uso de baricitinib y tocilizumab en monoterapia o combinados, en pacientes con neumonía intersticial secundaria al coronavirus COVID-19: Un estudio del mundo real

Palabras clave:
COVID-19
Baricitinib
Tocilizumab
Neumonía intersticial
UCI

R E S U M E N

Objetivo: Describir la experiencia con baricitinib (BARI) y/o tocilizumab (TCZ), en monoterapia o combinados en pacientes ingresados por neumonía intersticial (NI) por COVID-19 y durante los 30 días después del alta.
Método: Se revisaron retrospectivamente las historias clínicas de los pacientes ingresados por COVID-19 y NI, con PaO2/FiO2<300, tratados con BARI y/o TCZ y se compararon con pacientes que no los recibieron.
Resultados: Se incluyeron 60 pacientes; 43 (72%) varones, edad media 67 (DE: 14) años (< 50 años: 17%; 51-70: 30%; > 70: 53%), y 8,5 (DE: 1) días de síntomas. Dieciséis (27%) ingresaron en la unidad de cuidados intensivos (UCI) (94% < 70 años). Quince (25%) fallecieron (67% > 70 años); 11 (18%) de ellos en los primeros 15 días del ingreso y cuatro (7%) entre los días 16 y 30. Veintitrés (38%) pacientes recibieron BARI, 12 (52%) en monoterapia (Grupo 1), durante seis (DE: 2.6) días de promedio, ninguno de ellos ingresó en UCI y dos (17%) fallecieron. Treinta y un (52%) pacientes recibieron una dosis de TCZ, 20 (33%) en monoterapia (Grupo 2), 16 (52%) ingresaron en UCI y cuatro (20%) fallecieron. Entre los 11 (18%) pacientes que recibieron BARI (2,8 [DE: 2,5] días de promedio) y TCZ combinados (Grupo 3), tres (27%) ingresaron en UCI y fallecieron. No hubo efectos secundarios graves entre los que recibieron BARI y/o TCZ. Entre los 17 (28%) pacientes que no recibieron ni BARI ni TCZ (Grupo 4), ninguno ingresó en UCI y seis (35%) fallecieron. La PaO2/FiO2 media (DE) al ingreso entre los grupos fue respectivamente: 167 (82,3), 221 (114,9), 236 (82,3), 276 (83,2).
Conclusión: El tratamiento con BARI y TCZ no provocó efectos secundarios graves. Podrían considerarse precozmente en pacientes con NI secundaria a COVID-19 y deterioro de PaO2/PaFi.
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Introduction

Coronavirus disease 2019 (COVID-19), which started in China in December of 2019, has led to a pandemic extremely quickly, with effects on health in many countries.

When the immune response is unable to control infection, the virus activates macrophages and granulocytes, causing the progressive release of proinflammatory cytokines, especially IL6, IL1, IL10, interferon and TNF, provoking a real "cytokine storm".[1–5] In some patients, it induces the appearance of pulmonary infiltrates and rapid development of respiratory failure and severe acute respiratory syndrome (SARS), which is the main cause of mortality in these patients.[6–8] Although mortality vary between countries, it has been estimated 0–3% to 1% in general population infected and 14% among hospitalized cases (95% CI 3.9–32%).[9–12]

Management, especially in patients with severe disease, is one of the main problems posed by this disease. So far, it has been based on observational studies or on drugs used in other viral diseases. Although there are numerous clinical trials underway, there is no evidence to recommend a specific treatment.

In the first phase of the disease, treatment with antiviral drugs (remdesivir,[13] a combination of lopanivir/ritonavir,[14] or interferon β1b[15]), or drugs that may interfere with the development of the virus (hydroxychloroquine),[16] predominates. After a few days, in the second inflammatory phase, associated with the release of cytokines, the use of drugs such as tocilizumab (TCZ), with anti-IL6 action and therefore for the treatment of SARS, predominates.[5,8,17]

Given its high contagiousness, this virus has caused an explosion of cases, with saturation of the health system and of intensive care units (ICU). In Spain, 43% of infected patients required hospital admission and 3.9% ICU admission. Approximately 75% of patients admitted for COVID19 present positive imaging for interstitial pneumonia (IP).[10,18,19]

As in many other hospitals in Spain, with a large number of patients admitted for COVID19-IP, our center had to restructure most of the hospitalization areas and the activities of the entire medical staff at the times of greatest impact of the pandemic. In this context, and with the possibility of supply problems of drugs such as TCZ, in cases of SARS, possible therapeutic alternatives were sought, for their early administration or as a bridge to reduce the consumption of TCZ.

Baricitinib (BARI) is a selective JAK1/JAK2 intracellular route inhibitor drug, administered orally at a daily dose of 2–4 mg, and approved for the treatment of adult patients with rheumatoid arthritis.[20] Unlike other biological drugs, which are predominantly inhibitors of one cytokine, BARI inhibits multiple cytokines, such as IL-6 and interferon, among others.[21–22] In addition to its anti-inflammatory effect, there are data indicating that BARI, at the doses used in rheumatology, may have antiviral action, interfering with its binding to ACE2 receptors (angiotensin-converting enzyme).[23–24] This inhibits the entry of the virus into the cell and its intracellular coupling by binding to GAK (cyclin G-associated kinase), which regulates endocytosis and acts on AAK1 (Associated protein kinase 1), thus interfering with viral replication.[24–25]

The main objective of the study is to describe the experience of treatment with BARI and/or TCZ, in monotherapy or combined, in patients admitted for IP secondary to COVID19, and for 30 days after discharge.

Methods

This is a retrospective observational study. The medical records of the patients admitted to our center due to IP secondary to COVID19, demonstrated by PCR (polymerase chain reaction) technique, who started treatment with BARI and/or TCZ, from March 27 to April 2, 2020 and their clinical progress until discharge, was reviewed. Survival and serious complications were reviewed after 30 days of discharge.

Patients

Patients received, at the discretion of the responsible physician, standard antiviral treatment, and anti-cytokine therapy (BARI or TCZ), in patients with the following inclusion criteria: (1) Interstitial pneumonia and (2) PaO_2/FiO_2 (ratio between PaO_2 in mmHg and FiO_2 in%) <300. Exclusion criteria: pregnancy,

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previous thrombosis history, HBV infection, current bacterial infection, neutrophil<1000/mm^3, lymphocyte <300/mm^3, platelets <50,000/mm^3 and transaminases values 4-fold higher than the upper normal limit.

For analysis, they were divided into 4 groups: Group 1: patients treated with BARI, at an oral dose of 2 mg or 4 mg daily; Group 2: patients receiving an intravenous dose of TCZ, adjusted for weight (400 mg in patients weighing <75 kg or 600 mg in those weighing ≥75 kg); Group 3: patients who received BARI and TCZ combined and Group 4: patients who received neither BARI nor TCZ.

Data collection

General patient data, comorbidities and the Charlson Comorbidity Index, which includes the estimated 10-year survival were included. During admission: symptoms (fever, cough, dyspnea, diarrhea), time of progression of symptoms; chest x-ray; laboratory data: blood count, general biochemistry, arterial blood gas, D-dimer, sedimentation rate (ESR), C-reactive protein (CRP), O_2 saturation, PaO_2/FiO_2 (mild if <300, moderate if <200, and severe if <100),[26] respiratory rate (RR); treatment and doses of drug received: remdesivir, lopanivir/ritonavir, interferon β1b, hydroxychloroquine, azithromycin, and anti-inflammatory (corticosteroids, BARI, TCZ); and outcome: admission to the ICU, hospital discharge, or death.

The study was approved by the Spanish Agency for Medicine and Health Products and (AEMPS), and the Ethics Committee of the University General Hospital of Elche (Alicante), Spain (Code: COVID19-BARI/TCZ-HMB).

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables with normal distribution of data as mean and standard deviation (SD). The chi-square (χ^2) test and Student's *t*-test were used for comparison of qualitative and quantitative variables, respectively. Statistical significance was set at $p < 0.05$.

Results

Overall population characteristics

A total of 60 patients were included, of which 43 (72%) were male, with a mean age of 67 (SD: 14) years (range: 34–91 years; <50: 17%, 50–70: 30%, >70: 53%). The mean time of symptom progression was 8.5 (SD: 1) days and mean time of hospital admission, 11 (SD: 3.7) days. Comorbidities included, high blood pressure: 24 (40%) patients, diabetes mellitus: 10 (17%), ischemic heart disease: 9 (15%), COPD: 6 (10%), cancer: 6 (10%), liver cirrhosis: 2 (4%) and 1 (2%) patient respectively, liver transplant, ankylosing spondylitis in treatment with adalimumab, hepatitis C virus, and AIDS. The Charlson Comorbidity Index score was 3.41, with estimated 10-year survival of 59.8%.

Upon admission, 40 (67%), patients had a mean temperature of 37.5 °C (SD: 1.0), RR: 29 (SD: 7.6), O_2 saturation: 91% (SD: 6; range: 75%-96%) and PaO_2/FiO_2: 233.7 (SD: 100.9; range: 77–401). Forty-nine (82%) patients presented cough, 39 (65%) had dyspnea and 13 (22%) diarrhea. The mean CRP was 15.4 mg/dL (SD: 9.2), lymphocytes: 813/mm^3 (SD: 448; range: 300–2200), neutrophils > 1500/mm^3: 100%, LDH: 434 U/L (SD: 218), D-dimer: 7560 ng/mL (SD: 19,979; range: 511–107,000), GPT: 51 U/L (SD: 62). In 55 (92%) patients there were radiological bilateral pulmonary infiltrate (Table 1).

Treatments received during admission was: antiviral drugs: 28 (47%) patients, azithromycin: 53 (88%), hydroxychloroquine: 51 (85%), interferon: 14 (23%), corticosteroids: 49 (82%), of which in 42 (86%) patients as intravenous bolus of 250–500 mg. Thirty one (52%) patients received TCZ, 23 patients (38%) received BARI, both as monotherapy or combined and 17 (28%) patients did not receive any of the anti-cytokine drugs (Table 1). Neutropenia, thrombotic event, or other relevant side effect was not detected among patients who received BARI and/or TCZ.

Impact of age on mortality and ICU admission

Thirty-two (53%) patients were over 70 years old and 28 (47%) were under 70, 8 (14%) of them were under 50 and 20 (33%) between 51 and 70.

Fifteen (25%) patients died, 5 of them in ICU, 11 (18%) patients in the first 15 days of admission and 4 (7%) between days 16 to 30 (Table 1). Sixteen (27%) patients required ICU admission: 15 (94%) of them were under 70 years of age and 1 (6%) patient over 70. Among patients over 70 years versus those under 70, PaO_2/FiO_2 at admission was similar but presented numerically higher mortality (10 [31%] vs 5 [18%], $p = 0.59$), higher percentage of patients who did not receive BARI or TCZ (13 [41%] vs 4 [14%], $p = 0.32$) and lower percentage of ICU admission (1 [3%] vs 15 [94%], $p = 0.32$) (Table 2).

Baricitinib treatment

Of the 23 (38%) patients who were treated with BARI, 17 (74%) were male, mean aged of 69 (SD: 13.5) years (range: 30–85). Mean progression of symptoms: 9.3 (SD: 5.8) days and of admission 12 (SD: 3.6) days; the mean time in treatment with BARI: 4.5 (SD: 2.6) days (Fig. 1). In 9 (39%) patients the BARI dose received was 4 mg and in 14 (61%) 2 mg daily. Three (13%) patients received only one dose, prior to TCZ. Eight (35%) discontinued BARI at the start of TCZ and 3 (27%) continued BARI after receiving TCZ. Other treatments included antiviral: 10 (44%) patients, azithromycin: 18 (78%), hydroxychloroquine: 21 (91%), interferon: 6 (25%), and 23 (100%) patients received corticosteroids, of whom 18 (78%) received intravenous bolus of 250–500 mg.

When comparing the 23 patients who received BARI, to the 37 (62%) patients who did not (20 [54%] patients received TCZ), significant differences were detected at discharge or during the last evaluation, in RR (20, SD: 4.6 vs 24, SD: 7.4. $p < 0.05$).

Twelve (52%) patients received BARI monotherapy (Group 1), during 6 (SD: 2.6) days on average (Fig. 1). The PaO_2/FiO_2 average prior to receiving BARI and at discharge was: 167 (82.3) vs 214 (74.3). None of the patients required ICU and 2 (17%) died, in the first 15 days of admission (Table 1).

Tocilizumab treatment

Thirty-one (52%) patients received a dose of intravenous TCZ; 24 (77%) were male, mean age of 63 (SD: 14.3) years (range: 29–85), a mean time of progression of symptoms upon admission of 9.7 (SD: 6.8) days and of admission of 11 (3.8) days (Fig. 2).

Twenty (65%) patients received a dose of TCZ monotherapy (Group 2). The PaO_2/FiO_2 average previous receive TCZ and at discharge was: 221 (114.9) vs 222 (150.9). Thirteen (65%) patients required ICU and 4 (20%) died, in the first 15 days of admission there were no differences between the BARI and TCZ groups in monotherapy, except in the RR at discharge (Table 1).

Eleven (18%) patients received TCZ and BARI (Group 3). The PaO_2/FiO_2 average prior to receiving TCZ and at discharge was: 224 (103) vs 188 (136). Three (27%) patients required ICU and died, two of them in the first 15 days of admission (Table 1).

When comparing the 31 patients who received TCZ to the 29 (48%) patients who had not, the group receiving TCZ at admission

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Table 1
Characteristics of patients admitted for COVID 19, according to treatment received: (1) BARI monotherapy. (2) TCZ monotherapy. (3) The patients have received BARI and TCZ. (4) Patients not treated with either BARI or TCZ.

	(1) BARI monotherapy *N*: 12 (20%)	(2) TCZ monotherapy *N*: 20 (33%)	(3) BARI+TCZ *N*: 11 (18%)	(4) No BARI/No TCZ *N*: 17 (28%)
Age, mean (SD)	67.8 (13.6)	59.4 (14.5)$^{+}$	70.1 (13.6)	73.8 (14.8)
Male, n (%)	9 (75)	15 (75)	8 (73)	11 (65)
Days with symptoms, mean (SD)	8.3 (5.8)	9.2 (7.5)	10.4 (6.1)	6.1 (4.8)
Days admission, mean (SD)	11.6 (3.6)	10.7 (4.1)	11.9 (3.5)	9.1 (2.5)^
Days on BARI, mean (SD)	6 (2.6)§	–	2.8 (2.5)$^{\neq\neq}$	–
OH-CLQ, n (%)	10 (83)	15 (75)	11 (100)	14 (82)
Corticosteroids, n (%)	11 (92)	20 (100)	11 (100)	10 (59)
Interferon, n (%)	2 (17)	6 (30)	4 (36)	2 (12)
Symptoms				
Cough, *n* (%)	10 (83)	18 (90)	8 (73)	13 (76)
Dyspnea, *n* (%)	10 (83)	15 (75)	6 (55)‡	8 (47)
Diarrhea, *n* (%)	3 (25)	6 (30)	2 (18)	1 (6)
Temperature °C, mean (SD)				
Admission	37.5 (0.9)	38.1 (1.1)	37.8 (0.9)$^{\neq}$	37.1 (1.0)
Last or discharge	36.2 (0.3)*	36.5 (0.9)	36.5 (0.9)	36.6 (0.6)
CRP mg/dL, mean (SD)				
Admission	16.6 (10.2)	15.7 (7.6)	17.9 (11.5)	12.5 (8.3)
Last or discharge	2.4 (3.3)	4.8 (9.2)	2.3 (3.5)	5.7 (10.2)
Lymphocytes/mm^3, mean (SD)				
Admission	975 (417.1)	860 (396.3)	690 (430.8)	1.087 (471.4)
Last or discharge	980 (528.6)	1.328 (888.3)	1.011 (557.8)	1.093 (854.0)
LDH U/L, mean (SD)				
Admission	555 (221.5)**	472 (234.9)	414 (223.7)	316 (165.1)
Last or discharge	512 (314.7)*	404.6 (256.9)	401 (319.1)	278 (109.3)
D Dimer ng/mL, mean (SD)				
Admission	12.265 (23.267)	5.455 (10.388)	8.227 (28.500,6)	6.205 (16.880)
Last or discharge	6.708 (10.484)	2.865 (3.563)	4.876 (10.958.4)	1.902 (2.001)
Neutropenia/mm^3 last <1.000, n (%)	0	0	0	0
GPT last, mean (SD)	66.1 (49.1)	93.8 (86.9)$^{+}$	30 (51.4)	69 (63.8)
SatO_2, mean (SD)				
Admission	90.5 (6.9)	91.7 (4.5)	87.2 (7.3)	94.2 (4.6)^
Last or discharge	94.7 (2.9)	91.7 (12.6)	94.2 (3.0)	93.2 (8.9)
PaFI, mean (SD)				
Admission	167 (82.3)**	221 (114.9)	236 (82.3)	276 (83.2)
Pre-BARI	165 (66.0)	–	108.5 (67.7)	–
Last or discharge	214 (74.3)*	222 (150.9)$^{+}$	133.8 (77.8)	330 (183.0)^
Respiratory frequency, mean (SD)				
Admission	28 (7.6)	30 (7.8)	34 (7.9)	25 (7.5)^
Last or discharge	19 (4.6)¶	24 (7.1)	21 (4.8)	22 (7.6)
Chest X-ray bilateral pneumonia, n (%)	11 (92)	20 (100)$^{+}$	10 (91)	13 (76)
Severe adverse effects (SAE)	0	0	0	-
Charlson Comorbidity Index, n (*SD*)	2.9 (1.7)	2.1 (2.4)	3.8 (1.8)	5 (2.9)
10-Year survival (%)	70.1	73.4	53.4	42.1
Admission to ICU, n (%)	0	13 (65)	3 (27)	0
Hospital readmission 30 days after discharge, n (%)	1	1	0	0
Overall mortality since admission, n (%)	2 (17)	4 (20)	3 (27)	6 (35)
1–15 days	2	4	2	3
16–30 days	0	0	1	3

BARI: baricitinib. TCZ: tocilizumab. No BARI/No TCZ: not treated with baricitinib or tocilizumab.
(1) BARI monotherapy vs (2) TCZ monotherapy: $^{\P}p$: <0.5.
(1) BARI monotherapy vs (3) No BARI-No TCZ: $^{*}p$:<0.05. $^{**}p$: <0.01.
(1) BARI monotherapy vs (4) BARI+TCZ: $^{\neq}p < 0.05$. $^{\neq\neq}p < 0.01$.
(2) TCZ monotherapy vs (3) No BARI-No TCZ: ^{+}p: <0.05. ^{++}p: <0.01.
(2) TCZ monotherapy vs (4) BARI-TCZ: $^{\ddagger}p < 0.05$.
(3) No BARI-No TCZ vs (4) BARI-TCZ: $^{\wedge}p < 0.01$ $^{\wedge\wedge}p < 0.001$.

was younger: 63 (SD: 14) years vs 71 (SD: 14) years ($p < 0.05$), had higher temperature: 37.9 °C (SD: 0.9) vs 37.1 °C (SD: 1) ($p < 0.05$), were treated shorter time with BARI: 2.8 (SD: 2.5) vs 6 (2.6) days ($p < 0.0001$) in patients treated with BARI monotherapy (Fig. 1); and before starting BARI, had lower PaO_2/FiO_2 (108.5 [67.7] vs 165 [66.0], $p = 0.06$).

Patients not treated with Baricitinib or Tocilizumab

In the group of 17 (28%) patients who did not receive any of the anti-cytokine drugs (Group 4), 11 (65%) were male, mean age of 71.8 (SD: 14.8) years (range: 41–91; 76% >70 years old), a mean time of progression from symptoms upon admission of 6.1 (SD: 4.8)

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Table 2
ICU admission, mortality, PaO_2/FiO_2 and anticytokine drugs received in patients admitted with interstitial pneumonia.

	All *N*: 60 (%)	<50 years *N*: 8 (13%)	50–70 years *N*: 20 (33%)	≤70 years *N*: 28 (47%)	>70 years *N*: 32 (53%)
ICU admission (*n*: 16), *n* (%)	16 (27)	6 (75)	9 (45)	15 (54)	1 (3)
Mortality (*n*: 15), *n* (%)	15 (25)	1 (12)	4 (9)	5 (18)	10 (31)
PaO_2/FiO_2 upon admission, mean (SD)	233.7 (100.9)	207.9 (110.5)	259.0 (101.5)	242.0 (101.5)	225.0 (101.9)
BARI monotherapy (*n*: 12), *n* (%)	12 (20)	1 (12)	5 (25)	6 (21)	6 (19)
TCZ monotherapy (*n*: 20), *n* (%)	20 (33)	5 (62)	10 (50)	15 (54)	5 (16)
BARI+TCZ (*n*: 11), *n* (%)	11 (18)	1 (12)	2 (10)	3 (11)	8 (25)
No BARI-No TCZ (*n*: 17), *n* (%)	17 (28)	1 (12)	3 (15)	4 (14)	13 (41)

ICU: Intensive Care Unit. BARI: baricitinib. TCZ: tocilizumab.

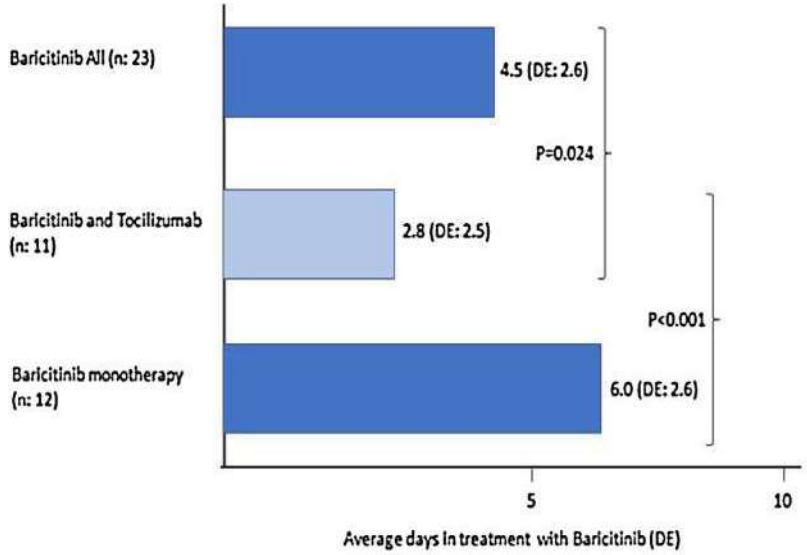


Figure 1. Average days in treatment with baricitinib: monotherapy or associated with tocilizumab.

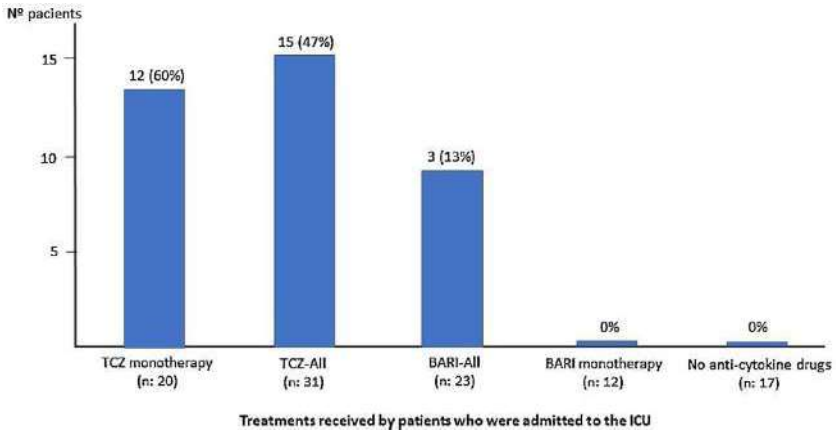


Figure 2. Percentage of patients admitted to the ICU, according to the treatment received. (BARI: baricitinib. TCZ: tocilizumab).

days, and of admission of 9.1 (2.5) days. The PaO_2/FiO_2 average at admission and at discharge was: 319 (193.8) vs 330 (183). None of the patients required ICU admission. However, 6 (35%) patients died, 3 (50%) of them in the first 15 days of admission (Table 1).

When comparing the patients of this group to patients who received BARI monotherapy, patients treated with BARI had a significantly higher LDH level upon admission (555 [SD: 221.5] vs 316 [SD: 165], $p < 0.01$) and at discharge (512 [SD: 314.7] vs 278 [SD: 109.3]), $p < 0.05$), and lower PaO_2/FiO_2 level upon admission (167 [SD: 82.3] vs 276 [SD: 83.2], $p < 0.01$) and at discharge (214 [SD: 74.3] vs 330 [SD: 183], $p < 0.05$). In both groups, none of the patients required admission to the ICU (Table 1).

When comparing the patients of this group with patients who received TCZ monotherapy (Table 1), patients treated with TCZ significantly presented upon admission, a higher percentage of bilateral radiological pneumonia (20 [100%], vs 13 [76%], $p < 0.05$), higher temperature (38.1 °C [SD: 1.0] vs 37.1 °C [SD: 1.1], $p < 0.01$), and higher LDH level (472 [SD: 235] vs 316 [165], $p < 0.05$).

Discussion

COVID19 infection causes mild illness in most patients. However, approximately 20% of patients can progress to SARS due to the appearance of IP, sepsis, or septic shock, requiring admission to

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an ICU in about 5% of cases.[27] Since many people become infected within a short period of time, it can lead to a health care collapse.

The current treatment of patients with IP by COVID19 is a challenge for clinicians. Pharmacological treatment is not based on the results of clinical trials, but on previous experiences with other viral infections. There are studies that demonstrate a direct relationship between IL6 level and patient severity.[28] Hence the interest in using drugs with anti-IL6 activity, such as TCZ, in these patients.

In general, TCZ was used after the first published efficacy data in China, due to its anti-IL6 action in the "cytokine storm", in patients with IP and SARS.[17] Given the possibility of difficulties in its supply in that time, the possible benefit of another drug with anti-IL6 action, such as BARI, administered orally, was assessed at our center at an early stage of respiratory failure due to COVID19.

Initially, BARI was introduced in our center for patients waiting to start TCZ, at a dose of 2 mg daily, due to the age of the patients and the presence of high levels of D-dimer. Subsequently, since all patients received prophylactic doses of low molecular weight heparin, it was changed to 4 mg daily, without finding relevant differences between both doses.

As expected, in our study patients receiving BARI and/or TCZ, presented more serious data upon admission, especially PaO_2/FiO_2. However, in the group who received BARI monotherapy, with the worst PaO_2/FiO_2 at admission, none of the patients was admitted to the ICU, as occurred in the group that was not treated with BARI and/or TCZ. Therefore, 3 patients, with $PaO_2/FiO_2 < 200$), received BARI before adding TCZ and continued to receive BARI at the same dose (sequential treatment), not requiring admission to the ICU. Regarding mortality, no differences were detected between all groups. On the other hand, patients who received TCZ, had the worst clinical evolution and therefore there was a higher percentage who entered the ICU, but with similar mortality. In addition, patients with poor clinical evolution or those did not respond to BARI, received TCZ, and presented a higher percentage of admission to ICU than the other groups.

These results could reinforce the idea of introducing BARI early, at the beginning of respiratory failure, measured with PaO_2/FiO_2, and TCZ could be add, if there is no clinical response and PaO_2/FiO_2 worsening, to prevent the need for ICU admission. On the other hand, a sequential treatment (BARI-TCZ-BARI) could be considered.

The length of time that the patient receives BARI and its early introduction, may be related to the possible efficacy of the drug. In patients of our study receiving BARI monotherapy, the mean treatment is 6 days compared to 2.8 days for the group receiving BARI and TCZ combined, mainly because in many patients BARI was started waiting for TCZ.

During the study, no relevant side effects related with BARI or TCZ have been recorded, even 30 days after discharge, such as thrombotic symptoms, herpes zoster, leukopenia, thrombopenia, or significant alteration of blood transaminases. This can be related to the short period of treatment received.

The age of the patients can be relevant for the prognosis. In our study, numerically relevant differences were detected between those over and under 70 years of age. In patients over 70, 3% of them were admitted to the ICU, but the mortality rate reached 31%. The mortality rate varies between series. In our study 15 (25%) patients died, all in the first 30 days after admission, but the 73% in the first 15 days. However, in the study of Chen,[12] 14% of 799 patients admitted died. In the registry from Spanish Society of Internal Medicine (SEMI), with 6.424 patients included, 8.5% received TCZ and 8% required ICU. The mortality rate was 21%, reaching 73% in patients over 70.[29]

So far, two studies from Italy have been published in patients treated with BARI for pneumonia due to COVID19. The first study, in 12 patients, although the patients were not randomized, they were compared with previous patients who did not receive BARI,[30] with promising results. Patients received standard treatment and BARI daily for 2 weeks and their clinical parameters, CRP, and respiratory evaluation improved in the first and second week. No severe side effects were detected and none of the patients required ICU admission. Recently, the same group has published a multicenter study with 113 patients to which BARI was added to the standard treatment and compared with 87 patients who received standard treatment. At 2 weeks of treatment, the BARI group had significantly lower mortality and ICU admission.[31]

Our study has obvious limitations: it is a retrospective and observational study, with a small number of patients and a great heterogeneity among patients treated with BARI or TCZ. It presents a confusion bias due to the severity of the disease, because the most severe patients, and therefore with greater probability of admission to the ICU and mortality, received treatment with anti-IL6 drugs. However, this study aims to draw attention to the possible benefit of BARI in severe cases of IP in this disease.

In summary, the treatment for patients with IP due to COVID19 has not been fully established. However, the combination of cytokine storm and IP, especially in those older than 70 years, darkens the prognosis. We have showed our experience with BARI and TCZ in this clinical situation. Treatment with BARI and TCZ did not cause serious side effects. They could be considered early in patients with NI secondary to COVID19 and impaired PaO2/PaFi. Randomized clinical studies with these drugs, including sequential therapy are required.

Ethical approval

This article does not contain any studies with animals performed by any of the authors. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The design of the study was approved by the AEMPS (Spanish Agency of Medicines and Medical Products) and by the Research Ethics Committee of University Hospital of Elche, Spain.

Authors' contribution

All authors contributed to the study conception, data collection and design. analysis were performed by José Rosas. The first draft of the manuscript was written by José Rosas and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Informed consent

As it is a retrospective study, it is not necessary to obtain informed consent.

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Conflict of interest

The authors have no conflict of interest.

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ANNEXURE-10

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Impact of high dose of baricitinib in severe COVID-19 pneumonia: a prospective cohort study in Bangladesh

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Abstract

Purpose: Hyperinflammation in severe COVID-19 infection increases the risk of respiratory failure and one of the cogent reasons of mortality associated with COVID-19. Baricitinib, a janus kinases inhibitor, can potentially suppress inflammatory cascades in severe COVID-19 pneumonia.

Methods: The objective of this study was to compare the clinical outcomes of high dose of baricitinib with its usual dose in patients with severe COVID-19 pneumonia. This prospective cohort study was conducted on 238 adult patients with severe COVID-19 pneumonia. Eight milligram and 4 mg of baricitinib was given orally to 122 patients in the high dose (HD) group and 116 patients the usual dose (UD) group, respectively daily for 14 days, and clinical outcomes were compared among the groups.

Results: Blood oxygen saturation level was stabilized (≥94% on room air) earlier in the HD group compared to the UD group [5 (IQR: 4–5)/8 (IQR: 6–9), $P < 0.05$]. Patients in the HD group required intensive care unit (ICU) and intubation supports more in the UD group than that in patients of the HD group [17.2%/9%, $P < 0.05$; 11.2%/4.1%, $P > 0.05$; $N = 116/122$, respectively]. The 30-day mortality and 60-day rehospitalization rate were higher in the UD group than the HD group [6%/3.3%, $P < 0.01$; 11.9%/7.6%, $P > 0.05$; $N = 116/122$, respectively].

Conclusion: The daily high dose of baricitinib in severe COVID-19 results in early stabilization of the respiratory functions, declined requirements of critical care supports, reduced rehospitalization with mortality rate compared to its daily usual dose.

Keywords: Baricitinib, Severe COVID-19 pneumonia, Cytokine storm, High dose, Usual dose

Background

The first outbreak of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, was expedited from the city of Wuhan, China in December 2019 [1, 2]. In January 2020, the World Health Organization (WHO) revealed the outbreak of a global health emergency, and in March 2020, WHO declared COVID-19 a pandemic infectious disease [2]. As of 22 November 2020, over 57.8 million confirmed COVID-19 cases and 1.3 million deaths reported across the world [3].

The outbreak first came under the spotlight as an unusual viral pneumonia and till to date, atypical upper respiratory tract pneumonia is the major feature of the severity of the disease [4]. This respiratory virus binds to angiotensin-converting enzyme 2 (ACE2) receptors by

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using its spike proteins to enter into the host cells. The entry of SARS-CoV-2 may result in the development of cytokine storm in the host body characterized by high plasma level of pro-inflammatory cytokines, including interleukin (IL)-6, IL-2, IL-7, IL-10, monocyte chemoattractant protein (MCP1), macrophage inflammatory protein (MIP1A), TNF (tumor necrosis factor)-alpha, and interferon gamma inducible protein (IP10) [5, 6]. The bronchoalveolar lavage taken from the patients with severe COVID-19 pneumonia showed high level of chemokines secreted from the macrophages [7]. Postmortem analysis of lung tissue of patients with severe COVID-19 pneumonia also found excessive amount of immune cell infiltration [8]. The up-regulation pattern of systemic cytokines in patients with severe COVID-19 pneumonia was found very similar to that in cytokine release syndromes, including macrophage activation syndrome, manifested by elevated level of cytokines, such as IL-6, IL-7, and TNF-alpha, and inflammatory chemokines like, CC-chemokine ligand 2 (CCL-2), CCL-3 and CXC-chemokine ligand 10 (CXCL-10), and the soluble form of the α-chain of the IL-2 receptor, resulting in the dysregulated activation of the mononuclear phagocyte (MNP) compartment leading to hyperinflammation in patients with COVID-19 pneumonia [9].

The United States' Food and Drug Administration (FDA) approved baricitinib for the treatment of active rheumatoid arthritis has recently been identified as a new hope for the treatment of COVID-19 pneumonia, and its use at a dose of 4 mg in COVID-19 has received the Emergency Use Authorization (EUA) from FDA on November 19, 2020 [10]. Baricitinib is a Janus kinases (JAK)-1 and JAK-2 inhibitor which exhibits dual role in the inhibition of hyperinflammation in COVID-19 pneumonia including, the inhibition of proinflammatory mediators release and endocytosis of the virus [11]. The cell-mediated signaling pathway between JAKs and signal transducers and activators of transcription proteins (STATs) is essential to activate phosphorylation process leading to cytokine release. Baricitinib inhibits this pathway selectively by blocking JAK-1 and-2 which results is down-regulation of cytokine storm in COVID-19 [11]. Recently, the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) found that compared to placebo, baricitinib combinedly with remdesivir in patients with COVID-19 revealed faster recovery time [95% confidence interval (CI), 7 to 9 day versus 6 to 8 day] and reduced 28-day mortality rate (7.8 and 5.1%, respectively), significantly [12]. Another recent case-control study found that an additional 8 mg oral loading dose of baticitinib followed by 4 mg daily revealed better clinical outcomes in patients with severe COVID-19 pneumonia compared to 4 mg baricitinib daily without loading dose [13]. Though there is no standard drug has yet been developed to manage the hyperinflammation in COVID-19 patients so, experimental high dosing strategy of the available drugs, including baricitinib with assuring drug safety may be effective at this crisis moment [14]. The primary objectives of this study were to evaluate the impact of high dose versus usual dose of baricitinib on the progression of the disease, normalization of breathing function, and reduction in demand of complementary oxygen. The secondary objectives were to compare the requirement of ICU support, 60-day rehospitalization after discharge, and 30-day mortality among the patients treated with high dose or usual dose of baricitinib.

Materials and methods

Study design and data collection

This prospective cohort study was conducted in the "Specialized COVID-19 Unit (SCU)" of Square Hospital Ltd., Dhaka, Bangladesh (a tertiary care 400-beded private hospital), on 238 adult patients (≥18 years) with severe COVID-19 pneumonia admitted to this hospital from July 1 to October 1, 2020 directly from home. The 238 patients were selected for the study (based on the inclusion and exclusion criteria) from the total 472 hospital admitted patients with confirmed COVID-19 to COVID-19 special unit of the hospital.

All the COVID-19 positive patients were passed through a two-step triage system in the emergency department of the hospital before getting their admission in the SCU and their COVID-19 infection was confirmed by positive reverse transcriptase polymerase chain reaction (RT-PCR) assay (instrument/device: Rotor Gene-Q/Cobas z480, and QIAGEN kits for real-time PCR, QIAGEN GmbH, Germany) of two separate specimens (nasal and oral swabs) in the Molecular laboratory of the hospital. Every patient's clinical diagnosis, comorbidities, and lab investigations were evaluated and recorded at the time of hospital admission.

All the data of patients and medications of this study were collected from the electronic patient database of the hospital and manually from the patients' prescriptions. A dedicated multidisciplinary team consisting of four doctors and two clinical pharmacists was charged for all the patients' data collection and drug-associated adverse event monitoring. Lab investigations and physical assessment of all the patients were performed routinely. The research related to human use has been complied with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Declaration of Helsinki, and has been approved by the Research Ethics Committee, Square Hospitals Ltd., Dhaka, Bangladesh (no. 2006SH-OR027) on June 10, 2020.Written consent was taken from all participants in this study.

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Study groups and treatment

Among the 238 patients, 122 (N) and 116 (N) patients were included into the "high dose group" (HD group) and "usual dose group" (UD group), respectively using the simple random sampling method. The HD and UD group's patients received 8 mg (into two divided doses) and 4 mg of baricitinib orally daily, respectively started within 4 h of hospital admission and continued for 14 days. Dexamethasone (corticosteroid) intravenously was given to all patients of both the groups along with the baricitinib at a dose of 0.25 mg/Kg of body weight once daily. Both baricitinib and dexamethasone was started at a time within 2 h of hospitalization in every patient. The source of baricitinib was: "Baritor 2" (baricitinib 2 mg film-coated tablet) by Square Pharmaceuticals Ltd., Dhaka, Bangladesh. Patients received intravenous remdesivir (antiviral) (200 mg loading followed by 100 mg once daily) either for 5 days (while the patient was not intubated or on bi-level positive airway pressure therapy or on high-flow nasal cannula oxygen therapy) or for 10 days (while the patient was intubated or on bi-level positive airway pressure therapy or on high-flow nasal cannula oxygen therapy). In addition, low molecular weight heparins (enoxaparin/dalteparin) for anticoagulation were used in patients of the study. In case of patients discharged to home before completing the course of recommended drug therapy, the residual therapy was given to patients at home solely facilitated by the hospital itself. All the patients in the study completed the total 14 days of baricitinib therapy (HD or UD) at the hospital except the patients died within 30-day of study period in both groups.

Inclusion criteria

Sample inclusion criteria were as follows:

a) SARS-CoV 2 is present in the nasal/oral swabs
b) no previous history of COVID-19 infection
c) having at least two additional signs of severe COVID-19 pneumonia with confirmed pneumonia lesions (bilateral ground-glass opacities) (> 50%) in the chest computerized tomography (CT) scan images at the time of admission: (1) dyspnoea; (II) oxygen saturation in blood (SpO_2) level ≤ 93% on room air; and (III) respiratory rate ≥ 30 breaths/min
d) Onset of symptom(s)-to-hospitalization no more than 10 days
e) No history of taking any anti-inflammatory drugs within last 3 months of hospital admission

Exclusion criteria

Sample exclusion criteria were as follows:

a) patient with pregnancy
b) any history of trauma or surgical procedure within the last 3 months of hospital admission
c) any history of acute/chronic autoimmune disease or active/latent tuberculosis infection
d) history of hospital stay for > 3 days for any purpose with the last 3 months
e) current evidence of bacterial or fungal coinfection
f) coming from another hospital or healthcare facility

Definition of severe COVID-19 pneumonia

The severe stage of COVID-19 infection in a patient is determined with the evidence of bilateral multi-focal opacities (pneumonia) in the CT-scan images (lung infiltrates > 50% within 24 to 48 h) and other (one or more) signs of disease severity, including dyspnoea, fast breathing rate (≥30 breaths/min), and SpO2 ≤ 93% on room air (RA) [15].

Data analysis

The statistical analyses were performed by Statistical Product and Service Software (SPSS ver. 22.0, Chicago, IL, USA). Descriptive statistics were presented through median value and interquartile range (IQR). Continuous variables were compared using Mann–Whitney U test, and categorical variables were compared using Pearson Chi-square test. To analyze overall survival in the groups (high dose vs usual dose) we plotted Kaplan-Meier curves. A P value of ≤0.05 was considered statistically significant.

Results

The number of male patients in both the groups was higher than the number of female patients with a median age of 63 (IQR: 54.8–69) and 59 (IQR: 54–68) in HD and UD group, respectively ($P > 0.05$). The median time from onset of symptoms-to-hospitalization was less than 10 days in all patients of this study. With fever [100 (IQR: 100–101)/101 (IQR: 100–101) ($P = 0.306$)], other symptoms, including dry cough (100%/100%), weakness (100%/100%), shortness of breath (78.7%/81%) ($P = 0.429$), anosmia (64.8%/75.9%) ($P = 0.029$), diarrhea (55.7%/49.1%), and sore throat (50.8%/60.3%)) were diagnosed in patients of HD ($N = 122$) and UD group ($N = 116$), respectively. Diabetes, hypertension, cardiovascular disease, bronchial asthma, chronic kidney disease, chronic obstructive pulmonary disease, obesity, peptic ulcer disease, chronic liver diseases, malignancy, and Parkinson's disease were found as predisposed chronic diseases in patients with COVID-19 of this study (Table 1). Clinical characteristics, including SpO_2 profile, respiratory and cardiac functions, kidney and liver functions, infection markers, inflammation marker, and hematological components of all the patients in both the groups are given in Table 1 and compared, statistically.

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Table 1 Baseline demographic information, symptoms of COVID-19, comorbidity and laboratory findings in patients during admission

Variable	HD group (*N* = 122)	UD group (*N* = 116)	*P* value
Male/female, n (%)	83/39 (68/32)	76/40 (66/34)	
Age (year), median (IQR)	63 (54.8–69)	59 (54–68)	0.655
Onset of symptom-to-hospitalization time, median (IQR)	6 (6–8)	7 (6–8)	0.144
Fever (°F), median (IQR)	101 (100–101)	101 (100–101)	0.306
Dry cough, n (%)	122 (100)	116 (100)	
Weakness, n (%)	122 (100)	116 (100)	
Shortness of breath, n (%)	96 (78.7)	94 (81)	0.429
Anosmia, n (%)	79 (64.8)	88 (75.9)	0.029
Diarrhea, n (%)	68 (55.7)	57 (49.1)	0.001
Sore throat, n (%)	62 (50.8)	70 (60.3)	0.001
Diabetes, n (%)	95 (77.9)	88 (75.9)	0.392
Hypertension, n (%)	86 (70.5)	81 (69.8)	0.166
CVD, n (%)	55 (45.1)	47 (40.5)	0.001
Bronchial asthma, n (%)	43 (35.2)	36 (31)	0.001
CKD, n (%)	21 (17.2)	23 (19.8)	0.001
COPD, n (%)	17 (13.9)	14 (12.1)	0.001
Obesity, n (%)	15 (12.3)	14 (12.1)	0.001
PUD, n (%)	11 (9)	16 (13.8)	0.001
CLD, n (%)	6 (4.9)	8 (6.9)	0.001
Malignancy, n (%)	3 (2.5)	4 (3.4)	0.001
PD, n (%)	2 (1.6)	1 (0.9)	0.001
SpO_2 (%), median (IQR)	90 (88–90.3)	90 (88–90)	0.628
RSO, median (IQR)	7 (4–11)	7 (4–10)	0.640
Respiratory rate, (breaths/min), median (IQR)	25 (21–26)	21 (19–25)	0.001
Heart rate (beat/min), median (IQR)	98 (85–106)	90 (85–102)	0.072
CRP (mg/L), median (IQR)	179 (76.9–263.5)	159 (44.5–231.4)	0.199
Procalcitonin (ng/mL), median (IQR)	1.04 (0.08–2.69)	0.9 (0.12–1.26)	0.001
WBC (K/μL), median (IQR)	9.5 (6.4–12.4)	9.2 (6.7–12.1)	0.915
Neutrophils (%), median (IQR)	86 (77.2–88.9)	86.3 (78.6–90.2)	0.110
Lymphocytes (%), median (IQR)	14.3 (11.5–16.5)	13.9 (10.8–16.4)	0.141
Platelet (K/μL), median (IQR)	188.5 (144.8–256)	215 (150.7–295.8)	0.327
D-dimer (mg /L FEU), median (IQR)	5.2 (3.9–6.8)	4.9 (2.6–6.3)	0.392
IL-6 (pg/mL), median (IQR)	47 (17.5–78)	45 (10.5–75.7)	0.153
Serum Ferritin (ng/mL), median (IQR)	605 (478–786)	641 (456–787.5)	0.144
LDH ((U/L), median (IQR)	489 (409–646.7)	474 (408.5–593)	0.088
Creatinine (mg/dL), median (IQR)	1.1 (0.8–1.9)	1.1 (0.7–1.7)	0.122
ALT (U/L), median (IQR)	58 (46–83)	56 (40.7–75.8)	0.485
AST (U/L), median (IQR)	36.5 (29–48)	35 (29–46)	0.011
MEWS, median (IQR)	3 (2–3)	3 (2–3)	0.001

IQR Interquartile range, *n* Number, % Percentage, *°F* Grade Fahrenheit, *CVD* Cardiovascular disease, *CKD* Chronic kidney disease, *COPD* Chronic obstructive pulmonary disease, *PUD* Peptic ulcer disease, *CLD* Chronic liver disease, *PD* Parkinson's disease, *SpO_2* Oxygen saturation in blood, *min* Minute, *RSO* Requirement of supplemental oxygen, *CRP* C-reactive protein, *mg* Milligram, *L* Liter, *FEU* Fibrinogen equivalent units, ng Nanogram, *WBC* White blood cells, *K/μL* Thousand cells per micro liter, *IL* Interleukin, *pg/mL* Picograms per milliliter, *LDH* Lactate dehydrogenase, *U/L* Units per liter, *dL* Deciliter, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *MEWS* Modified Early Warning Score

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Patients in HD group treated with high dose (8 mg) of baricitinib developed thrombocytosis and mouth sore significantly more than the patients received 4 mg usual dose of baricitinib (UD group) (9.8%/2.6 and 2.4%/0.8%, $N = 122/116$, respectively) within the duration of therapy (Fig. 1). Platelet count did not exceed 700 K/μL of blood in any patient of HD or UD group after receiving baricitinib (high or usual dose) and all the patients ($N = 238$) in the study completed the full course (14-day) of baricitinib (high or usual dose) therapy. In clinical justification, no bacterial or fungal or any other opportunistic infections were developed due to baricitinib therapy in patients of both the groups.

The median day to reach the targeted SpO_2 (≥94% on RA) was significantly less in the HD group [5 (IQR: 4–5)] than that in the UD group [8 (IQR: 6–9)], and the median day to return in zero supplemental oxygen demand was significantly less in the HD group [5 (IQR: 4–5)] than that in the UD group [8 (IQR: 6–9)]. Nine-percent and 4.1% of patients ($N = 122$) in HD group and 17.2 and 11.2% of patients ($N = 116$) in UD group underwent ICU ($P = 0.020$) and intubation support ($P = 0.001$) due to exacerbation of the disease during their hospitalization time. The median day of hospitalization was lower in the HD group [11 (IQR: 9.5–14)] than that in the UD group [13 (IQR: 10–17.5)] ($P = 0.072$). The 30-day all-cause mortality rate was significantly higher in the usual dose group (6%, $N = 116$) than in the HD group (3.3%, $N = 122$) (Table 2). The Kaplan-Meier 30-day survival curve was analyzed using groups (HD vs UD) and illustrated in Fig. 2. In HD and UD group, 118 ($N = 122$) and 109 ($N = 116$) patients, respectively were discharged to home with acceptable health condition upon medical advice. After discharging from hospital, more patients in UD group were rehospitalized (11.9%, $n = 109$) again due to breathing problems within 60-day of first hospital admission than the patients in HD group (7.6%, $n = 118$) ($P > 0.05$) (Fig. 3).

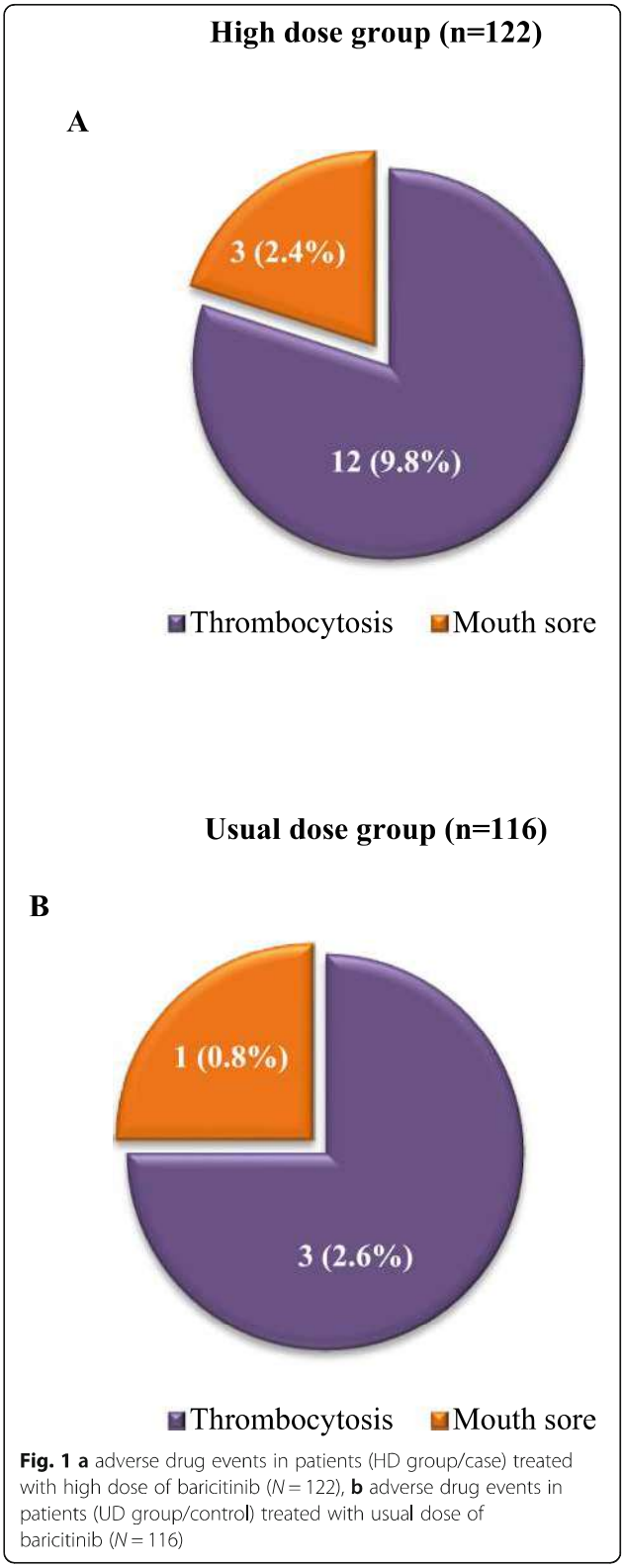


Fig. 1 **a** adverse drug events in patients (HD group/case) treated with high dose of baricitinib ($N = 122$), **b** adverse drug events in patients (UD group/control) treated with usual dose of baricitinib ($N = 116$)

Discussion

In this study, patients with severe COVID-19 pneumonia treated with high oral dose (8 mg in two divided doses, daily) of baricitinib (started at early hours of hospitalization) showed early stabilization of the respiratory functions ($SpO_2 \geq 94\%$ on RA and no requirement of supplemental oxygen), lower risk of ICU and intubation support due to exacerbation of the severity of the disease, and length of hospital stay compared to patients treated with usual dose (4 mg once daily) of baricitinib for a period of 14 days. In our recent case-control study on 37 patients with moderate-to-severe COVID-19 pneumonia, we found that compared to usual daily dose regimen (4 mg) of baricitinib, a single 8 mg oral loading dose-based daily usual dose (4 mg) regimen of baricitinib for 14 days revealed better clinical outcomes, including early normalization of SpO_2 (≥95%) on RA and restoration of normal breathing function [4 (IQR: 4–5)/3

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Table 2 Clinical outcomes in patients with severe COVID-19 pneumonia treated with high or usual dose of baricitinib

Parameters	HD group (*n* = 122)	UD group (*n* = 116)	*P* value
Days for SpO_2 ≥ 94% on room air, median (IQR)	5 (4–5)	8 (6–9)	0.001
Days for no supplemental oxygen demand, median (IQR)	5 (4–5)	8 (6–9)	0.001
Days for respiratory rate < 20 breaths per min	6 (5–6)	8.5 (8–9)	0.001
ICU support, n (%)	11 (9)	20 (17.2)	0.020
Intubation required, n (%)	5 (4.1)	13 (11.2)	0.001
Length of hospital stay (day), median (IQR)	15 (9–18.5)	12 (10–14)	0.072
30-day all-cause mortality, n (%)	4 (3.3)	7 (6)	0.001

HD High dose, *UD* Usual dose, *SpO_2* Peripheral capillary oxygen saturation, *IQR* Interquartile range, *ICU* Intensive care unit, *n* Number, % Percentage

(IQR: 2–8), $P > 0.05$; 8 (IQR: 7–10)/ 5 (IQR: 4–5), $P < 0.05$, respectively] [13].

Several studies reported that among the hospital admitted patients with COVID-19, 15.7 to 26.1% cases are severe and often difficult to clinically justify on the basis of abnormal laboratory investigations and CT scan report [16–18]. Though, there is no standard anti-inflammatory drug therapy for the treatment of severe pneumonia in COVID-19 infection, so early diagnosis and initiation of treatment upon hospital admission with the available drugs may attribute favorable clinical outcome [12, 19]. In this study, along with the antiviral and steroid therapy, the anti-inflammatory drug baricitinib was started in both the groups' patients with severe COVID-19 pneumonia within 4 h of hospital admission.

In severe state of COVID-19 infection, the activated polyfunctional CD4+ and CD8+ T lymphocytes make the biggest defense against the coronavirus and decreasing their count results in lymphopenia in about 85% of patients with severe COVID-19 infection [20]. In response to reduced T cell count, excessive amount of proinflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) are released along with upregulation of chemokines (CCL2, CXCL10, CXCL9, and IL-8). This hyperstimulated inflammatory cascade triggers up the cytokine storm which may ultimately results in acute lung injury

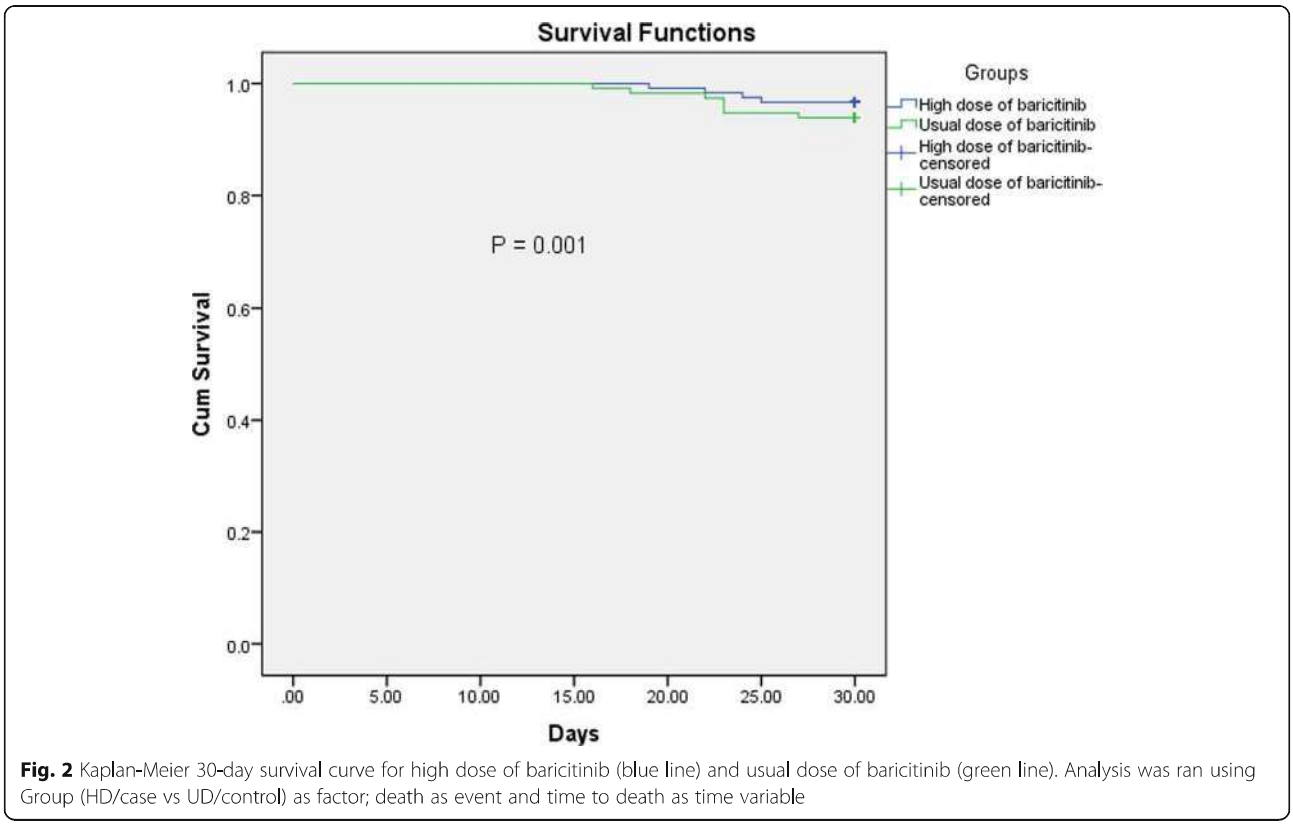


Fig. 2 Kaplan-Meier 30-day survival curve for high dose of baricitinib (blue line) and usual dose of baricitinib (green line). Analysis was ran using Group (HD/case vs UD/control) as factor; death as event and time to death as time variable

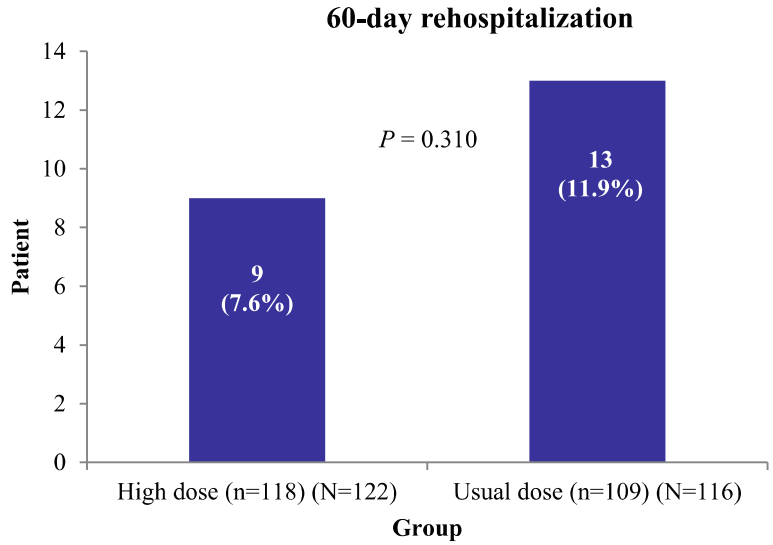


Fig. 3 60-day rehospitalization rate of patients with severe COVID-19 infection treated with high (case) or usual (control) oral dose of baricitinib for 14 days

(ALI) and acute respiratory distress syndrome (ARDS) leading to respiratory failure [5, 6]. The oral JAK1/JAK2 inhibitor baricitinib has been intended to use as an anti-inflammatory or anti-cytokine agent in COVID-19 in a few setups across the world [12, 13].

A recent in vitro pharmacology study showed that baricitinib selectively inhibits cytokine-dependent inhibition of phosphorylated STAT, a group of transcription factors that are highly regulated by JAK/STAT signaling pathway, following a concentration versus response curve. This baricitinib-driven blockage in cytokine-mediated JAK/STAT signaling pathway potentially leads to reduction in the concentration of L-2, IL-6, IL-10, IFN-γ, and G-CSF, with lower IC (inhibitory concentration) 50 values [21]. The systemic exposure of orally taken baricitinib is dose-dependent [12], and in healthy human volunteers, following oral administration of baricitinib, the peak plasma concentration attained within 1.5 h, pharmacodynamics shows linear dose versus time invariant, accumulates minimally in blood following repeat oral dosing, and pharmacokinetics is directly proportional to its systemic concentration [22]. In our study, 8 mg (4 mg at 12 h interval) oral daily dose of baricitinib (HD group) showed better suppression of pro-inflammatory cytokine release in patients with severe COVID-19 pneumonia with higher systemic drug concentration, and as a result, total breathing function was restored earlier with a reduction in ICU and intubation support compared to the patients in UD group treated with 4 mg orally daily [9%/17.2%, $N = 122/116$, $P < 0.05$; 4.1%/11.2%, $N = 122/116$, $P > 0.05$, respectively]. Antiviral role of baricitinib is an additional benefit of baricitinib therapy, and study mentioned that in combination with antiviral remdesivir, baricitinib may reduce viral load and strongly aberrant host inflammatory response in COVID-19 [23]. In our study, we used baricitinib with remdesivir (5 days) and steroid (14 days) in both the groups.

Multiple studies reported that massive systemic inflammation and multiple organ failure are the major causes of high hospital mortality rate in patients with severe COVID-19 pneumonia. Respiratory failure (41.6%) was the most common in severe COVID-19 infection followed by acute myocardial infarction (38.9%), acute liver injury (25.7%), and acute kidney injury (23.0%) [14, 17, 18, 24]. A study found that early initiation of baricitinib-based antiviral therapy reduced both the ICU admission and mortality in patients with moderate COVID-19 pneumonia [12]. Studies showed that among the post-COVID-19 patients who were discharged to home, 3.6 to 4.4% of patients readmitted in hospital where the most common cause was respiratory distress (50%) [25, 26]. In this study, 8 mg of oral baricitinib in two-divided dosages (12 h apart) daily in severe COVID-19 cases reduced 30-day mortality, significantly compared to 4 mg once daily dosing regimen [3.3% ($N = 122$)/6% ($N = 116$), respectively], and patients treated with high dose of baricitinib for 14 days (HD group) re-admitted to hospital within 60-day of first hospitalization with positive COVID-19 symptoms with breathing problem less than the patients treated with usual dose of baricitinib (UD group) [7.6% ($N = 122$)/11.9% ($N = 116$), $P > 0.05$].

Baricitinib is well tolerated in patients with COVID-19 and associated complications are very rare as mentioned in recent studies [12, 27]. In this study, adverse events

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(AEs) associated with prescribed medications including baricitinib were monitored and recorded continuously, and 9.8 and 2.4% of patients in HD group ($N = 122$) developed baricitinib-induced thrombocytosis and mouth sore, respectively which was less in the patients of UD group (thrombocytosis/mouth sore: 2.6 and 0.8%, respectively). But these AEs were not serious or life-threatening. No patient in the study (HD/UD group) experienced an elevated platelet count above 700 K/μL of blood during hospital stay and all the patients completed 14-day long baricitinib therapy. Mouth sore was healed with the application of amlexanox 50 mg/g oral paste four times a day. Study found that baricitinib at an 8-fold higher systemic concentration attained after a 4 mg dose does not cause hepatic cell damage [21]. However, the 14-day duration of the baricitinib therapy was not reduced in any group (HD or UD) of this study due to the development of AEs. Because a recent study highlighted that recurrent SARSCov-2 was detected in nasopharyngeal swabs in rapidly recovered and discharged-to-home patients treated with a 10-day long baricitinib therapy [21].

The recent EUA from US FDA regarding the use of baricitinib in COVID-19 is a new hope for frontline clinicians around the globe in order to save their patients from hyperinflammation and other serious complications in-advance associated with moderate-to-severe severe COVID-19 infections [10]. Soon, some randomized controlled studies are highly required to make evidence the benifits of using high dose of baricitinib in severe COVID-19 pneumonia rather than usual dose. The major limitations of this study were: single-center study on same origin of population (South Asian), small sample size, non blinded study, and no pharmacokinetics study to determine the systemic drug exposure level.

Conclusion

Hyperinflammatory response-associated serious complications leading to multiple organ failures are life-threatening situation in severe COVID-19 infection. Baricitinib has been spotlighted as a potential anti-inflammatory agent in COVID-19 infection. This study found that an 8 mg daily oral dose of baricitinib for 14-day revealed early normalization of respiratory function, reduced need of ICU and intubation support, declined 30-day mortality rate, and minimized 60-day rehospitalization rate compared to usual 4 mg daily oral dose of baricitinib in severe COVID-19 pneumonia.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; ACE2: Angiotensin-converting enzyme 2; IL-6: Interleukin-6; MCP1: Monocyte chemoattractant protein; MIP1A: Macrophage inflammatory protein; TNF-alpha: Tumor necrosis factor; IP10: Interferon gamma inducible protein; CCL-2: CC-chemokine ligand 2; CXCL-10: CXC-chemokine ligand 10; MNP: Mononuclear phagocyte; FDA: Food and Drug Administration; EUA: Emergency Use Authorization; JAK: Janus kinases; STATs: Signal transducers and activators of transcription proteins; ACTT-2: Adaptive COVID-19 Treatment Trial 2; CI: Confidence interval; SCU: Specialized COVID-19 Unit; RT-PCR: Reverse transcriptase polymerase chain reaction; HD: High dose; UD: Usual dose; CT: Computerized tomography; SpO_2: Oxygen saturation; RA: Room air; SPSS: Statistical product and service software; IQR: Interquartile range; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; IC: Inhibitory concentration; AE: Adverse event

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Code availability

None.

Authors' contributions

Study concept: MJH. Draft and critical revision of study protocol: MJH, RR, AMA, SMRH, MMIP. Database query: MJH, SSTN, SCB. Statistical analyses: MJH. Data evaluation and result presentation: MJH, AMA. Draft and critical revision of the article: MJH, RR, AMA, SMRH, MMIP, SSTN. Overall responsibility: MJH. The author(s) read and approved the final manuscript.

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Availability of data and materials

Study data are available upon request to corresponding author.

Declarations

Ethics approval and consent to participate

The Ethical permission was taken for this study from the Research Ethics Committee, Square Hospitals Ltd., Dhaka, Bangladesh (no. 2006SH-OR027) on June 10, 2020.
Written consent was taken from all participants to participate in the study.

Consent for publication

Written consent was taken from all participants to publish data in the study.

Competing interests

No conflict of interest to declare by the authors.

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U.S. FOOD & DRUG ADMINISTRATION

November 19, 2020

Eli Lilly and Company
Attention: Jillian Venci Fuhs, JD, PharmD
Advisor, Global Regulatory Affairs – North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Fuhs:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in certain hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Baricitinib (Olumiant) is approved by FDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. Baricitinib has not been approved by FDA for the treatment of COVID-19.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

Based on review of the data from the randomized, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone, also called ACTT-2 (NCT04401579), data for baricitinib that FDA reviewed for the FDA-approved indication of rheumatoid arthritis (NDA 207924), and data from populations studied for other indications, including pediatric patients, it is reasonable to believe that baricitinib may be effective, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of baricitinib for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of baricitinib for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that baricitinib, in combination with remdesivir, may be effective in treating suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used in combination with remdesivir to treat COVID-19 in such patients outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.[3, 4]

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[4] On October 22, 2020, remdesivir was approved to treat COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization. Remdesivir is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-COV-2. Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19. The Adaptive COVID-19 Treatment Trial 2 (ACTT-2) trial provided scientific evidence that the combination of baricitinib plus

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- The baricitinib covered by this authorization will be used only by healthcare providers, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized[5] adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO; and

- The use of baricitinib covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

Baricitinib is a Janus kinase (JAK) inhibitor. Baricitinib is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface. Baricitinib tablets are to be taken orally or can be crushed, dispersed in water, and given via a gastrostomy tube. The authorized baricitinib includes commercially available[6] Olumiant (baricitinib) supplied in 30 count bottles as follows:

- OLUMIANT (baricitinib) 1 mg (NDC 0002-4732-30)
- OLUMIANT (baricitinib) 2 mg (NDC 0002-4182-30)

Baricitinib should be stored at 20° to 25°C (68° to 77°F) with excursions permitted to 15° to 30°C (59° to 86°F).

Baricitinib is authorized for emergency use with the FDA-approved package insert and the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Lilly's website at *www.baricitinibemergencyuse.com*:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Baricitinib

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Baricitinib

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remdesivir provided a potential clinically meaningful benefit as compared to remdesivir alone in time to recovery, NIAID Ordinal Scale outcome at Day 15, and progression to ventilation or death at Day 29. Veklury's FDA-approved indication is for a narrower population than the use authorized for baricitinib under this EUA.

[5] Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

[6] For the purposes of this Letter of Authorization, commercially available Olumiant (baricitinib) tablets refers to product in United States distribution under the approved New Drug Application 207924.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of baricitinib, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that baricitinib may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that baricitinib (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), baricitinib is authorized, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Eli Lilly and Company (Lilly) and Authorized Distributors[7]

A. Lilly and authorized distributor(s) will ensure that the authorized baricitinib is distributed and the FDA-approved package insert and authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Lilly and authorized distributor(s) will ensure that appropriate storage is maintained until the authorized product is delivered to healthcare facilities and/or healthcare providers.

C. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized baricitinib. Lilly will provide to all relevant

[7] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized baricitinib.

stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Lilly may request changes to this authorization, including to the authorized Fact Sheets for baricitinib, that do not alter the analysis of benefits and risks that underlies this authorization and FDA may determine that such changes may be permitted without amendment of this EUA. That determination must be made by joint decision of the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research (CDER), the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER, and Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist/Office of the Commissioner.

E. Lilly will report to FDA serious adverse events and all medication errors associated with the use of the authorized baricitinib that are reported to Lilly using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "Baricitinib treatment under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

F. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

G. Lilly will submit information to the Agency within three working days of receipt of any information concerning any batch of authorized baricitinib (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; and (2) information concerning any bacteriological or microscopic contamination, or any significant chemical, physical, or other change in deterioration in the drug product, or any failure of one or more batches of the drug product to meet the established specifications. Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

H. Lilly will not implement any changes to the description of the authorized product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency.

I. Lilly will manufacture and test authorized baricitinib per the process and methods, including in-process sampling and testing and finishing product testing (release and stability) to meet all specifications as detailed in Lilly's EUA request.

J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized baricitinib (i.e., lot numbers, quantity, receiving site, receipt date).

K. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom the Authorized Baricitinib Is Distributed and Healthcare Providers Administering the Authorized Baricitinib

L. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of baricitinib for the authorized use.

M. Healthcare facilities and healthcare providers will track serious adverse events that are considered to be potentially attributable to the authorized baricitinib use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "Baricitinib treatment under Emergency Use Authorization (EUA)" at the beginning of the question "Describe Event" for further analysis.

N. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the authorized product is administered consistent with the terms of this letter.

O. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized baricitinib (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

P. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

Q. All descriptive printed matter, advertising, and promotional material, relating to the use of the baricitinib under this authorization shall be consistent with the authorized labeling, as

well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

R. No descriptive printed matter, advertising, or promotional material, relating to the use of baricitinib under this authorization may represent or suggest that such products are safe or effective when used, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

S. All descriptive printed matter, advertising, and promotional material, relating to the use of the baricitinib under this authorization clearly and conspicuously shall state that:

- the baricitinib has not been approved, but has been authorized for emergency use by FDA, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

- the baricitinib is authorized, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the baricitinib under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

ANNEXURE-12

Karnataka adds new medicines to Covid treatment protocol

Baricitinib, DRDO's 2-deoxy-D-glucose reduce O2 dependence of patients

Share

Published: 12th May 2021 05:16 AM | Last Updated: 13th May 2021 04:28 PM

A+ A A-



(File photo | Shriram BN)

By Iffath Fathima

Express News Service

BENGALURU: As the intense second Covid-19 wave continues to ravage the state, the State Government is adding new medicines to the treatment protocol. Baricitinib tablets of 1mg, 2mg and 4mg strength, manufactured by Natco Pharma and approved by the Central Drugs Standard Control Organisation for emergency use, is one of the drugs that has been included.

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Baricitinib is used in combination with Remdesivir. It is administered orally and inhibits the intracellular signalling pathway of cytokines known to be elevated in severe Covid cases.The state allowed the use of the drug three days ago on some oxygenated patients, along with other drugs that were already in the treatment protocol. The experts saw a reduction in oxygen requirement among patients.



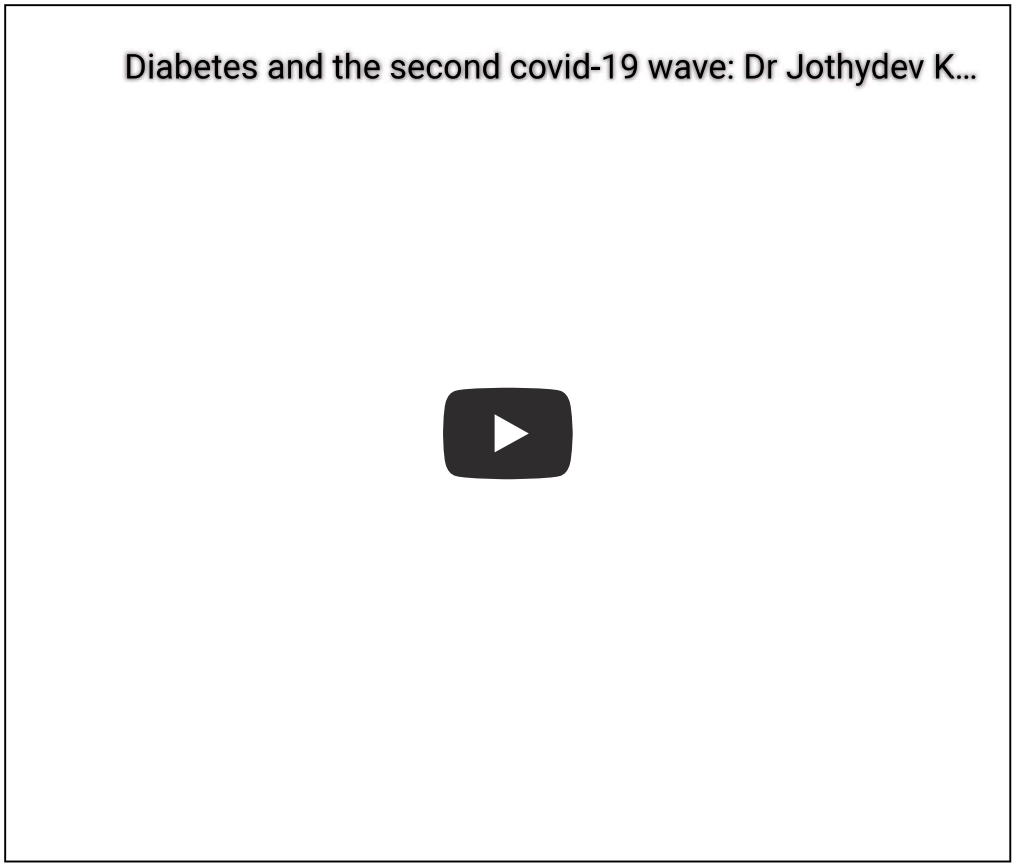
Dr Anoop Amarnath, Head, Scientific Board and Chairman-Geriatric Medicine, Manipal Hospital and member of state's Critical Care Support Team, said, "The treatment involves Baricitinib 4mg tablet given once daily for 14 days. We are doing a procalcitonin level check to rule out infection before administering the medicine. Very early data seems promising with reduction in oxygen requirement."

Another emergency approval medicine is Regeneron. In the New England Journal of Medicine, a study showed that REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group.

"Regeneron has not been made available yet. We are expecting the availability and approval in the last week of May. The medicine is given to mild and moderate patients to prevent them from entering the severity stage. This drug will also be used along with the regular treatment protocols," Dr Amarnath said.

Another drug, approved by the Drugs Controller General of India and developed by Defence Research Development Organisation, is 2-deoxy-D-glucose (2-DG). The clinical trial results have shown that this molecule helps in faster recovery of hospitalised patients and reduces supplemental oxygen dependence. Dr Amarnath, however, didn't comment on the drug.

ALSO WATCH:



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Legal Status : Inforce

Due date of next renewal : 10/03/2022

Patent Number	:	270765	Date of Patent	:	10/03/2009
Application Number	:	1863/MUMNP/2010	Date of Grant	:	18/01/2016
Type of Application	:	PCT NATIONAL PHASE APPLICATION	Date of Recordal	:	18/01/2016
Parent Application Number	:	---	Appropriate Office	:	MUMBAI
PCT International Application Number	:	PCT/US2009/036635	PCT International Filing Date	:	10/03/2009
Grant Title	:	"AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS"			

Sl No	Name of Grantee	Grantee Address
1	INCYTE CORPORATION	Experimental Station Building 336 Route 141 & Henry Clay Road City of Wilmington State of Delaware United States of America.

Sl No	Name of Patentee	Address of Patentee
1	INCYTE HOLDINGS CORPORATION	1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States of America

Address of Service	:	K & S PARTNERS INTELLECTUAL PROPERTY ATTORNEYS B1-601, 6TH FLOOR, MARATHON NEXTGEN INNOVA, OPPOSITE PENINSULA CORPORATE PARK, OFF G.K. MARG, LOWER PAREL, MUMBAI-400013, INDIA
Additional Address of Service	:	--

Priority Date : 11/03/2008

Year	Due dates for Renewal		CBR No	CBR Date	Renewal Amount	Renewal Certificate No	Date of Renewal	Renewal Period:	
	Normal Due Date	Due Date with Extension						From	To
3rd year	18/04/2016	18/10/2016	4122	08/03/2016	4000	2362	08/03/2016	10/03/2011	10/03/2012
4th year	18/04/2016	18/10/2016	4122	08/03/2016	4000	2363	08/03/2016	10/03/2012	10/03/2013
5th year	18/04/2016	18/10/2016	4122	08/03/2016	4000	2364	08/03/2016	10/03/2013	10/03/2014
6th year	18/04/2016	18/10/2016	4122	08/03/2016	4000	2365	08/03/2016	10/03/2014	10/03/2015
7th year	18/04/2016	18/10/2016	4122	08/03/2016	12000	2366	08/03/2016	10/03/2015	10/03/2016
8th year	18/04/2016	18/10/2016	4122	08/03/2016	12000	2367	08/03/2016	10/03/2016	10/03/2017
9th year	10/03/2017	10/09/2017	3050	09/02/2017	12000	1386	09/02/2017	10/03/2017	10/03/2018
10th year	10/03/2018	10/09/2018	1639	30/01/2018	12000	1255	30/01/2018	10/03/2018	10/03/2019
11th year	10/03/2019	10/09/2019	2482	04/02/2019	24000	1937	04/02/2019	10/03/2019	10/03/2020
12th year	10/03/2020	10/09/2020	594	09/01/2020	24000	708	09/01/2020	10/03/2020	10/03/2021
13th year	10/03/2021	10/09/2021	5077	03/03/2021	24000	5811	03/03/2021	10/03/2021	10/03/2022
14th year	--	--	--	--	--	--	--	--	--
15th year	--	--	--	--	--	--	--	--	--
16th year	--	--	--	--	--	--	--	--	--
17th year	--	--	--	--	--	--	--	--	--
18th year	--	--	--	--	--	--	--	--	--

19th year	--	--	--	--	--	--	--	--	--
20th year	--	--	--	--	--	--	--	--	--

Sl No	Date of Entry	Particulars/Remarks
1	05/07/2019	In pursuance of Form 16 filed (dated 18/06/2019) for the record of Licence agreement (dated 18/12/2009)between INCYTE CORPORATION (Patentee/Grantee/ Licencor)on the on e part and on the other part Eli Lilly & Company (License); On the request of Licensee the copy of agreement to keep the terms of the license secure as provided under provisions of Section 69(4) is allowed;
2	07/08/2017	"In pursuance of an application received on the 04/07/2016 made by " INCYTE HOLDINGS CORPORATION" registered as Proprietor by virtue of a deed of assignment dated 01-01-2015 and made between INCYTE CORPORATION of the one part and INCYTE HOLDINGS CORPORATION of the other part."

Information u/s 146 (Working of Patents)

Sl No	Patent Number	Year	
1	270765	2016-2017	No Document
2	270765	2016-2017	View Document
3	270765	2017-2018	View Document
4	270765	2018-2019	View Document
5	270765	2018-2019	View Document
6	270765	2018-2019	View Document
7	270765	2019-2020	View Document
8	270765	2019-2020	View Document
9	270765	2019-2020	View Document
10	270765	2020-2021	View Document

View Documents

FORM 2

GRANTED

THE PATENTS ACT, 1970
(39 of 1970)
&
THE PATENTS RULES, 2003

COMPLETE SPECIFICATION
(See section 10, rule 13)

270765
18/01/2016

"AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS"

INCYTE CORPORATION, a corporation of the State of Delaware, United States of America, having a principal place of business at Experimental Station Building 336, Route 141 & Henry Clay Road, City of Wilmington, State of Delaware, United States of America.

The following specification particularly describes the invention and the manner in which it is to be performed.

1863/MUMNP/2010
1-9-2010

AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS

FIELD OF THE INVENTION

The present invention relates to azetidine and cyclobutane derivatives, as well as their compositions and methods of use and preparation, which are JAK inhibitors useful in the treatment of JAK-associated diseases including, for example, inflammatory and autoimmune disorders, as well as cancer.

BACKGROUND OF THE INVENTION

Protein kinases (PKs) are a group of enzymes that regulate diverse, important biological processes including cell growth, survival and differentiation, organ formation and morphogenesis, neovascularization, tissue repair and regeneration, among others. Protein kinases exert their physiological functions through catalyzing the phosphorylation of proteins (or substrates) and thereby modulating the cellular activities of the substrates in various biological contexts. In addition to the functions in normal tissues/organs, many protein kinases also play more specialized roles in a host of human diseases including cancer. A subset of protein kinases (also referred to as oncogenic protein kinases), when dysregulated, can cause tumor formation and growth, and further contribute to tumor maintenance and progression. Thus far, oncogenic protein kinases represent one of the largest and most attractive groups of protein targets for cancer intervention and drug development.

The Janus Kinase (JAK) family plays a role in the cytokine-dependent regulation of proliferation and function of cells involved in immune response. Currently, there are four known mammalian JAK family members: JAK1 (also known as Janus kinase-1), JAK2 (also known as Janus kinase-2), JAK3 (also known as Janus kinase, leukocyte; JAKL; L-JAK and Janus kinase-3) and TYK2 (also known as protein-tyrosine kinase 2). The JAK proteins range in size from 120 to 140 kDa and comprise seven conserved JAK homology (JH) domains; one of these is a functional catalytic kinase domain, and another is a pseudokinase domain potentially serving a regulatory function and/or serving as a docking site for STATs.

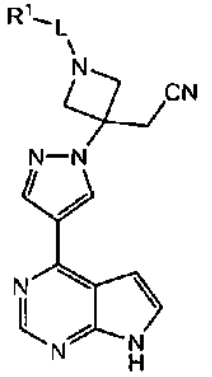
Blocking signal transduction at the level of the JAK kinases holds promise for developing treatments for inflammatory diseases, autoimmune diseases, myeloproliferative

diseases, and human cancers, to name a few. Inhibition of the JAK kinases is also envisioned to have therapeutic benefits in patients suffering from skin immune disorders such as psoriasis, and skin sensitization. Accordingly, inhibitors of Janus kinases or related kinases are widely sought and several publications report effective classes of compounds. For example, certain JAK inhibitors, including pyrrolopyridine and pyrrolopyrimidines, are reported in U.S. Ser. No. 11/637,545, filed December 12, 2006.

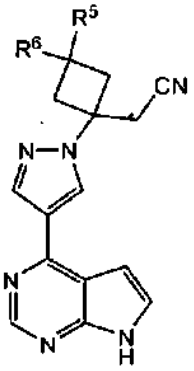
Thus, new or improved agents which inhibit kinases such as Janus kinases are continually needed for developing new and more effective pharmaceuticals to treat cancer and other diseases. The compounds and processes described herein are directed toward these needs and other ends.

SUMMARY OF THE INVENTION

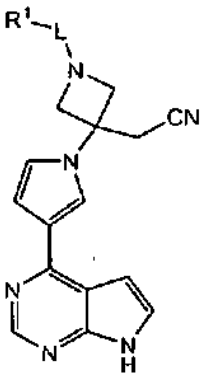
The present invention provides, *inter alia*, JAK inhibitors of Formulas I, II, III, and IV:



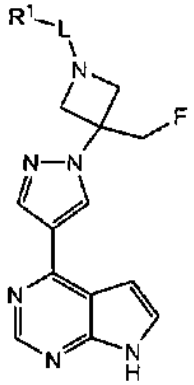
I



II



III



IV

or pharmaceutically acceptable salts thereof, wherein constituent members are defined below.

The present invention further provides pharmaceutical compositions comprising a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention further provides methods of treating any of the various JAK-associated diseases and disorders named herein by administering to a patient a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt of the same.

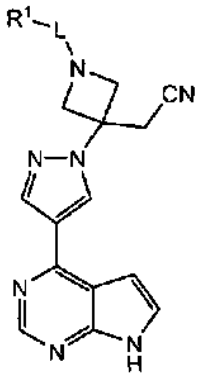
The present invention further provides compounds of Formulas I, II, III, and IV, or pharmaceutically acceptable salts thereof, for use in therapy.

The present invention further provides use of the compounds of Formulas I, II, III, and IV, or pharmaceutically acceptable salts thereof, for the production of a medicament for use in therapy.

The present invention further provides methods for the preparation of the compounds of Formulas I, II, III, and IV.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, JAK inhibitors of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

L is SO_2 or CO;

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR^2R^3, or OR^4, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and C_{1-4} alkyl;

R^2 and R^3 are independently selected from H, C_{1-4} alkyl, and phenyl; and

R^4 is C_{1-5} alkyl, phenyl, or benzyl.

In some embodiments, when L is SO_2, then R^1 is other than OR^4.

In some embodiments, when L is SO_2, then R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5- or 6-membered heteroaryl, or NR^2R^3, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F and C_{1-4} alkyl.

In some embodiments, when L is CO, then R^1 is C_{3-7} cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR^2R^3, or OR^4, wherein said cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from CN and C_{1-4} alkyl.

In some embodiments, L is SO_2.

In some embodiments, L is CO.

In some embodiments, R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, 2-methylprop-1-yl, 1-methylprop-1-yl, each optionally substituted with 1, 2, or 3 F.

In some embodiments, R^1 is C_{1-4} alkyl.

In some embodiments, R^1 is ethyl.

In some embodiments, R^1 is C_{3-7} cycloalkyl optionally substituted by C_{1-4} alkyl.

In some embodiments, R^1 is phenyl optionally substituted with F, methyl, or CN.

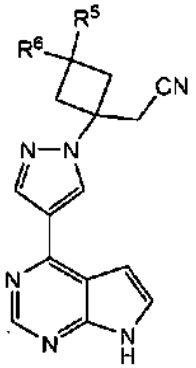
In some embodiments, R^1 is 5-membered heteroaryl selected from thienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, and isoxazolyl, each optionally substituted with C_{1-4} alkyl.

In some embodiments, R^1 is pyridinyl.

In some embodiments, R^1 is NR^2R^3 or OR^4.

In some embodiments, L is SO_2 and R^1 is C_{1-6} alkyl.

The present invention further provides compounds of Formula II:



II

or pharmaceutically acceptable salts thereof, wherein:

R^5 and R^6 are independently selected from H, F, CN, OH, C_{1-4} alkyl, benzyloxy, C_{2-8} dialkylaminosulfonyl, and 5-membered heteroaryl, wherein said alkyl is optionally substituted by 1, 2, or 3 substituents selected from F, OH, CN, and C_{1-4} alkoxy, and wherein said 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl.

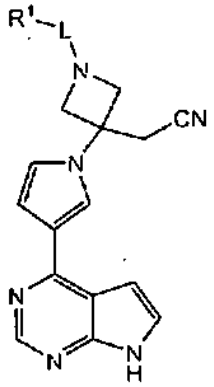
In some embodiments, when one of R^5 and R^6 is OH, then the other of R^5 and R^6 is other than CN or F.

In some embodiments, one of R^5 and R^6 is H and the other is selected from H, F, CN, OH, C_{1-4} alkyl, benzyloxy, C_{2-8} dialkylaminosulfonyl, and 5-membered heteroaryl, wherein said alkyl is optionally substituted by 1, 2, or 3 substituents selected from F, OH, CN, and C_{1-4} alkoxy, and wherein said 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl.

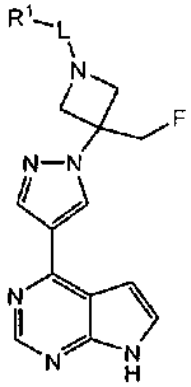
In some embodiments, R^5 and R^6 are independently selected from H, F, CN, OH, and methyl.

In some embodiments, R^5 and R^6 are independently selected from H and CN.

The present invention further provides a compound of Formula III or IV:



III



IV

or a pharmaceutically acceptable salt thereof, wherein:

L is SO_2 or CO;

R^1 is C_{1-5} alkyl, C_{3-7} cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR^2R^3, or OR^4, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and C_{1-4} alkyl;

R^2 and R^3 are independently selected from H, C_{1-4} alkyl, and phenyl; and

R^4 is C_{1-5} alkyl, phenyl, or benzyl;

wherein when L is SO_2, R^1 is other than OR^4.

In some embodiments, L is SO_2.

In some embodiments, L is CO.

In some embodiments, R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, 2-methylprop-1-yl, 1-methylprop-1-yl, each optionally substituted with 1, 2, or 3 F.

In some embodiments, R^1 is C_{1-4} alkyl.

In some embodiments, R^1 is ethyl.

In some embodiments, R^1 is C_{3-7} cycloalkyl optionally substituted by C_{1-4} alkyl.

In some embodiments, R^1 is phenyl optionally substituted with F, methyl, or CN.

In some embodiments, R^1 is 5-membered heteroaryl selected from thienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, and isoxazolyl, each optionally substituted with C_{1-4} alkyl.

In some embodiments, R^1 is pyridinyl.

In some embodiments, R^1 is NR^2R^3 or OR^4.

In some embodiments, L is SO_2 and R^1 is C_{1-6} alkyl.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group *which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et),* propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, sec-butyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, sec-pentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms. A linking alkyl group is referred to herein as "alkylene."

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Cycloalkyl

groups also include cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

As used herein, "heteroaryl" refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl is pyridinyl. In some embodiments, the heteroaryl is thienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, or isoxazolyl. In some embodiments, the heteroaryl is indolyl. In some embodiments, any ring-forming N in a heteroaryl moiety can be substituted by oxo. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "*benzyloxy*" refers to –O-benzyl.

As used herein, "dialkylaminosulfonyl" refers to $-SO_2-N(alkyl)_2$.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present

invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. Where a compound capable of stereoisomerism or geometric isomerism is designated in its structure or name without reference to specific R/S or cis/trans configurations, it is intended that all such isomers are contemplated.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention further include hydrates and solvates, as well as anhydrous and non-solvated forms.

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

All compounds, and pharmaceuticaly acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

In some embodiments, the compounds of the invention, and salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by

conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

Synthesis

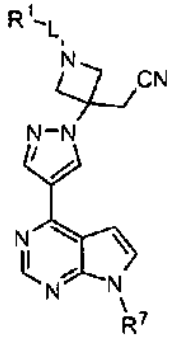
Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

The present invention provides a method of forming a compound of Formula I as shown below in Schemes 1, 2, and 3. Accordingly, in step (i) of Scheme 1, the compound of Formula I is prepared by a method comprising treating a compound of Formula Ia:



Ia

to remove the R^7 moiety; wherein:

L is SO_2 or CO;

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR^2R^3, or OR^4, wherein the alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and C_{1-4} alkyl;

R^2 and R^3 are independently selected from H, C_{1-4} alkyl, and phenyl;

R^4 is C_{1-6} alkyl, phenyl, or benzyl; and

R^7 is a protecting group;

wherein when L is SO_2, R^1 is other than OR^4.

Appropriate R^7 protecting groups include, but are not limited to the protecting groups for amines delineated in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. In some embodiments, the protecting group for the R^7 group is one which is stable to conditions for removing the R^{10} protecting group in step (vi) of Scheme 2. In some embodiments, the protecting group for the R^7 group is one which is stable to conditions for removing the R^9 protecting group in step (iv) of Scheme 1. In some embodiments, R^7 is a group which is resistant to room temperature acidic conditions. In some embodiments, the R^7 is a group which is not removed in 1 to 5 N hydrochloric acid at room temperature, at a temperature from about 10 °C to about 40 °C, at a temperature from about 15 °C to about 40 °C, or at a temperature from about 15 °C to about 30 °C. In some embodiments, R^7 is benzyloxycarbonyl (Cbz), 2,2,2-trichloroethoxycarbonyl (Troc), 2-(trimethylsilyl)ethoxycarbonyl (Teoc), 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl (Tsc), t-butoxycarbonyl (BOC), 1-adamantyloxycarbonyl (Adoc), 2-adamantylcarbonyl (2-Adoc), 2,4-dimethylpent-3-yloxycarbonyl (Doc), cyclohexyloxycarbonyl (Hoc), 1,1-dimethyl-2,2,2-

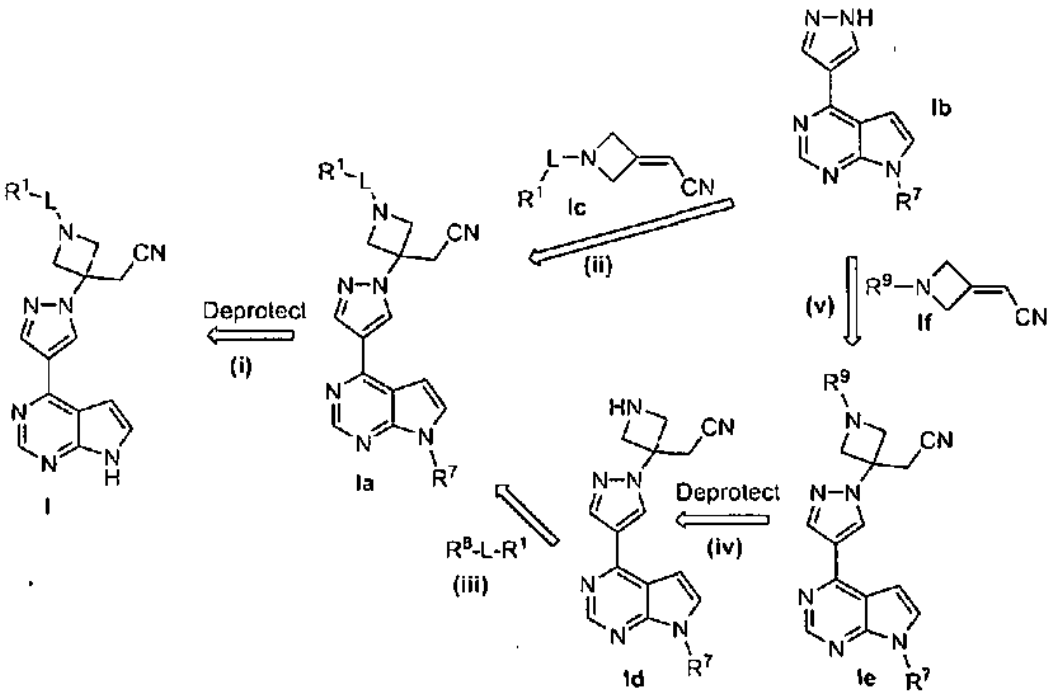
trichloroethoxycarbonyl (TcBOC), vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, 2-nitrobenzyl, 4-nitrobenzyl, diphenyl-4-pyridylmethyl, N',N'-dimethylhydrazinyl, methoxymethyl, t-butoxymethyl (Bum), benzyloxymethyl (BOM), or 2-tetrahydropyranyl (THP). In some embodiments, R^7 is 2-(trimethylsilyl)ethoxymethyl (SEM). In some embodiments, R^7 is N-pivaloyloxymethyl (POM).

Treatment of the compound of Formula Ia to remove the R^7 group can be accomplished by methods known in the art for the removal of particular protecting groups for amines, such as those in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. For example, in some embodiments, the R^7 group is removed by treating with fluoride ion (e.g., treating with tetrabutylammonium fluoride), hydrochloric acid, pyridinium p-toluenesulfonic acid (PPTS), or a Lewis acid (e.g., lithium tetrafluoroborate)). In some embodiments, the treating comprises treating with lithium tetrafluoroborate, followed by treating with ammonium hydroxide (e.g., when R^7 is 2-(trimethylsilyl)ethoxymethyl). In some embodiments, the treating comprises treating with base (e.g., R^7 is N-pivaloyloxymethyl). In some embodiments, the base is an alkali metal hydroxide. In some embodiments, the base is sodium hydroxide. In some embodiments, the treating comprises treating with sodium hydroxide or ammonia in a solvent such as methanol or water.

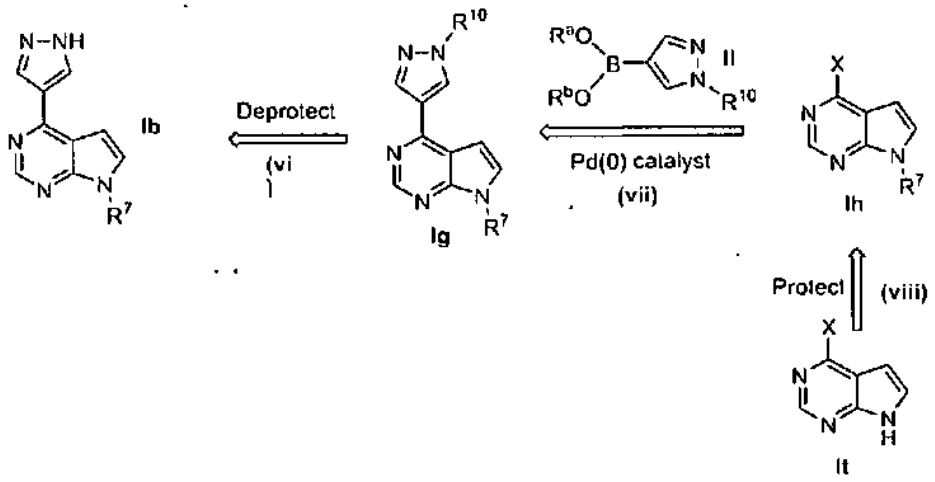
In some embodiments, to deprotect the SEM-protection group, a mild, two stage protocol is employed. The SEM-protected substrate of Formula Ia is treated with lithium tetrafluoroborate ($LiBF_4$) or trifluoroborate etherate in aqueous acetonitrile at ambient or elevated temperature (in some embodiments, at about 80 °C) for ten to twenty hours. The resulting corresponding hydroxymethyl intermediate is then subsequently treated with aqueous ammonium hydroxide (NH_4OH) at room temperature to provide the compound of Formula I.

In some embodiments, for the POM-deprotection, an aqueous sodium hydroxide (NaOH) or lithium hydroxide (LiOH) solution is used. Thus, a suspension of the POM-protected compound of Formula Ia, is treated with a 1 N aqueous sodium hydroxide solution at room temperature for two to three hours. The desired product of Formula I can be obtained after the typical acid-base work-up.

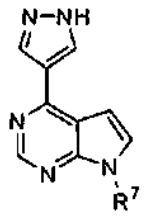
Scheme 1



Scheme 2

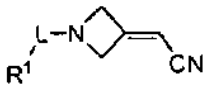


In step (i), the compound of Formula Ia is formed by a method comprising reacting a compound of Formula Ib:



Ib

with a compound of Formula Ic:



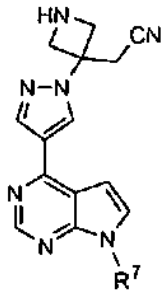
Ic

to form the compound of Formula Ia.

Step (ii) of Scheme 1 is a Michael addition reaction between the compound of Formula Ib and the compound of Formula Ic. The Michael addition may be promoted by a Michael addition catalyst, such as base. In some embodiments, the Michael addition catalyst is a tetraalkylammonium halide, tetraalkylammonium hydroxide, guanidine, amidine, hydroxide, alkoxide, silicate, alkali metal phosphate, oxide, tertiary amine, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydrogen phosphate, phosphine, or alkali metal salt of a carboxylic acid. In some embodiments, the Michael addition catalyst is tetramethyl guanidine, 1,8-diazabicyclo(5.4.0)undec-7-ene, 1,5-diazabicyclo(4.3.0)non-5-ene, 1,4-diazabicyclo(2.2.2)octane, tert-butyl ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, tripotassium phosphate, sodium silicate, calcium oxide, triethylamine, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, potassium hydrogen phosphate, triphenyl phosphine, triethyl phosphine; potassium acetate, or potassium acrylate. In some embodiments, the Michael addition catalyst is 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). In some embodiments, a stoichiometric or a catalytical amount of base is used to facilitate the Michael addition reaction.

In some embodiments, the reaction is conducted in an organic solvent, such as acetonitrile or dimethylacetamide, at room temperature for two to six hours. Under the optimized reaction conditions, the desired Michael adduct, the compound of Formula Ia, may be obtained in high yield and purity.

Alternatively, the compound of Formula Ia can be formed by the process shown in step (iii) of Scheme 1. Accordingly, the compound of Formula Ia is formed by a method comprising reacting a compound of Formula Id:



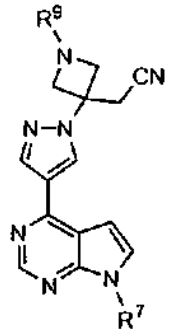
Id

with a compound of formula R^8-L-R^1 to form the compound of Formula Ia; wherein R^8 is a leaving group.

In some embodiments, R^8 is any good leaving group known in the art. In some embodiments, R^8 is halogen or C_{1-4} alkoxy. In some embodiments, R^8 is chloro.

In some embodiments, the reacting of the compound of Formula Id with the compound of formula R^8-L-R^1 is performed in the presence of a base. In some embodiments, the base is a tertiary amine, such as triethylamine, diisopropylethylamine, N-methylmorpholine, and the like. In some embodiments, the base is diisopropylethylamine.

In step (iv) of Scheme 1, the compound of Formula Id is formed by a method comprising treating a compound of Formula Ic:



Ic

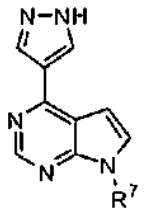
to remove the R^9 group thereby forming the compound of Formula Id; wherein R^9 is a protecting group.

Appropriate R^9 protecting groups include, but are not limited to the protecting groups for amines delineated in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. R^9 is a protecting group which can be selectively removed under conditions which do not displace the R^7 protecting group. In some embodiments, the R^9 is a protecting group which can be removed under acidic

conditions at room temperature, at a temperature from about 15 °C to about 40 °C, or at a temperature from about 15 °C to about 30 °C. In some embodiments, R^9 is C_{1-6} alkoxycarbonyl. In some embodiments, R^9 is tert-butoxycarbonyl. As used herein, "alkoxycarbonyl" refers to a group of formula -C(=O)O-alkyl.

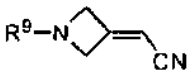
Treatment of the compound of Formula Ie to remove the R^9 group can be accomplished by methods known in the art for the removal of particular protecting groups for amines, such as those in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. Appropriate treatment conditions do not displace the R^7 protecting group. In some embodiments, the treating comprises subjecting the compound of Formula Ie to acidic conditions at room temperature, at a temperature from about 15 °C to about 40 °C, or at a temperature from about 15 °C to about 30 °C. In some embodiments, the treating of the compound of Formula Ie comprises treating with hydrochloric acid in 1,4-dioxane.

In step (v) of Scheme 1, the compound of Formula Ia ic is formed by a method comprising reacting a compound of Formula Ib:



Ib

with a compound of Formula If:



If

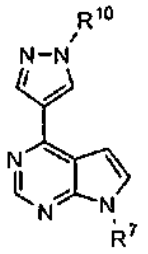
to form the compound of Formula Ic.

Step (v) of Scheme 1 is a Michael addition reaction between the compound of Formula Ib and the compound of Formula If. The Michael addition may be promoted by a Michael addition catalyst, such as base. In some embodiments, the Michael addition catalyst is a tetraalkylammonium halide, tetraalkylammonium hydroxide, guanidine, amidine, hydroxide, alkoxide, silicate, alkali metal phosphate, oxide, tertiary amine, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydrogen phosphate, phosphine, or alkali metal salt of a carboxylic acid. In some embodiments, the Michael addition catalyst is

tetramethyl guanidine, 1,8-diazabicyclo(5.4.0)undec-7-ene, 1,5-diazabicyclo(4.3.0)non-5-ene, 1,4-diazabicyclo(2.2.2)octane, tert-butyl ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, tripotassium phosphate, sodium silicate, calcium oxide, triethylamine, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, potassium hydrogen phosphate, triphenyl phosphine, triethyl phosphine, potassium acetate, or potassium acrylate. In some embodiments, the Michael addition catalyst is 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). In some embodiments, a stoichiometric or a catalytical amount of base is used to facilitate the Michael addition reaction.

In some embodiments, the reaction is conducted in an organic solvent, such as acetonitrile or dimethylacetamide, at room temperature for two to six hours. Under the optimized reaction conditions, the desired Michael adduct, the compound of Formula Ia, may be obtained in high yield and purity.

In step (vi) of Scheme 2, the compound of Formula Ig is formed by a method comprising treating a compound of Formula Ig:



Ig

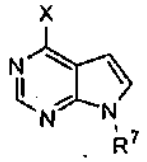
to remove the R^{10} group thereby forming the compound of Formula Ib; wherein R^{10} is a protecting group.

Appropriate R^{10} protecting groups include, but are not limited to the protecting groups for amines delineated in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. R^{10} is a protecting group which can be selectively removed under conditions which do not displace the R^7 protecting group. In some embodiments, the R^{10} is a protecting group which can be removed under acidic conditions at room temperature, at a temperature from about 15 °C to about 40 °C, or at a temperature from about 15 °C to about 30 °C. In some embodiments, R^{10} is a group which is deprotected under room temperature acidic conditions. In some embodiments, R^{10} is 1-(ethoxy)ethyl, tri(C_{1-6} alkyl)silyl (e.g., t-butyldimethylsilyl or triisopropylsilyl), p-

methoxybenzyl (PMB), triphenylmethyl (Tr), diphenylmethyl, hydroxymethyl, methoxymethyl (MOM), diethoxymethyl, or t-butyldimethylsilylmethyl. In some embodiments, R^{10} is 1-(ethoxy)ethyl.

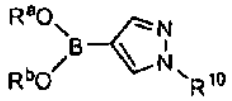
Treatment of the compound of Formula Ig to remove the R^{10} group can be accomplished by methods known in the art for the removal of particular protecting groups for amines, such as those in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety. In some embodiments, the treating comprises treating the compound of Formula Ig under acidic conditions (e.g., hydrochloric acid or trifluoroacetic acid) at room temperature, at a temperature from about 15 °C to about 40 °C, or at a temperature from about 15 °C to about 30 °C. In some embodiments, the treating comprises treating the compound of Formula Ig with an aqueous solution of from about 1 N to about 5 N hydrochloric acid at a temperature of from about 10 °C to about 30 °C.

In step (vii) of Scheme 2, the compound of Formula Ig is formed by a method comprising reacting a compound of Formula Ih:



Ih

with a compound of Formula II:



II

in the presence of a palladium catalyst and a base to form the compound of Formula Ig; wherein:

X is a tosylate group, a triflate group, iodo, chloro, or bromo; and

R^a and R^b are each independently H or C_{1-6} alkyl; or

R^a and R^b, together with the oxygen atoms to which they are attached and the boron atom, form a 5- to 6-membered heterocyclic ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups.

Step (vii) is a Suzuki coupling reaction, which can be initiated using a number of palladium(0) and palladium(II) catalysts and performed under conditions known in the art

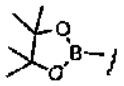
(see, e.g., Miyaura and Suzuki, *Chem. Rev.* 1995, 95, 2457-2483, which is hereby incorporated in its entirety). In some embodiments, the palladium catalyst is $Pd(PPh_3)_4$ and $Pd(dppf)_2Cl_2$. In some embodiments, the palladium catalyst is tetrakis(triphenylphosphine)palladium(0) or tetrakis(tri(*o*-tolyl)phosphine)palladium(0). In some embodiments, the palladium catalyst is tetrakis(triphenylphosphine)palladium(0).

In some embodiments, the palladium catalyst loading is from about 1×10^{-4} to about 0.1 equivalents. In some embodiments, the palladium catalyst loading is from about 0.0010 to about 0.0015 equivalents. In some embodiments, the stoichiometric ratio of the compound of Formula Ih to the compound of Formula II is from about 1 to about 1.05, or from about to 1 to about 1.35. In some embodiments, the solvent for step (vii) comprises water and an organic solvent. In some embodiments, the organic solvent is 1,4-dioxane, 1-butanol, 1,2-dimethoxyethane (DME), 2-propanol, toluene or ethanol, or a combination thereof. In some embodiments, the organic solvent comprises a combination of 1-butanol and DME.

In some embodiments, the base is an inorganic base. In some embodiments, the base is an organic base. In some embodiments, the base is an alkali metal carbonate or an alkali metal hydrogen carbonate. In some embodiments, the base is potassium carbonate (K_2CO_3). In some embodiments, two to five equivalents of base (e.g., K_2CO_3) are used. In some embodiments, two to five equivalents of base (e.g., $NaHCO_3$) are used.

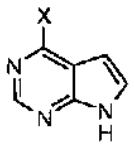
In some embodiments, the Suzuki coupling reaction is conducted at a temperature of about 80 to about 100 °C. In some embodiments, the reaction is carried out for two to twelve hours.

In some embodiments, R^a and R^b, together with the oxygen atoms to which they are attached and the boron atom, form the moiety:



In some embodiments, X is chloro, bromo, or iodo. In some embodiments, X is chloro.

In step (viii) of Scheme 2, the compound of Formula Ih is formed by protecting a compound of Formula It:



It

~~19~~ 20

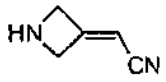
with a R^7 group.

The R^7 group is chosen as described above. In some embodiments, R^7 is 2-(trimethylsilyl)ethoxymethyl. In some embodiments, R^7 is N-pivaloyloxymethyl.

Addition of the R^7 protecting groups can be added by methods known in the art for attachment of protecing groups for amines (see e.g., Wuts and Green referred to above). For example, the indole nitrogen can be deprotonated with a base (e.g., with sodium hydride (NaH)) in an organic solvent (e.g., THF, 1,4-dioxane, 1,2-dimethoxyethane (DME), or *N,N*-dimethylacetamide (DMAC)) at low temperature (e.g., from about 0 to about 5 °C) before being treated with an electrophile, such as trimethylsilylethoxymethyl chloride (SEM-Cl) or pivaloyloxymethyl chloride (POM-Cl). The SEM- or POM-protected 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine can then isolated or *in-situ* generated as the starting materials for subsequent Suzuki reaction with or without further purification.

The compound of Formula Ic can be formed by the methods shown in Scheme 3 below.

Accordingly, in step (ix) of Scheme 3, the compound of Formula Ic is formed by a method comprising reacting the compound of Formula Ik:



Ik

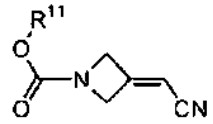
or salt thereof, with a compound of formula R^8-L-R^1 in the presence of a base to form the compound of Formula Ic; wherein R^8 is a leaving group.

The R^8 group can be any appropriate leaving group known in the art for adding a sulfonyl or carbonyl containing moiety. In some embodiments, R^8 is halogen or C_{1-4} alkoxy. In some embodiments, R^8 is chloro, bromo, or iodo. In some embodiments, R^8 is chloro.

In some embodiments, the base is a tertiary amine, such as triethylamine, diisopropylethylamine, N-methylmorpholine, and the like. In some embodiments, the base is diisopropylethylamine. In some embodiments, the salt of the compound of Formula Ik is the hydrochloride salt.

A compound of Formula If can be formed by protecting the amino group of a compound of Formula Ik with an appropriate R^9 group by methods known in the art (see e.g., Wuts and Green above). Alternatively, a compound of Formula Im may be used in place of the compound of Formula If.

In step (x) of Scheme 3, the compound of Formula Ik is formed by a method comprising treating a compound of Formula Im:

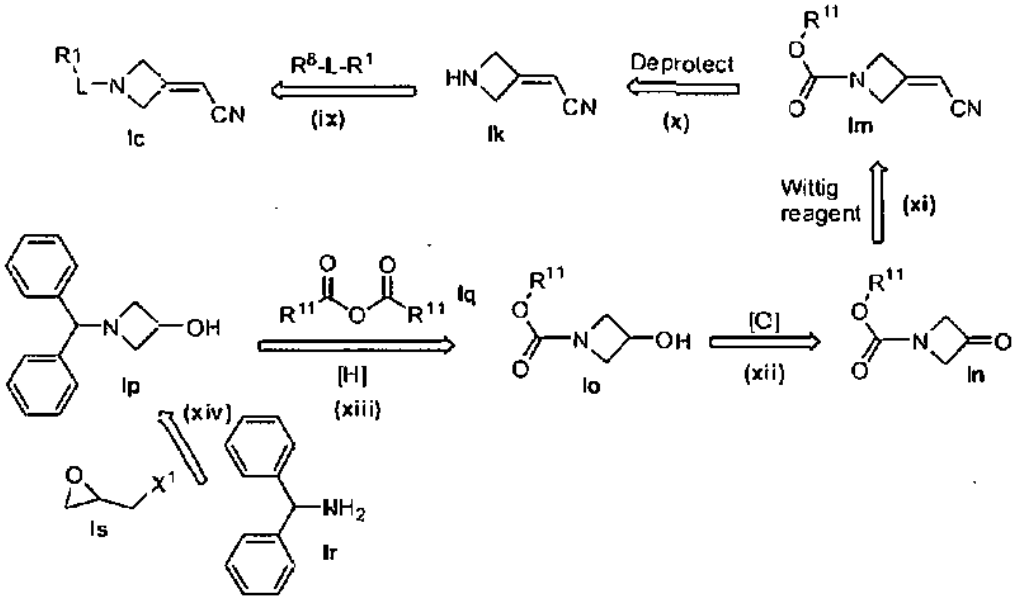


Im

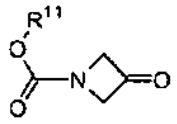
to remove the -C(=O)OR^{11} moiety thereby forming the compound of Formula Ik; wherein R^{11} is is C_{1-6} alkoxycarbonyl.

In some embodiments, R^{11} is tert-butoxycarbonyl (BOC). In some embodiments, the treating of the compound of Formula Im comprises any method known in the art for removing an alkoxycarbonyl group from an amine (e.g., a BOC group) (see e.g., Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, pages 696-887 (and, in particular, pages 872-887) (2007), which is incorporated herein by reference in its entirety). In some embodiments, the treating of the compound of Formula Im comprises treating with aqueous hydrochloric acid.

Scheme 3



In step (xi) of Scheme 3, the compound of Formula Im is formed by a method comprising reacting a compound of Formula In:



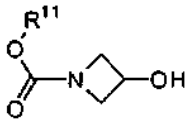
In

with a Wittig-type reagent containing a cyanomethyl or cyanomethyl ylide group to form the compound of Formula Im.

As used herein, the term "Wittig-type reagent" refers to reagents used in the Wittig reaction, the Wadsworth-Emmons reaction, and the Horner-Wittig reaction as described in the art (see e.g., Carey and Sundberg, Advanced Organic Chemistry, Part B: Reactions and Synthesis, 4th ed , Kluwer Academic/Plenum Publishers:New York, pages 111-119 (2001); and March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 3rd ed., John Wiley & Sons:New York, pages 845-855 (1985), each of which is incorporated herein by references in its entirety). Exemplative Wittig-type reagents containing a cyanomethyl or cyanomethyl ylice group include, but are not limited to, compounds of general formula $(R'O)_2P(=O)$-L-R^1, $R"_3P(+)$-L(-)-R^1, $R"_2P(=O)$-L-R^1, and $(R'N)_2P(=O)$-L-R^1, wherein R' is C_{1-6} alkoxy or optionally substituted phenyl; R" is optionally substituted phenyl; L is -CH_2- or -CH-; and R^1 is cyano. In some embodiments, the Wittig-type reagent is diethyl cyanomethyl phosphate. In some embodiments, the reacting of the compound of Formula In with the Wittig-type reagent in the presence of a base. In some embodiments, the base is a strong base. In some embodiments, the base is potassium t-butoxide, sodium t-butoxide, sodium hydride, sodium ethoxide, sodium hydroxide, potassium carbonate, or sodium carbonate. In some embodiments, the base is an alkali metal alkoxide. In some embodiments, the base is an alkali metal t-butoxide. In some embodiments, the base is potassium t-butoxide. In some embodiments, the olefination of the azetidine ketone of Formula In with a Wittig reagent is conducted in an organic solvent, such as THF, under the influence a base, such as potassium *tert*-butoxide, at a temperature from about 0 to about 5 °C.

The azetidinones of Formula In can be prepared by a modified procedure reported by Gaertner (*J. Org. Chem.*, 1967, *32*, 2972) (see e.g., steps (xii) to (xiv)). In one embodiment, the "one-part" formation of the corresponding carbamate protected azetidinols of Formula Io from the compounds of Formula Ip under the catalytic hydrogenolysis conditions in the presence an electrophile, such as di-*tert*-butyl dicarbonate, simplifies the process to prepare the protected azetidinols compared to other modified procedures (Zhengming, Chen et al, WO 00/63168). TEMPO-catalyzed oxidation of the protected azetidinols of Formula Io to the corresponding ketones of Formula In provides almost quantitative yield under the mild reaction conditions. As the di-funtionalized compounds, *N*-protected azetidinones of Formula Io are very useful synthetic intermediates for the preparation of complex organic molecules.

Accordingly, in step (xii) of Scheme 3, the compound of Formula In is formed by a method comprising treating a compound of Formula Io:

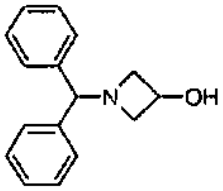


Io

with an oxidizing agent component to form the compound of Formula In.

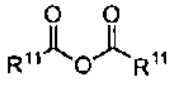
As used herein, the term "oxidizing agent component" refers to one or more oxidizing agents known in the art for oxidizing a secondary alcohol to a ketone (see, e.g., Carey and Sundberg, Advanced Organic Chemistry, Part B: Reactions and Synthesis, 4th ed., Kluwer Academic/Plenum Publishers:New York, pages 747-757), which is incorporated herein by references in its entirety). In some embodiments, the oxidizing agent component comprises a transition-metal oxidant, including, but not limited to, a chromium (VI) reagent (e.g., a Collins reagent, pyridinium dichromate (PDC), or pyridinium chlorochromate (PCC)), potassium permanganate, manganese(IV) dioxide, a ruthenium (II) reagent (e.g., $RuCl_2$(p-cymene)$_2$), ruthenium tetraoxide, or a combination of a manganese(IV) dioxide, a ruthenium (II) reagent and benzoquinone; DMSO and an electrophilic reagent such as a carbodiimide reagent (e.g., dicyclohexylcarbodiimide), acetic anhydride, trifluoroacetic anhydride, oxalyl chloride, or sulfur trioxide; dimethyl sulfide and N-chlorosuccinimide; DMSO and chlorine; or a Dess-Martin reagent. In some embodiments, the oxidizing agent component comprises 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and a stoichiometric oxidant (e.g., sodium hypochlorite or N-chlorosuccinimide (NCS)). In some embodiments, the oxidizing agent component comprises TEMPO and sodium hypochlorite.

In step (xiii) of Scheme 3, the compound of Formula Io is formed by a method comprising reacting a compound of Formula Ip:



Ip

with a compound of Formula Iq:



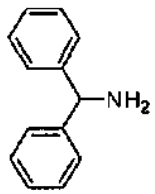
Iq

under catalytic hydrogenation conditions to form the compound of Formula Io.

In some embodiments, the catalytic hydrogenation conditions comprises hydrogen gas and a palladium on carbon catalyst.

In step (xiv) of Scheme 3, the compound of Formula Ip is prepared by a method comprising the steps of:

(a) reacting a compound of Formula Ir:



Ir

with a compound of Formula Is:



Is

to form the halide salt of the compound of Formula Ip; and

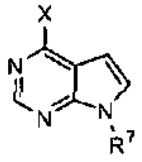
(b) treating the salt of the compound of Formula Ip with a base to form the compound of Formula Ip;

wherein X^1 is halogen.

In some embodiments, X^1 is chloro.

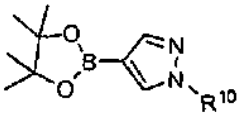
The present invention further provides a method of forming a compound of Formula I comprising:

(a) reacting a compound of Formula Ih:

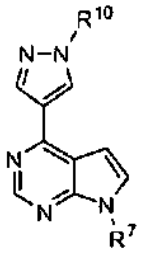


Ih

with a compound of formula:

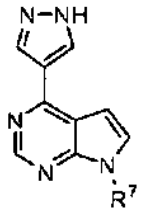


in the presence of tetrakis(triphenylphosphine)palladium(0) and an alkali metal carbonate or alkali metal hydrogen carbonate base to form a compound of Formula Ig:



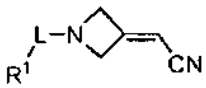
Ig ;

(b) treating the compound of Formula Ig to remove the R^{10} group to form a compound of Formula Ib:



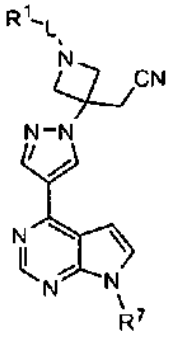
Ib ;

(c) reacting the compound of Formula Ib with a compound of Formula Ic:



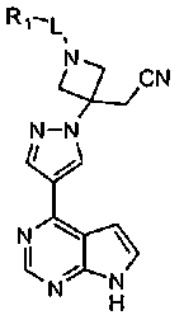
Ic

in the presence of a catalytic or stoichiometric amount of 1,8-diazabicyclo(5.4.0)undec-7-ene to form the compound of Formula Ia:



Ia;

(d) treating the compound of Formula Ia to remove the R^7 moiety to form a compound of Formula I:



I

wherein:

L is SO_2;

R^1 is C_{1-6} alkyl;

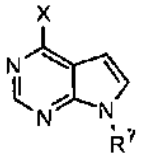
R^7 is 2-(trimethylsilyl)ethoxyethyl or 2-pivaloyloxymethyl;

R^{10} is 1-(ethoxy)ethyl; and

X is chloro.

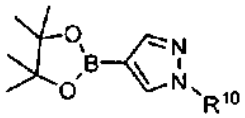
The present invention further provides a method of forming a compound of Formula I comprising:

(a) reacting a compound of Formula Ih:

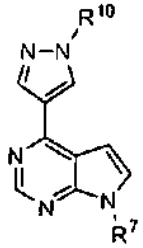


Ih

with a compound of formula:

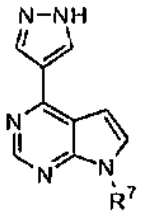


in the presence of tetrakis(triphenylphosphine)palladium(0) and an alkali metal carbonate base to form a compound of Formula Ig:



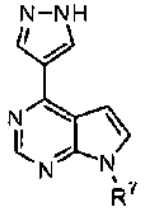
Ig ;

(b) treating the compound of Formula Ig to remove the R^{10} group to form a compound of Formula Ib:



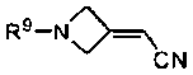
Ib ;

(c) reacting a compound of Formula Ib:



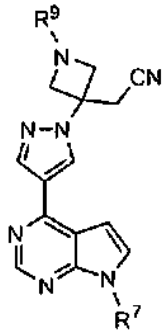
Ib

with a compound of Formula If:



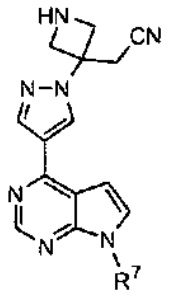
If

in the presence of a catalytic or stoichiometric amount of 1,8-diazabicyclo(5.4.0)undec-7-ene to form a compound of Formula Ic:



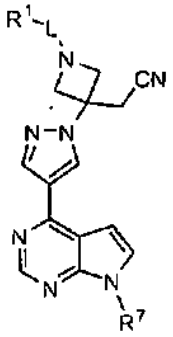
Ic ;

(d) treating the compound of Formula Ic to remove the R^9 group thereby forming a compound of Formula Id:



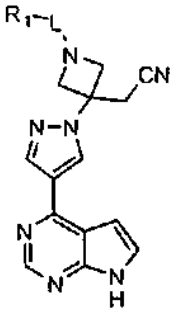
Id

(e) reacting the compound of Formula Id with a compound of formula R^8-L-R^1 to form a compound of Formula Ia:



Ia ;

(f) treating the compound of Formula Ia to remove the R^7 moiety to form a compound of Formula I:



I

wherein:

L is SO_2;

R^1 is C_{1-6} alkyl;

R^7 is 2-(trimethylsilyl)ethoxyethyl or 2-pivaloyloxymethyl;

R^8 is chloro;

R^9 is tert-butoxycarbonyl;

R^{10} is 1-(ethoxy)ethyl; and

X is chloro.

The methods may be used to produce any of the compounds described in the embodiments herein, or combinations thereof, or any of the compounds of the examples. The present invention provides any combination of the individual methods for forming compounds of Formula I, compounds of Formula Ia, etc. The present invention further provides any of the intermediates above, or salts thereof.

In some embodiments, the compound of Formula I produced by the methods, or combination thereof, is {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile. The present invention further provides each of the corresponding intermediates of Formula Ia, Ib, Ic, etc., for producing {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile.

In some embodiments, the methods further comprise reacting the compound of Formula I with phosphoric acid to form the phosphate salt. The phosphoric acid salt of the compound of Formula I may be produced by treating a solution of the corresponding free base in an organic solvent, such as ethanol (EtOH), with a solution of phosphoric acid in an organic solvent, such as ethanol, at room temperature or at an elevated temperature (e.g., from about 60 to about 70 °C). The produced crude phosphate salt may then be further purified by recrystallization or re-slurry in an organic solvent or a mixed organic solvent system.

In some embodiments, the compound produced by the method is {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile phosphoric acid salt.

In some embodiments, the compounds of Formulas I, II, III, and IV can be prepared according to the synthetic procedures described below in the Example section.

Methods

Compounds of the invention can modulate activity of one or more Janus kinases (JAKs). The term "modulate" is meant to refer to an ability to increase or decrease the activity of one or more members of the JAK family of kinases. Accordingly, compounds of the invention can be used in methods of modulating a JAK by contacting the JAK with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of one or more JAKs. In further

embodiments, the compounds of the invention can be used to modulate activity of a JAK in an individual in need of modulation of the receptor by administering a modulating amount of a compound of Formula I, II, III, or IV.

JAKs to which the present compounds bind and/or modulate include any member of the JAK family. In some embodiments, the JAK is JAK1, JAK2, JAK3 or TYK2. In some embodiments, the JAK is JAK1 or JAK2. In some embodiments, the JAK is JAK2. In some embodiments, the JAK is JAK3.

Another aspect of the present invention pertains to methods of treating a JAK-associated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. A JAK-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the JAK, including overexpression and/or abnormal activity levels. A JAK-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating JAK activity.

Examples of JAK-associated diseases include diseases involving the immune system including, for example, organ transplant rejection (*e.g.*, allograft rejection and graft versus host disease).

Further examples of JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, autoimmune thyroid disorders, and the like. In some embodiments, the autoimmune disease is an autoimmune bullous skin disorder such as pemphigus vulgaris (PV) or bullous pemphigoid (BP).

Further examples of JAK-associated diseases include allergic conditions such as asthma, food allergies, atopic dermatitis and rhinitis. Further examples of JAK-associated diseases include viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV).

Further examples of JAK-associated diseases or conditions include skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (*e.g.*, contact dermatitis or allergic contact dermatitis). For example, certain substances including some pharmaceuticals when topically applied can cause skin sensitization. In some embodiments, co-administration or sequential administration of at least one JAK inhibitor of the invention together with the agent causing unwanted

sensitization can be helpful in treating such unwanted sensitization or dermatitis. In some embodiments, the skin disorder is treated by topical administration of at least one JAK inhibitor of the invention.

In further embodiments, the JAK-associated disease is cancer including those characterized by solid tumors (*e.g.*, prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, melanoma etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example cutaneous T-cell lymphomas include Sezary syndrome and mycosis fungoides.

JAK-associated diseases can further include those characterized by expression of a mutant JAK2 such as those having at least one mutation in the pseudo-kinase domain (*e.g.*, JAK2V617F).

JAK-associated diseases can further include myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis with myeloid metaplasia (MMM), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like. In some embodiments, the myeloproliferative disorder is primary myelofibrosis (PMF) or post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF).

Further JAK-associated diseases include inflammation and inflammatory diseases. Example inflammatory diseases include inflammatory diseases of the eye (*e.g.*, iritis, uveitis, scleritis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (*e.g.*, the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis, and other inflammatory diseases.

The JAK inhibitors described herein can further be used to treat ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest. The JAK inhibitors described herein can further be used to treat anorexia, cachexia, or fatigue such as that resulting from or associated with cancer. The JAK inhibitors described herein can further be used to treat restenosis, scleroderma, or fibrosis. The JAK inhibitors described herein can further be used to treat conditions associated with hypoxia or astrogliosis such as, for example, diabetic retinopathy, cancer, or neurodegeneration. See,

e.g., Dudley, A.C. *et al. Biochem. J.* 2005, 390(Pt 2):427-36 and Sriram, K. *et al. J. Biol. Chem.* 2004, 279(19):19936-47. Epub 2004 Mar 2. The JAK inhibitors described herein can be used to treat Alzheimer's disease.

The JAK inhibitors described herein can further be used to treat other inflammatory diseases such as systemic inflammatory response syndrome (SIRS) and septic shock.

The JAK inhibitors described herein can further be used to treat gout and increased prostate size due to, e.g., benign prostatic hypertophy or benign prostatic hyperplasia.

The JAK inhibitors described herein, as well as other JAK inhibitors capable of influencing IL-6/STAT3 signalling, can further be used to treat inflammation-associated proliferative diseases. Inflammation has been shown to be linked to the development of certain types of cancers. For example, patients suffering from inflammatory bowel disease such as ulcerative colitis have been shown to have a much higher risk of developing colorectal cancer. These types of inflammation-linked cancers have been termed colitis-associated cancer (CAC). Several studies have shown that the IL-6/STAT3 signaling is involved in promoting CAC. For example, mice deficient in STAT3 intestinal epithelial cells had decreased tumor size and incidence in an animal model of CAC. Bromberg, et al., "Inflammation and cancer: IL-6 and STAT3 complete the link", *Cancer Cell*, 15:79-80 (2009). Similar results were obtained with IL-6 deficient mice, which developed fewer and smaller adenomas than wild-type mice. Grivennikov, et al., "IL-6 and STAT3 are required for survival of intestinal epithelial cells and the development of colitis-associated cancer", *Cancer Cell*, 15:103-111 (2009). See also, Bollrath, et al., "gp130-Mediated STAT3 activation in enterocytes regulatres cell survival and cell-cycle progression during colitis-associated tumorigenesis", *Cancer Cell*, 15:91-102 (2009); and Kortylewski, et al., "Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment", *Cancer Cell*, 15:114-123 (2009).

Accordingly, in some embodiments, JAK inhibitors of the invention and those which influence IL-6/STAT3 signaling, can be used to treat inflammation-associated cancers. In some embodiments, the cancer is associated with inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammation-associated cancer is colitis-associated cancer. In some embodiments, the inflammation-associated cancer is colon cancer or colorectal cancer. In some embodiments, the cancer is gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), adenocarcinoma, small intestine cancer, or rectal cancer. In addition to the compounds

provided herein, example JAK inhibitors that can be used in the treatment of inflammation-associated cancers include those described in US 2006/0106020; US 2006/0183906; US 2007/0149506; US 2007/0135461; US 2008/0188500; US 2008/0312258; US 2008/0312259; and U.S. Ser. No. 12/270,135.

JAK inhibitors can be tested in animal models for potential efficacy in treating inflammation-associated cancers. For example, CAC can be induced in treated (e.g., with JAK inhibitors) or untreated mice by the method summarized in Grivennikov, et al., "IL-6 and STAT3 are required for survival of intestinal epithelial cells and the development of colitis-associated cancer", *Cancer Cell*, 15:103-111 (2009). Progression of the disease can be followed by measuring body weight and monitoring for signs of rectal bleeding and diarrhea. After sacrifice of the animals, portions of the distal colon are removed for analysis.

In some embodiments, the JAK inhibitors described herein can further be used to treat a dry eye disorder. As used herein, "dry eye disorder" is intended to encompass the disease states summarized in a recent official report of the Dry Eye Workshop (DEWS), which defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." Lemp, "The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop", The Ocular Surface, 5(2), 75-92 April 2007, which is incorporated herein by reference in its entirety. Dry eye is also sometimes referred to as keratoconjunctivitis sicca. In some embodiments, the treatment of the dry eye disorder involves ameliorating a particular symptom of dry eye disorder, such as eye discomfort, visual disturbance, tear film instability, tear hyperosmolarity, and inflammation of the ocular surface.

As summarized in the DEWS report, dry eye can be classified into two different classes: aqueous tear-deficient dry eye and evaporative dry eye, which in turn encompass various subclasses. Accordingly, in some embodiments, the dry eye disorder is aqueous tear-deficient dry eye (ADDE). In further embodiments, the dry eye disorder is evaporative dry eye. In further embodiments, the dry eye disorder is selected from any of the subclasses of ADDE or evaporative dry eye disorder, or appropriate combinations thereof. As noted by the author of the DEWS report, however, the various classes and subclasses are not mutually exclusive. Hence, dry eye can occur via different mechanism in different subclasses or a dry eye disease state originating in one subclass can lead to events that cause dry eye by a mechanism in another subclass.

The first class of dry eye, aqueous tear-deficient dry eye (ADDE), is also known as tear deficient dry eye and lacrimal tear deficiency. In ADDE, dry eye is believed to be due to a failure of lacrimal tear secretion. While not wishing to be bound by any theory, it is believed that dryness results from reduced lacrimal tear secretion and volume, causing tear hyperosmolarity. Tear film hyperosmolarity can cause hyperosmolarity of the ocular surface epithelial cells, stimulating inflammatory events involving various kinases and signaling pathways.

Two subclasses of ADDE are Sjogren syndrome dry eye (SSDE), where the lacrimal glands are targeted by an autoimmune process, and non-Sjogren syndrome dry eye (NSSDE). Accordingly, in some embodiments, the eye disorder is SSDE. In other embodiments, dry eye disorder is non-Sjogren syndrome dry eye. In SSDE, it is believed that activated T-cells can infiltrate the lacrimal glands, causing cell death of acinar and ductular cells and hyposecretion of tears. The effects of locally released cytokines or circulating antibodies can amplify the effects of hyposecretion. The two major forms of SSDE are primary and secondary forms Primary SS can occur in combination with dry mouth (xerostomia). Secondary SSDE occurs with the symptoms of primary SSDE together with an autoimmune connective disease such as rheumatoid arthritis (RA), systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary bilary sclerosis, or mixed connective tissue disease. Diagnostic criteria for each of these connective diseases is known in the art. Further, primary SSDE may be associated with systemic manifestations of disease which may involve the lungs, kdneys, liver, blood vessels and joints.

In NSSDE, the systemic autoimmune characteristics of Sjogren syndrome dry eye are excluded. Forms of NSSDE include primary lacrimal gland deficiencies (including age-related dry eye, congenital alacrima, and familial dysautonomia), secondary lacrimal deficiencies (including inflammatory infiltration of the lacrimal gland by sarcoid granulomata, lymphomatous cells, and AIDS related T-cells; that associated with graft vs. host disease; and that resulting from lacrimal gland ablation or lacrimal gland denervation), obstruction of the lacrimal gland ducts (including that caused by cicatrizing conjunctivitis including trachoma, cicatricial pemphigoid and mucous membrane pemphigoid, erythema multiforme, and chemical or thermal burns), and reflex hyposecretion (including reflex sensory block, such as that associated with contact lens wear, diabetes mellitus, and neurotrophic keratitis, and reflex motor block, including that associated with VII cranial nerve damage, multiple neuromatosis, and exposure to systemic drugs such as antihistamines,

beta blockers, antispasmodics, diuretics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other psychotropic drugs).

The second major class of dry eye disorder is evaporative dry eye, which is caused by excessive water loss from the exposed ocular surface in the presence of normal lacrimal secretory function. Intrinsic causes of evaporative dry eye include Meibomian gland dysfunction (MGD) (including that caused by a reduced number of glands due to congenital deficiency acquired-MGD; MGD associated with dystichiasis, dystichiasis lymphedema syndrome, and metaplasia; hypersecretory MGD associated with Meibomian seborrhea, hypersecretory MGD associated with retinoid therapy, primary and secondary obstructive MGD, focal or diffuse obstructive MGD, simple or cicatricial obstructive MGD, atrophic or inflammatory obstructive MGD; Simple MGD primary or secondary to anterior blepharitis, acne rosacea; seborrhoeic dermatitis, ectrodactyly syndrome, Turner syndrome, systemic toxicity from 13-cis retinoic acid, polychlorinated biphenyls, and epinephrine; and cicatricial MGD primary or secondary to chemical burns, pemphigoid, acne rosacea, erythema multiforms, VKC and AKC), disorders of the lid aperture and lid/globe congruity or dynamic (such as that occurring with craniostenosis, endocrine and other forms of proptosis, myopia, and after plastic surgery on the lids), and low blink rate (including that caused by an extrapyramidal disorder such as Parkinson's disease). Extrinsic causes of evaporative dry eye include ocular surface disorders (including xerophthalmia caused by vitamin A deficiency; and that associated with topical drugs and preservatives such as topical anesthesia and benzalkonium chloride), contact lens wear, ocular surface disease (including allergic eye disease), allergic conjunctivitis (including aseasonal allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis), and the use of anti-histamines.

Patients in need of treatment of a dry eye disorder can be identified by a variety of diagnostic methods known in the art, including the diagnostic methods summarized in Bron, et al., "Methodologies to Diagnose and Monitor Dry Eye Disease: Report of the Diagnostic Methodology Subcommittee of the International Dry Eye Workshop (2007)", The Ocular Surface, 5(2), 108-152 (April 2007), which is hereby incorporated herein by reference in its entirety. These include, but are not limited to: (1) symptom questionnaires (e.g., Begley, et al., "Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye", Cornea, 2002:21:664-70); (2) staining of the ocular surface to check for surface damage (e.g., Rose Bengal or fluorescein staining or other staining method such as those techniques summarized in Barr et al., "Corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: baseline prevalence

and repeatability of detection", Cornea 1999;18(1):34-46; Lemp, "Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes", CLAO J 1995;21(4):221-31; Nichols, et al., "The repeatability of clinical measurements of dry eye", Cornea 2004;23:272-85; Bron, et al., "Grading of corneal and conjunctival staining in the context of other dry eye tests", Cornea 2003;22(7):640-50); (3) measurement of tear film break-up time to test for tear film stability (e.g., Abelson, et al., "Alternate reference values for tear film break-up time in normal and dry eye populations", Adv Exp Med Biol 2002;506,Part B:1121-1125; Bron AJ, et al., "Grading of corneal and conjunctival staining in the context of other dry eye tests", Cornea 2003;22:640-50; Cho et al, "Review of the tear break-up time and a closer look at the tear break-up time of Hong Kong Chinese", Optom Vis Sci 1993;70(1):30-8; Craig et al. "Tear lipid layer structure and stability following expression of the meibomian glands. Ophthalmic Physiol Opt 1995, 15(6):569-74; Eliason, et al., "Staining of the conjunctiva and conjunctival tear film", Br J Ophthalmol 1990;74:519-22; Farrell et al., "A classification for dry eyes following comparison of tear thinning time with Schirmer tear test", Acta Ophthalmol (Copenh) 1992; 70(3):357-60; Johnson et al., "The effect of instilled fluorescein solution volume on the values and repeatability of TBUT measurements", Cornea 2005;24:811-7; Lemp et al., "Corneal desiccation despite normal tear volume", Ann Ophthalmol 1973;284:258-261; Lemp "Report of National Eye Institute/Industry Workshop on clinical trials in dry eyes", CLAO J 1995;21:221-232; Madden et al. Comparative study of two non-invasive tear film stability techniques. Curr Eye Res 1994; 13(4):263-9; Marquardt et al., "Modification of tear film break-up time test for increased reliability" in Holly ed. The Preocular Tear Film inHealth, Disease and Contact Lens Wear. Lubbock, Texas: Dry Eye Institute, 1986:57-63; Mengher et al., "Non-invasive tear film break-up time: sensitivity and specificity", Acta Ophthalmol (Copenh) 1986; 64(4):441-4; Nichols et al., "The repeatability *of clinical measurements of dry eye" Cornea 2004;23:272-85; Pflugfelder et al. "Evaluation* of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea 1998; 17(1):38-56; Vitali et al. "The European Community Study Group on diagnostic criteria for Sjogren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjogren's syndrome." 1992; Ann Rheum Dis 53(10):637-47; Welch et al., "An approach to a more standardized method of evaluating tear film break-up time" Invest Ophthalmol Vis Sci 2003; 2485/B324.); (4) the Schirmer test (an estimation of tear flow stimulated reflexly by insertion of a filter paper into the conjunctival sac) (e.g., van Bijsterveld, "Diagnostic tests in the sicca syndrome" Arch Ophthalmol 1969;82:10-14; Holly et al., "Lacrimation kinetics as determined by a novel

technique", in Holly FJ (ed). The preocular tear film. Lubbock TX, Lubbock Dry Eye Institute, 1986, pp 76-88); (5) measurement of tear osmolarity (e.g., Farris, "Tear osmolarity--a new gold standard?" Adv Exp Med Biol 350:495-503, 1994; Nelson et al., "Tear film osmolality determination: an evaluation of potential errors in measurement" Curr Eye Res Sep;5(9):677-81, 1986; Sullivan et al., "4th International Conference on the Lacrimal Gland, Tear Film & Ocular Surface and Dry Eye Syndromes, 11/20/04"; White et al., "Human basic tear fluid osmolality. I. Importance of sample collection strategy", Acta Ophthalmol (Copenh) Aug;71(4):524-9, 1993; (6) measurement of tear meniscus radius, height and cross sectional area to diagnose aqueous tear deficiency (e.g., Cermak et al, "Is complete androgen insensitivity syndrome associated with alterations in the meibomium gland and ocular surface", Cornea 2003;22:516-521; Farrell et al., "A clinical procedure to predict the value of temporary occlusion therapy in keratoconjunctivitis sicca" Ophthal Physiol Opt 2003;23:1-8; Glasson et al., "Differences in clinical parameters and tear film of tolerant and intolerant contact lens wearers", Invest Ophthalmol Vis Sci 2003;44:5116-5124; Mainstone et al., "Tear meniscus measurement in the diagnosis of dry eye", Curr Eye Res 1996; 15:653-661; Nichols et al., "The repeatability of clinical measurements of dry eye", Cornea 2004a; 23:272-285; Nichols et al., "The lack of association between signs and symptoms in patients with dry eye disease", Cornea 2004b; 23:762-770; Oguz et al., "The height and radius of the tear meniscus and methods for examining these parameters", Cornea 2000;19:497-500; Yokoi et al., "Non-invasive methods of assessing the tear film", Exp Eye Res 2004;78:399-407); (7) tear film lipid layer interferometry to diagnose aqueous tear deficient dry eye (ATD) or precorneal lipid tear deficiency (Danjo et al., "Observation of precorneal tear film in patients with Sjogren's syndrome", Acta Ophthalmol Scand 1995;73:501-5; Doane, "An instrument for in vivo tear film interferometry", Optom Vis Sci 1989; 66: 383-8; Goto et al., "Computer-synthesis of an interference color chart of human tear lipid layer by a colorimetric approach",Invest Ophthalmol Vis Sci 2003;44:4693-7; Goto et al., "Differentiation of lipid tear deficiency dry eye by kinetic analysis of tear interference images", Arch Ophthalmol 2003;121:173-80; Goto E, et al., "Kinetic analysis of tear interference images in aqueous tear deficiency dry eye before and after punctal occlusion. Invest Ophthalmol Vis Sci 2003;44:1897-905; Goto et al., "Color mapping of tear lipid layer thickness distribution from the image analysis in DR-1 tear lipid layer interference images (ARVO abstract). ARVO 2004; Guillon, "Tear film photography and contact lens wear", J Br Contact Lens Assoc 1982;5:84-7; King-Smith et al., "Three interferometric methods for measuring the thickness of layers of the tear film", Optom Vis Sci 1999;76:19-32; Korb, et al., "Increase in tear film

lipid layer thickness following treatment of meibomian gland dysfunction", Adv Exp Med Biol 1994;350:293-8; Korb et al., "The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms", Optom Vis Sci 2005; 82: 594-601; Mathers et al., "Assessment of the tear film with tandem scanning confocal microscopy", Cornea 1997;16:162-8; Maruyama et al., "Effect of environmental conditions on tear dynamics in soft contact lens wearers", Invest Ophthalmol Vis Sci 2004;45(8):2563-8; Tiffany, "Refractive index of meibomian and other lipids", Curr Eye Res 1986;5:887-9; Tiffany et al., "Meniscometry using the Tearscope-plus (ARVO abstract). Invest Ophthalmol Vis Sci 2001;42, s37; Yokoi et al., "Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye", Am J Ophthalmol 1996;122:818-24; Yokoi et al., "Assessment of meibomian gland function in dry eye using meibometry", Arch Ophthalmol 1999;117:723-9); (8) Tear Stability Analyses System (TSAS) to diagnose tear instability (e.g., Goto et al., "Tear Film Stability Analysis System: Introducing a new application for videokeratography", Cornea 2004a; Nov;23(8):S65-S70; Goto et al., "Evaluation of the tear film stability after laser in situ keratomileusis using the tear film stability analysis system", Am J Ophthalmol 2004b Jan;137(1):116-20; Kojima et al., "A new noninvasive tear stability analysis system for the assessment of dry eyes" Invest Ophthalmol Vis Sci 2004;May;45(5):1369-74); (9) meibometry to assess Meibomian gland dysfunction (e.g., Chew et al., "An instrument for quantifying meibomian lipid on the lid margin: the Meibometer", Curr Eye Res 1993a;12:247-254; Chew et al., "The casual level of meibomian lipids in humans", Current Eye Research 1993b;12:255-259; Komuro et al., "Assessment of meibomian gland function by a newly developed laser meibometer", Adv Exp Med Biol 2002;506:517-520; Yokoi et al., "Assessment of meibomian gland function in dry eye using meibometry" Arch Ophthalmol 1999;117:723-729); (10) meibography or meiboscopy to measure Meibomian gland dysfunction (e.g., Kaercher, "Ocular symptoms and signs in patients with ectodermal dysplasia symdromes", Grafes Arch Clin Exp Ophthalmol 2004;495-500; Jester et al., "In vivo biomicroscopy and photography of meibomian glands in a rabbit model of meibomian gland dysfunction", Invest Ophthalmol Vis Sci 1982;22:660-7; Mathers et al., "Video imaging of the meibomian gland", Arch Ophthalmol 1994;112:448-9; Pflugfelder, et al., "Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation", Cornea 1998;17(1):38-56; Robin et al., "In vivo transillumination biomicroscopy and photography of meibomian gland dysfunction. Ophthalmology 1985;92:1423-6; Shimazaki et al., "Meibomian gland dysfunction in patients with Sjogren syndrome", Ophthalmology 1998;105(8):1485-8; Yokoi

et al., "A newly developed video-meibography system featuring a newly designed probe", Jpn J Ophthalmol 2007; 51: 53-6); (11) Brush Cytology Technique (e.g., Fukagawa et al., "Histological evaluation of brush cytology of rabbit conjunctiva", Nippon Ganka Gakkai Zasshi 1993;97:1173-8; Fujihara et al., "Evaluation of human conjunctival epithelium by a combination of brush cytology and flow cytometry: an approach to the quantitative technique", Diagn Cytopathol 1997;17:456-60; Miyoshi et al., "Interleukin-8 concentrations in conjunctival epithelium brush cytology samples correlate with neutrophil, eosinophil infiltration, and corneal damage", Cornea 2001;20:743-7; Takano et al., "Inflammatory cells in brush cytology samples correlate with the severity of corneal lesions in atopic keratoconjunctivitis", Br J Ophthalmol 2004;88:1504-5; Tsubota et al., "Brush cytology for the evaluation of dry-eye", Nippon Ganka Gakkai Zasshi 1990a ;94:224-30; Tsubota et al., "Conjunctival brush cytology", Acta Cytol 1990 b;34:233-5; Tsubota et al., "Detection by brush cytology of mast cells and eosinophils in allergic and vernal conjunctivitis"; Cornea 1991;10:525-31); (12) Flow cytometry in impression cytology to detect conjuctivial inflammation (e.g., Baudouin et al., "Flow cytometry in impression cytology specimens. A new method for evaluation of conjunctival Inflammation", Invest Ophthalmol Vis Sci 1997a;38:1458-1464; Bourcier et al., "Expression of CD40 and CD40 ligand in the human conjunctival epithelium", Invest Ophthalmol Vis Sci 2000;41:120-126; Brignole et al., "Expression of Fas antigen (CD95) in the human conjunctival epithelium. Positive correlation with class II HLA DR expression in inflammatory conditions", Exp Eye Res 1998;67:687-697; Brignole et al., "Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes" Invest Ophthalmol Vis Sci 2000; 41:1356-1363; Brignole et al., "Flow cytometric analysis of inflammatory markers in KCS: 6-month treatment with topical cyclosporin A", Invest Ophthalmol Vis Sci 2001;42:90-95; Brignole et al., "Flow cytometry in conjunctival impression cytology: a new tool for exploring ocular surface pathologies", Exp Eye Res 2004;78:473-481; Fujihara et al., "Evaluation of human conjunctival epithelium by a combination of brush cytology and flow cytometry: an approach to the quantitative technique" Diagn Cytopathol 1997;17:456-460; Pisella et al., "Flow cytometric analysis of conjunctival epithelium in ocular rosacea and keratoconjunctivitis sicca. Ophthalmology 2000;107:1841-1849; Pisella, et al., "Conjunctival proinflammatory and proapoptotic effects of latanoprost, preserved timolol and unpreserved timolol: an ex vivo and in vitro study. Invest Ophthalmol Vis Sci 2004;45:1360-1368); (13) the Ferning test to diagnose the quality of tears (electrolyte concentration), KCS, and hyperosmolarity (e.g., Albach et al., "Diagnosis of keratoconjunctivitis sicca in rheumatoid arthritis. The value of

various tests", Ophthalmologe 1994 Apr;91(2):229-34; Golding et al., "X-ray and scanning electron microscopic analysis of the structural composition of tear ferns", Cornea 1994 Jan;13(1):58-66; Norn, "Quantitative tear ferning. Clinical investigations", Acta Ophthalmol (Copenh) 1994 Jun;72(3):369-72; Pearce et al., "Spatial location studies on the chemical composition of human tear ferns", Ophthalmic Physiol Opt 2000;Jul;20(4):306-13; Pensyl et al., "The repeatability of tear mucus ferning grading", Optom Vis Sci 1998 Aug;75(8):600-4; Rolando, "Tear mucus ferning test in normal and keratoconjunctivitis sicca eyes. Chibret Int J Ophthalmol 1984;2(4):32-41; Rolando et al., "Tear mucus ferning test in keratoconjunctivitis sicca",in: Holly FJ, Lamberts DW, MacKeen DL (eds.): The preocular tear film in health, disease, and contact lens wear,. 1st Intern Tear Film Symposium. Lubbok (Texas, USA), Dry Eye Institute, 1986, 203-210; Rolando et al., "The effect of hyperosmolarity on tear mucus ferning", Fortschr Ophthalmol 1986;83:644-646; Rolando et al., "Tear mucus crystallization in children with cystic fibrosis", Ophthalmologica 1988;197(4):202-6); (14) Ocular Protection Index (OPI) to assess ocular surface protection and risk of ocular surface damage (e.g., Ousler et al., "Factors that influence the inter-blink interval (IBI) as measured by the ocular protection index (OPI)", (Poster presentation) ARVO 2002; Nally et al., "Ocular discomfort and tear film break-up time in dry eye patients: A correlation", Invest Ophthalmol Vis Sci 2000;41:4:1436; Abelson et al., "Alternate reference values for tear film break-up time in normal and dry eye populations", Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3 Part B", Adv Exp Med Biol 2002; 506:1121-1125; Abelson et al., "Dry eye syndrome: diagnosis, clinical trials, and pharmaceutical treatment—'improving clinical trials'. Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3 Part B", Adv Exp Med Biol 2002; 506:1079-86); (15) fluorophotometry (fluorimetry) of tear flow to assess changes in tear flow in aqueous tear deficiency (ATD) (e.g., Gobbels et al., "Tear secretion in dry eyes as assessed by objective fluorophotometry. Ger J Ophthalmol 1992; 1:350-353; Kuppens et al., "Basal tear turnover and topical timolol in glaucoma patients and healthy controls by Fluorophotometry", Invest Ophthalmol Vis Sci 1992; 33:3442-3448; Mishima, "Some physiological aspects of the precorneal tear film", Arch Ophthalmol 1965;73:233-241; Mishima S, "Determination of tear volume and tear flow", Invest Ophthalmol 1966; 5:264-275; Mathers et al., "Tear film and evaporation in patients with and without dry eye", Ophthalmology 1996; 103:664-669; Mathers et al., "Tear film changes associated with normal aging", Cornea 1996; 15:229-334; Mathers, "Evaporation from the ocular surface", Exp Eye Res 2004; 78:389-394; Van Best et al., "Measurement of basal tear turnover using a standardized protocol", Graefe's Arch Clin Exp Ophthalmol 1995; 233:1-7; McNamara et al.,

"Fluorometry in contact lens research: The next step", Optom Vis Sci 1998; 75:316-322; Pearce, "An improved fluorophotometric method for tear turnover assessment", Optom Vis Sci 2001; 78:30-36), and combinations of these diagnostic tests, the disclosures of each reference are incorporated herein by reference in their entireties. These methods can also be used to assess the clinical efficacy of the compounds described herein in treating dry eye disorders.

In a further aspect, the present invention provides a method of treating conjunctivitis, uveitis (including chronic uveitis), chorioditis, retinitis, cyclitis, scleritis, episcleritis, or iritis; treating inflammation or pain related to corneal transplant, LASIK (laser assisted in situ keratomileusis), photorefractive keratectomy, or LASEK (laser assisted sub-epithelial keratomileusis); inhibiting loss of visual acuity related to corneal transplant, LASIK, photorefractive keratectomy, or LASEK; or inhibiting transplant rejection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or pharmaceutically acceptable salt or N-oxide thereof. In some embodiments, the compound, or pharmaceutically acceptable salt or N-oxide thereof, is administered preoperatively to a patient about to undergo a procedure selected from corneal transplant, LASIK, photorefractive keratectomy, and LASEK. In some embodiments, the compound, or pharmaceutically acceptable salt or N-oxide thereof, suppresses or lessens inflammation or pain during and after the procedure. In some embodiments, the compound, or pharmaceutically acceptable salt or N-oxide thereof, is administered about 1 day to about 2 days prior to the procedure. In some embodiments, the compound, or pharmaceutically acceptable salt or N-oxide thereof, is administered postoperatively to a patient who has undergone a procedure selected from corneal transplant, LASIK, photorefractive keratectomy, and LASEK. In some embodiments, inhibiting loss of visual acuity means lessening the loss of visual acuity. In some embodiments, the postoperative or preoperative treatment lessens the amount of scarring and fibrous deposits following the procedure. In some embodiments, inhibiting loss of visual acuity means that the patient retains visual acuity. In some embodiments, inhibiting transplant rejection means that the compound, or pharmaceutically acceptable salt or N-oxide thereof, is immunosuppressive, thereby preventing total rejection of the corneal transplant.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a JAK with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a JAK, as well as, for example,

introducing a compound of the invention into a sample containing a cellular or purified preparation containing the JAK.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

Combination Therapies

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, or other agents can be used in combination with the compounds of the present invention for treatment of JAK-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example chemotherapeutic include proteosome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine etoposide, carmustine, and the like.

Example steroids include coriticosteroids such as dexamethasone or prednisone.

Example Ber-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

In some embodiments, one or more of the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, one or more JAK inhibitors of the invention can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Ber-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a JAK inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with a JAK inhibitor of the present invention. The agents can be combined with the present compounds in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with at least one JAK inhibitor where the dexamethasone is administered intermittently as opposed to continuously.

In some further embodiments, combinations of one or more JAK inhibitors of the invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

In some embodiments, at least one additional therapeutic agent can be used in connection with treatment of dry eye disorders and other disorders of the eye. In some embodiments, the additional therapeutic agent is fluocinolone acetonide (Retisert®), or rimexolone (AL-2178, Vexol, Alcon). In some embodiments, the additional therapeutic agent is cyclosporine (Restasis®). In some embodiments, the additional therapeutic agent is a corticosteroid. In some embodiments, the corticosteroid is triaminolone, dexamethasone, fluocinolone, cortisone, prednisolone, or flumetholone.

In some embodiments, the additional therapeutic agent is selected from Dehydrex™ (Holles Labs), Civamide (Opko), sodium hyaluonate (Vismed, Lantibio/TRB Chemedia), cyclosporine (ST-603, Sirion Therapeutics), ARG101(T) (testosterone, Argentis), AGR1012(P) (Argentis), ecabet sodium (Senju-Ista), gefarnate (Santen), 15-(s)-hydroxyeicosatetraenoic acid (15(S)-HETE), cevilemine, doxycline (ALTY-0501, Alacrity), minocycline, iDestrin™ (NP50301, Nascent Pharmaceuticals), cyclosporine A (Nova22007, Novagali), oxytetracycline (Duramycin, MOL1901, Lantibio), CF101 (2S,3S,4R,5R)-3,4-dihydroxy-5-[6-[(3-iodophenyl)methylamino]purin-9-yl]-N-m ethyl-oxolane-2-carbamyl, Can-Fite Biopharma), voclosporin (LX212 or LX214, Lux Biosciences), ARG103 (Agentis), RX-10045 (synthetic resolvin analog, Resolvyx), DYN15 (Dyanmis Therapeutics), rivoglitazone (DE011, Daiichi Sanko), TB4 (RegeneRx), OPH-01 (Ophtalmis Monaco), PCS101 (Pericor Science), REV1-31 (Evolutec), Lacritin (Senju), rebamipide (Otsuka-Novartis), OT-551 (Othera), PAI-2 (University of Pennsylvania and Temple University), pilocarpine, tacrolimus, pimecrolimus (AMS981, Novartis), loteprednol etabonate, rituximab, diquafosol tetrasodium (INS365, Inspire), KLS-0611 (Kissei Pharmaceuticals), dehydroepiandrosterone, anakinra, efalizumab, mycophenolate sodium, etanercept (Embrel®), hydroxychloroquine, NGX267 (TorreyPines Therapeutics), or thalidomide.

In some embodiments, the additional therapeutic agent is an anti-angiogenic agent, cholinergic agonist, TRP-1 receptor modulator, a calcium channel blocker, a mucin secretagogue, MUC1 stimulant, a calcineurin inhibitor, a corticosteroid, a P2Y2 receptor agonist, a muscarinic receptor agonist, another JAK inhibitor, Ber-Abl kinase inhibitor, Flt-3 kinase inhibitor, RAF kinase inhibitor, and FAK kinase inhibitor such as, for example, those described in WO 2006/056399. In some embodiments, the additional therapeutic agent is a tetracycline derivative (e.g., minocycline or doxycline).

In some embodiments, the additional therapeutic agent(s) are demulcent eye drops (also known as "artificial tears"), which include, but are not limited to, compositions containing polyvinylalcohol, hydroxypropyl methylcellulose, glycerin, polyethylene glycol

(e.g. PEG400), or carboxymethyl cellulose. Artificial tears can help in the treatment dry eye by compensating for reduced moistening and lubricating capacity of the tear film. In some embodiments, the additional therapeutic agent is a mucolytic drug, such as N-acetyl-cysteine, which can interact with the mucoproteins and, therefore, to decrease the viscosity of the tear film.

In some embodiments, the additional therapeutic agent includes an antibiotic, antiviral, antifungal, anesthetic, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; naphthyridine; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; comolyn; lodoxamide; levocabastin; naphazoling; antazoline; pheniramimane; or azalide antibiotic.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers (excipients). In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, for example see International Patent Application No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary

dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders.

The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, *for example, the particular use for which the treatment is made, the manner of* administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100

mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In some embodiments, the compound of the invention, or pharmaceutically acceptable salt thereof, is administered as an ophthalmic composition. Accordingly, in some embodiments, the methods comprise administration of the compound, or pharmaceutically acceptable salt thereof, and an ophthalmically acceptable carrier. In some embodiments, the ophthalmic composition is a liquid composition, semi-solid composition, insert, film, microparticles or nanooparticles.

In some embodiments, the ophthalmic composition is a liquid composition. In some embodiments, the ophthalmic composition is a semi-solid composition. In some embodiments, the ophthalmic composition is an topical composition. The topical compositions include, but are not limited to liquid and semi-solid compositions. In some embodiments, the ophthalmic composition is a topical composition. In some embodiments, the topical composition comprises aqueous solution, an aqueous suspension, an ointment or a gel. In some embodiments, the ophthalmic composition is topically applied to the front of the eye, under the upper eyelid, on the lower eyelid and in the cul-de-sac. In some embodiments, the ophthalmic composition is sterilized. The sterilization can be accomplished by known techniques like sterilizing filtration of the solution or by heating of the solution in the ampoule ready for use. The ophthalmic compositions of the invention can further contain pharmaceutical excipients suitable for the preparation of ophthalmic formulations. Examples of such excipients are preserving agents, buffering agents, chelating agents, antioxidant agents and salts for regulating the osmotic pressure.

As used herein, the term "ophthalmically acceptable carrier" refers to any material that can contain and release the compound, or pharmaceutically acceptable salt or N-oxide thereof, and that is compatible with the eye. In some embodiments, the ophthalmically acceptable carrier is water or an aqueous solution or suspension, but also includes oils such as those used to make ointments and polymer matrices such as used in ocular inserts. In some embodiments, the composition may be an aqueous suspension comprising the compound, or pharmaceutically acceptable salt or N-oxide thereof. Liquid ophthalmic compositions, including both ointments and suspensions, may have a viscosity that is suited for the selected

route of administration. In some embodiments, the ophthalmic composition has a viscosity in the range of from about 1,000 to about 30,000 centipoise.

In some embodiments, the liquid composition further comprises a polymer. These polymers may be used to improve the bioavailability, raise viscosity, or reduce drainage from the eye for a liquid formulation. In some embodiments, the polymers include, but are not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.*, pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the polymer is sodium hyaluronase, chitosan, a cyclodextrin (e.g., hydroxypropyl β-cyclodextrin), polygalactoronic acid, xyloglucan, xanthan gum, gellan gum, a thiomer, a poly(ortho ester) (e.g., as described in Einmahl, *Adv. Drug. Deliv. Rev.* 53:45-73 (2001), which is incorporated herein by reference in its entirety), or a tamarind seed polysaccharide (e.g., as described in Ghelardi, et al., Antimicrob. Agents Chemother. 48:3396-3401 (2004), which is incorporated herein by reference in its entirety).

In some embodiments, the ophthalmic compositions may further comprise one or more of surfactants, adjuvants, buffers, antioxidants, tonicity adjusters, preservatives (e.g., EDTA, BAK (benzalkonium chloride), sodium chlorite, sodium perborate, polyquaterium-1), thickeners or viscosity modifiers (e.g., carboxymethyl cellulose, hydroxymethyl cellulose, polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose, hydroxpropyl-guar, hyaluronic acid, and hydroxypropyl cellulose) and the like. Additives in the formulation may include, but are not limited to, sodium chloride, sodium bicarbonate, sorbic acid, methyl paraben, propyl paraben, chlorhexidine, castor oil, and sodium perborate.

Aqueous ophthalmic compositions (solutions or suspensions) generally do not contain physiologically or ophthalmically harmful constituents. In some embodiments, purified or deionized water is used in the composition. The pH may be adjusted by adding any physiologically and ophthalmically acceptable pH adjusting acids, bases or buffers to within the range of about 5.0 to 8.5. Ophthalmically acceptable examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, trishydroxymethylamino-methane, and the like. Salts and buffers include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

In some embodiments, the osmotic pressure of the ophthalmic composition may be from about 10 milliosmolar (mOsM) to about 400 mOsM, or from 260 to about 340 mOsM. In some embodiments, the osmotic pressure can be adjusted by using appropriate amounts of physiologically and ophthalmically acceptable salts or excipients. In further embodiments, sodium chloride may be used to approximate physiologic fluid. In other embodiments, the composition comprises sodium chloride ranging from about 0.01% to about 1% by weight, or from about 0.05% to about 0.45% by weight, based on the total weight of the composition. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above stated range. Similarly, a sugar such as mannitol, dextrose, sorbitol, glucose and the like can also be used to adjust osmolality.

In some embodiments, the methods involve forming or supplying a depot of the therapeutic agent in contact with the external surface of the eye. A depot refers to a source of therapeutic agent that is not rapidly removed by tears or other eye clearance mechanisms. This allows for continued, sustained high concentrations of therapeutic agent be present in the fluid on the external surface of the eye by a single application. Without wishing to be bound by any theory, it is believed that absorption and penetration may be dependent on both the dissolved drug concentration and the contact duration of the external tissue with the drug containing fluid. As the drug is removed by clearance of the ocular fluid and/or absorption into the eye tissue, more drug is provided, e.g. dissolved, into the replenished ocular fluid from the depot. Accordingly, the use of a depot may more easily facilitate loading of the ocular tissue for more insoluble therapeutic agents. In some embodiments, the depot can remain for up to eight hours or more. In some embodiments, the ophthalmic depot forms includes, but is not limited to, aqueous polymeric suspensions, ointments, and solid inserts.

In some embodiments, a semi-solid composition is a liquid formulation which increases in viscosity upon application to the eye, usually because of a polymer in the liquid formulation. This viscosity increase may be triggered by a change in temperature, pH, or electrolyte concentration. In some embodiments, the polymer include, but are not limited to, those described for semi-solid dosage forms in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.*, pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the polymer is celluloseacetophthalate, polyacrylic acid, gellan gum, hyaluronase, chitosan, salts of alginic

acid (e.g., sodium alginate), or a block copolymer of ethylene oxide and propylene oxide (e.g., Pluronic®, BASF; poloxamer). In some embodiment, the polyacrylic acid is crosslinked acrylic acid (e.g., Carbopol®). In some embodiments, the semi-solid composition comprises a mixture of carbopol and a block copolymer of ethylene oxide and propylene oxide; a mixture of methyl cellulose and hydroxyethyl cellulose; or a mixture of polyethylene glycol and a block copolymer of ethylene oxide and propylene oxide.

In some embodiments, the ophthalmic composition is an ointment or gel. In some embodiment, the ophthalmic composition is an oil-based delivery vehicle. In some embodiments, the composition comprises a petroleum or lanolin base to which is added the active ingredient, usually as 0.1 to 2%, and excipients. Common bases may include, but are not limited to, mineral oil, petrolatum and combinations thereof. In some embodiments, the ointment is applied as a ribbon onto the lower eyelid.

In some embodiment, the ophthalmic composition is an ophthalmic insert. In some embodiments, the ophthalmic insert is biologically inert, soft, bio-erodible, viscoelastic, stable to sterilization after exposure to therapeutic agents, resistant to infections from air borne bacteria, bio- erodible, biocompatible, and/or viscoelastic. In some embodiments, the insert comprises an ophthalmically acceptable matrix, e.g., a polymer matrix. The matrix is typically a polymer and the therapeutic agent is generally dispersed therein or bonded to the polymer matrix. In some embodiments, the therapeutic agent may slowly released from the matrix through dissolution or hydrolysis of the covalent bond. In some embodiments, the polymer is bioerodible (soluble) and the dissolution rate thereof can control the release rate of the therapeutic agent dispersed therein. In another form, the polymer matrix is a biodegradable polymer that breaks down such as by hydrolysis to thereby release the therapeutic agent bonded thereto or dispersed therein. In further embodiments, the matrix and therapeutic agent can be surrounded with an additional polymeric coating to further control release. In some embodiments, the insert comprises a biodegradable polymer such as polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacrylate, polyurethane, a nylon, or poly (dl-lactide-co-glycolide) (PLGA), or a copolymer of any of these. In some embodiments, the therapeutic agent is dispersed into the matrix material or dispersed amongst the monomer composition used to make the matrix material prior to polymerization. In some embodiments, the amount of therapeutic agent is from about 0.1 to about 50%, or from about 2 to about 20%. In further embodiments, the biodegradable or bioerodible polymer matrix is used so that the spent insert does not have to

be removed. As the biodegradable or bioerodible polymer is degraded or dissolved, the therapeutic agent is released.

In further embodiments, the ophthalmic insert comprises a polymer, including, but are not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.*, pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the insert comprises a polymer selected from polyvinylpyrrolidone (PVP), an acrylate or methacrylate polymer or copolymer (e.g., Eudragit® family of polymers from Rohm or Degussa), hydroxymethyl cellulose, polyacrylic acid, poly(amidoamine) dendrimers, poly(dimethyl siloxane), polyethylene oxide, poly(lactide-co-glycolide), poly(2-hydroxyethylmethacrylate), poly(vinyl alcohol), or poly(propylene fumarate). In some embodiments, the insert comprises Gelfoam® R. In some embodiments, the insert is a polyacrylic acid of 450 kDa-cysteine conjugante.

In some embodiments, the ophthalmic composition is a ophthalmic film. Polymers suitable for such films include, but are not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.*, pages 12-17 (Jan. 2008), In some embodiments, the film is a soft-contract lense, such as ones made from copolymers of N,N-diethylacrylamide and methacrylic acid crosslinked with ethyleneglycol dimethacrylate.

In some embodiments, the insert comprises a core comprising the therapeutic agent and an outer tube (see e.g., U.S. Patent Pub. No. 20040009222, which is incorporated herein by reference in its entirety). In some embodiments, the outer tube may be permeable, semi-permeable, or impermeable to the drug. In some embodiments, the drug core may include a polymer matrix which does not significantly affect the release rate of the drug. In some embodiments, the outer tube, the polymer matrix of the drug core, or both may be bioerodible. In some embodiments, the co-extruded product can be segmented into drug delivery devices. In some embodiments, the devices may be left uncoated so that their respective ends are open, or the devices may be coated with, for example, a layer that is permeable to the therapeutic agent, semi-permeable to the therapeutic agent, or bioerodible. In certain embodiments, the therapeutic agent and at least one polymer are admixed in powder form. In some embodiments, the insert is formed by forwarding a polymeric material to a first extrusion device, forwarding an therapeutic agent to a second extrusion device, co-extruding a mass including the polymeric material and the therapeutic agent, and forming the mass into at least one co-extruded drug delivery device which comprises a core including the therapeutic agent and an outer layer including the polymeric material. In certain

embodiments, the therapeutic agent forwarded to the second extrusion device is in admixture with at least one polymer. In certain embodiments, the therapeutic agent and at least one polymer are admixed in powder form. In certain embodiments, this act includes forwarding more than one drug to the second extrusion device. In certain embodiments, the polymeric material is one of impermeable, semi-permeable, or permeable to the therapeutic agent. The polymeric material may be bioerodible and/or radiation curable. In latter instances, the insert may be irradiated.

In certain embodiments, the insert is in a tubular form, and may be segmented into a plurality of shorter products. In certain embodiments, the insert further comprises a coating of the plurality of shorter products with one or more layers including at least one of a layer that is permeable to the therapeutic agent, a layer that is semi-permeable to the therapeutic agent, and a layer that is bioerodible. The polymeric material may include any biocompatible polymer, such as polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacrylate, polyurethane, a nylon, or poly (dl-lactide-co-glycolide) (PLGA), or a copolymer of any of these.

In some embodiments, the insert comprises a therapeutically effective amount of at least one therapeutic agent coated by or dispersed in a polymer matrix, wherein the therapeutic agent is in granular or particulate form. In some embodiments, the therapeutic agent is released from the formulation as drug from the granules dissolves into or within the matrix, diffuses through the matrix, and is released into the surrounding physiological fluid. In some embodiments, the rate of release is limited primarily by the rate of dissolution of the therapeutic agent from the granules/particles into the matrix; the steps of diffusion through the matrix and dispersion into the surrounding fluid are primarily not release-rate-limiting. In certain embodiments, the polymer matrix is non-bioerodible, while in other embodiments it is bioerodible. Exemplary non-bioerodible polymer matrices can be formed from polyurethane, polysilicone, poly(ethylene-co-vinyl acetate) (EVA), polyvinyl alcohol, and derivatives and copolymers thereof. Exemplary bioerodible polymer matrices can be formed from polyanhydride, polylactic acid, polyglycolic acid, polyorthoester, polyalkylcyanoacrylate, and derivatives and copolymers thereof.

In some embodiments, the insert comprises a collagenous material. In some embodiments, the insert may be a soluble ophthalmic drug insert (SODI, e.g., a polymeric oval film that can be introduced in the upper conjuctival sac for drug delivery; an elliptical insert such as OCUSERT® (Pilocarpine ocular therapeutic system, developed by Alza Corporation) which is made of ethylene vinyl acetate; OCUFIT® (developed by Escalon

Ophthalmics Inc., Skillman, NS), which is a rod shaped silicone elastomer; Lacrisert®, a rod shaped insert made of cellulose; New Ophthalmic Drug Delivery Systems (NODS), made of poly (vinyl alcohol); and the inserts described in Fabrizio, *Advanced Drug Delivery Reviews* 16: 95 -106, 1998, which is incorporated herein by reference in its entirety. In further embodiments, the insert can be placed, depending on the location and the mechanism used to hold the insert in position, by either the patient or the doctor. In further embodiments, the insert comprises collagen, gelatin, or a polymer, wherein the polymer is selected from polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacralate, polyurethane, a nylon, poly(dl-lactide-co-glycolide) (PLGA), or a copolymer of any of the aforementioned. In some embodiments, the insert is implanted under the upper eyelid. In some embodiments, the insert is implanted in the posterior segment of the eye, in the chroidal space, or in the sclera. In some embodiments, the insert is implanted intravitreally or sub-retinally. In some embodiments, the insert is injected sub-retinally. Methods of administration and techniques for their preparation are set forth in Remington's Pharmaceutical Sciences, which is incorporated herein by reference in it entirety.

In other embodiments, the insert provides a sustained release of the therapeutic agent to the vitreous of the eye. As used herein, "sustained release" means that the composition releases the therapeutic agent over an extended period of time in a controlled fashion. In some embodiments, the insert releases the therapeutic agent at a rate such that the aqueous therapeutic agent concentration remains less than the vitreous therapeutic agent concentration during the release. In some embodiments, the aqueous therapeutic agent concentration is from about 0.002 µg/mL to about 0.01 µg/mL, or from about 0.01 µg/mL to about 0.05 µg/ml., or less than about 0.05 µg/mL. In some embodiments, the therapeutic agent is released at a rate of about 1 µg/day to about 50 µg/day, or from about 1 µg/day to about 10 µg/day. In some embodiments, the insert further comprises an additional therapeutic agent, as detailed above, e.g., fluocinolone acetonide (such as that found in the ophthalmic insert Retisert®).

In some embodiments, the ophthalmic compositon comprises microspheres or nanoparticles. In some embodiment, the microspheres comprise gelatin. In some embodiments, the microspheres are injected to the posterior segment of the eye, in the chroidal space, in the sclera, intravitreally or sub-retinally. In some embodiments, the micospheres or nanoparticles comprises a polymer including, but not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems",

Asian J. Pharm., pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the polymer is chitosan, a polycarboxylic acid such as polyacrylic acid, albumin particles, hyaluronic acid esters, polyitaconic acid, poly(butyl)cyanoacrylate, polycaprolactone, poly(isobutyl)caprolactone, poly(lactic acid-co-glycolic acid), or poly(lactic acid). In some embodiments, the microspheres or nanoparticles comprise solid lipid particles.

In some embodiments, the ophthalmic composition comprises an ion-exchange resin. In some embodiments, the ion-exchange resin is an inorganic zeolite or synthetic organic resin. In some embodiments, the ion-exchange resin includes, but is not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.*, pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the ion-exhange resin is a partially neutralized polyacrylic acid.

In some embodiments, the ophthalmic composition is an aqueous polymeric suspension. In some embodiments, the therapeutic agent or a polymeric suspending agent is suspended in an aqueous medium (e.g., having the properties as described above). In some embodiment, the therapeutic agent is suspended. In some embodiments, the therapeutic agent is in solution. In further embodiments, the suspending agent serves to provide stability to the suspension, to increase the residence time of the dosage form on the eye, or to enhance the sustained release of the drug in terms of both longer release times and a more uniform release curve. Examples of polymeric suspending agents include, but are not limited to, dextrans, polyethylene glycols, polyvinylpyrolidone, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose, and carboxy-containing polymers such as polymers or copolymers of acrylic acid, as well as other polymeric demulcents. In some embodiments, the polymeric suspending agent is a water swellable, water insoluble polymer, especially a crosslinked carboxy-containing polymer. In some embodiments, the polymeric suspending agent comprises from at least about 90% to about 99.9%, or from about 95% to about 99.9%, by weight based on the total weight of monomers present, of one or more carboxy-containing monoethylenically unsaturated monomers. In some embodiments, the carboxy-containing monoethylenically unsaturated monomer includes acrylic acid, methacrylic acid, ethacrylic acid, methylacrylic acid (crotonic acid), cis- α-methylcrotonic acid (angelic acid), trans-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, phenylacrylic acid

(cinnamic acid), coumaric acid (o-hydroxycinnamic acid), and umbellic acid (p-hydroxycoumaric acid). In some embodiments, the polymers may be crosslinked by a polyfunctional crosslinking agent (e.g., a difunctional crosslinking agent). In further embodiments, the amount of crosslinking should be sufficient to form insoluble polymer particles, but not so great as to unduly interfere with sustained release of the therapeutic agent. In some embodiment, the polymers are only lightly crosslinked. In some embodiments, the crosslinking agent is contained in an amount of from about 0.01% to about 5%, or from about 0.1% to about 5.0%, or from about 0.2% to about 1%, based on the total weight of monomers present. In some embodiments, the crosslinking agents are nonpolyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide; polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, e.g., alkenyl ether groupings containing terminal $H_2C=C<$groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as insoluble diacrylates and polyacrylates and methacrylates of diols and polyols, diisocyanate hydroxyalkyl acrylate or methacrylate reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like.

In some embodiments, the crosslinked polymers may be made from a carboxy-containing monoethylenically unsaturated monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. In some embodiments, the polymers are ones in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxy-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomer or monomers containing only physiologically and ophthalmically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethylmethacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like (see Mueller et al. U.S. Pat. No. 4,548,990, the entire contents of which are incorporated herein by reference, for a more extensive listing of such additional monoethylenically unsaturated

monomers). In some embodiments, the polymers include polycarbophil (Noveon AA-1), Carbopol®, and DuraSite®. In some embodiments, the crosslinked polymers are prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter. In some embodiments, the average dry particle size is from about 1 to about 30 μm, or from about 3 to about 20 μm in equivalent spherical diameter. In some embodiments, the polymer particles are obtained by mechanically milling larger polymer particles. In further embodiments, such polymers will have a molecular weight from about 250,000 to about 4,000,000, and from 3,000,000,000 to 4,000,000,000. In other embodiments, the particles of crosslinked polymer are monodisperse, meaning that they have a particle size distribution such that at least about 80%, about 90% or about 95%, of the particles fall within a μm band of major particle size distribution. In further embodiments, the monodisperse particle size means that there is no more than about 20%, about 10%, or about 5% particles of a size below 1 μm. In some embodiments, the aqueous polymeric suspension comprises from about 0.05 to about 1%, from about 0.1 to about 0.5%, or from about 0.1 to about 0.5%, of the therapeutic agent and from about 0.1 to about 10%, from about 0.5 to about 6.5%, from about 0.5 to about 2.0%, from about 0.5% to about 1.2%, from about 0.6 to about 0.9%, or from about 0.6 to about 0.8% of a polymeric suspending agent. Although referred to in the singular, it should be understood that one or more species of polymeric suspending agent can be used with the total amount falling within the stated ranges. In one embodiment, the amount of insoluble lightly crosslinked polymer particles, the pH, and the osmotic pressure can be correlated with each other and with the degree of crosslinking to give a composition having a viscosity in the range of from about 500 to about 100,000 centipoise, and preferably from about 1,000 to about 30,000 or about 1,000 to about 10,000 centipoise, as measured at room temperature (about 25° C.) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. In some embodiments, the viscosity is from about 10 to about 400 centipoise, from about 10 to about 200 centipoises or from about 10 to about 25 centipoise.

In some embodiments, the aqueous polymeric suspensions may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. In some embodiments, they may be formulated so that there is increased gelation upon contact with tear fluid. For instance, when a formulation containing DuraSite® or other similar polyacrylic acid-type polymer is administered to the eye at a pH

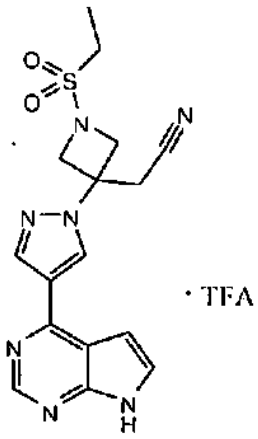
of less than about 6.7, the polymer may swell upon contact with tear fluid since it has a higher pH (around 7). This gelation or increase in gelation may lead to entrapment of the suspended particles, thereby extending the residence time of the composition in the eye. In some embodiments, the therapeutic agent is released slowly as the suspended particles dissolve over time. In some embodiments, this delivery route increases patient comfort and increased therapeutic agent contact time with the eye tissues, thereby increasing the extent of drug absorption and duration of action of the formulation in the eye. The therapeutic agents contained in these drug delivery systems may be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

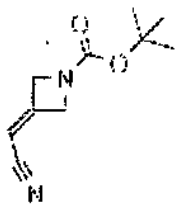
EXAMPLES

Example 1. {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt



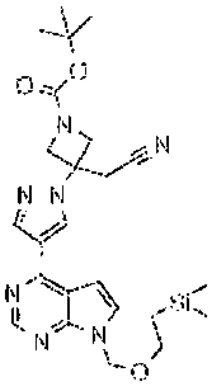
· TFA

Step 1. tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate



To a suspension of sodium hydride (60% dispersion in mineral oil, 0.257 g, 6.42 mmol) in tetrahydrofuran (32 mL) at 0 °C under a nitrogen atmosphere was added diethyl cyanomethylphosphonate (1.19 g, 6.72 mmol) (purchased from Aldrich). The reaction was then stirred for 45 minutes at room temperature. A solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.00 g, 5.84 mmol) (purchased from Alfa Aesar) in tetrahydrofuran (8.8 mL) was introduced dropwise and the mixture was stirred for 16 hours. Brine and ethyl acetate were added and the layers separated. The aqueous layer was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated to afford product, used without further purification in Step 2 (1.12 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (p, 1H), 4.73-4.68 (m, 2H), 4.64-4.59 (m, 2H), 1.46 (s, 9H).

Step 2. tert-butyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

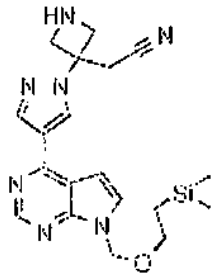


To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (4.61 g, 14.6 mmol) (prepared according to the method of WO

2007/070514 in Example 65, Step 2) and tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate (2.84 g, 14.6 mmol) in acetonitrile (100 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.19 mL, 14.6 mmol). The reaction was stirred at room temperature for 16 hours. The acetonitrile was removed *in vacuo* and the residue was dissolved in ethyl acetate. This solution was sequentially washed with 1N HCl and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 80% ethyl acetate/hexanes to afford desired product (5.36 g, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.44 (s, 1H), 8.34 (s, 1H), 7.42 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.54 (d, 2H), 4.29 (d, 2H), 3.59-3.51 (m, 2H), 3.33 (s, 2H), 1.47 (s, 9H), 0.96-0.89 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 510.2.

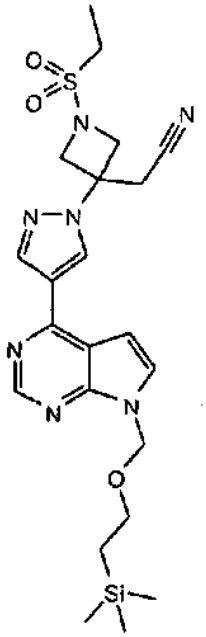
Step 3. 3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile



To a solution of tert-butyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (5.36 g, 10.5 mmol) in 1,4-dioxane (100 mL) was added 4.00 M of hydrogen chloride in 1,4-dioxane (40 mL, 160 mmol) and the mixture was stirred at room temperature for 16 hours. The reaction was poured into saturated sodium bicarbonate solution sufficient to neutralize. The product was extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford product which was used without further purification (3.0 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 7.41 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.30 (d, 2H), 3.88 (d, 2H), 3.58-3.51 (m, 2H), 3.42 (s, 2H), 0.96-0.89 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 410.2.

Step 4. 1-(ethylsulfonyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile



To a solution of 3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile (0.100 g, 0.244 mmol) in tetrahydrofuran (2 mL) containing N,N-diisopropylethylamine (0.085 mL, 0.49 mmol) was added ethanesulfonyl chloride (0.023 mL, 0.24 mmol). After stirring for 1.5 hours, the reaction mixture was poured into dilute HCl and extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated to afford product, used without further purification in Step 5 (111 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.63 (s, 1H), 8.35 (s, 1H), 7.45 (d, 1H), 6.83 (d, 1H), 5.68 (s, 2H), 4.63 (d, 2H), 4.26 (d, 2H), 3.54 (t, 2H), 3.42 (s, 2H), 3.09 (q, 2H), 1.41 (t, 3H), 0.92 (t, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 502.1.

Step 5. 1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetate salt

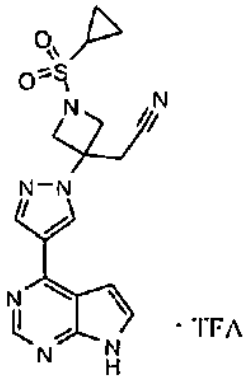
To a solution of 1-(ethylsulfonyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile (0.111 g, 0.22 mmol) in methylene chloride (3 mL) was added trifluoroacetic acid (2 mL) and the solution was stirred for 1.5 hours. The solvents were removed *in vacuo* and the residue was dissolved in

methanol (3 mL) and ethylenediamine (0.1 mL) was added. After stirring for 3 hours, the volume was reduced *in vacuo* and the product was purified by preparative-HPLC/MS, (SunFire C18 column, eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford the product as the trifluoroacetic acid salt (50 mg, 47%).

^{1}H NMR (400 MHz, d_6-dmso): δ 12.55 (br d, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.56 (s, 1H), 7.79-7.75 (m, 1H), 7.24-7.19 (m, 1H), 4.59 (d, 2H), 4.26 (d, 2H), 3.71 (s, 2H), 3.25 (q, 2H), 1.24 (t, 3H); LCMS $(M+H)^+$: 372.1.

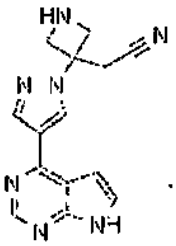
Alternatively, the deprotection and sulfonylation steps could be performed in the reverse order, as in Example 2.

Example 2. 1-(cyclopropylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt



· TFA

Step 1. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt



· 2TFA

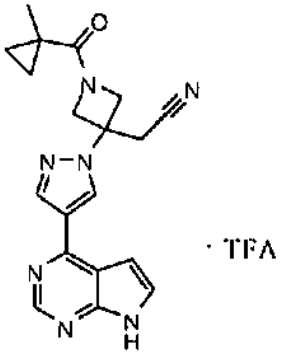
A solution of tert-butyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate, as prepared in Example 1, Step 2 (0.60 g, 1.2 mmol) in trifluoroacetic acid (10 mL) and methylene chloride

(40 mL) was stirred for 5 hours. The solvents were removed *in vacuo* and the residue stirred in a solution of methanol (40 mL) and 14.50 M of ammonium hydroxide in water (10 mL) overnight. The solvent was evaporated, the residue reconstituted in methanol and purified by preparative-HPLC/MS (SunFire C18 column, eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford the product as the trifluoroacetic acid salt (526 mg, 88%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.36 (br s, 1H), 9.37 (br s, 1H), 9.15 (br s, 1H), 9.05 (s, 1H), 8.77 (s, 1H), 8.56 (s, 1H), 7.71 (dd, 1H), 7.14 (dd, 1H), 4.75-4.65 (m, 2H), 4.48-4.39 (m, 2H), 3.74 (s, 2H); LCMS $(M+H)^+$: 280.1.

Step 2. 1-(cyclopropylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetate salt

To 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile bis(trifluoroacetate) (0.400 g, 0.788 mmol) in tetrahydrofuran (38 mL) and triethylamine (0.55 mL, 3.9 mmol) was added cyclopropanesulfonyl chloride (0.084 mL, 0.83 mmol). The reaction was stirred at room temperature for a few hours with periodic addition of cyclopropanesulfonyl chloride until the starting amine was consumed as evidenced by LCMS. To dissolve insolubles, methanol (0.16 mL) was added. The THF was removed *in vacuo* and MeOH was used to reconstitute the sample for purification by preparative-HPLC/MS (SunFire C18 column, eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford the product as the trifluoroacetate salt (193 mg, 49%).
^{1}H NMR (300 MHz, d_6-dmso): δ 12.53 (br s, 1H), 9.05 (s, 1H), 8.82 (s, 1H), 8.55 (s, 1H), 7.76 (dd, 1H), 7.21 (dd, 1H), 4.65 (d, 2H), 4.31 (d, 2H), 3.70 (s, 2H), 2.90-2.80 (m, 1H), 1.07-0.97 (m, 4H); LCMS $(M+H)^+$: 384.1.

Example 3. 1-[(1-methylcyclopropyl)carbonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt



· TFA

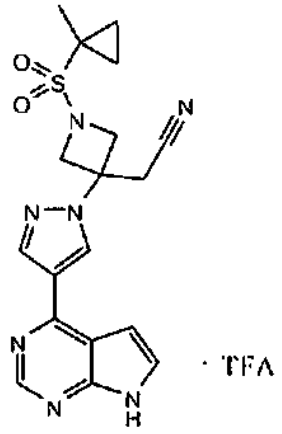
DP-65

To a solution of 1-methylcyclopropanecarboxylic acid (4.3 mg, 0.043 mmol) and N,N-diisopropylethylamine (0.018 g, 0.14 mmol) in N,N-dimethylformamide (1.5 mL) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.016 g, 0.043 mmol) (purchased from Aldrich). The reaction was stirred for 15 minutes followed by the addition of 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile bis(trifluoroacetate) salt from Example 2, Step 1 (0.014 g, 0.029 mmol). The reaction was stirred for 16 hours. The product was purified by preparative-HPLC/MS, (SunFire C18 column, eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford the product as the trifluoroacetate salt (6 mg, 45%).

^{1}H NMR (300 MHz, d_6-dmso): δ 12.82 (br s, 1H), 9.10 (s, 1H), 8.91 (s, 1H), 8.59 (s, 1H), 7.86 (s, 1H), 7.31 (s, 1H), 5.07-4.07 (br, 4H), 3.72 (s, 2H), 1.28 (s, 3H), 0.98 (s, 2H), 0.54 (s, 2H); LCMS(M+H)$^+$: 362.2.

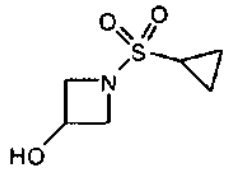
In some cases, a modification to Example 3 was used where THF was substituted for DMF as the solvent. In Table 1, this is indicated by modification A.

Example 4. 1-[(1-methylcyclopropyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt



· TFA

Step 1. 1-(cyclopropylsulfonyl)azetidin-3-ol

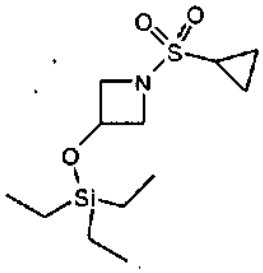


To a solution of azetidin-3-ol hydrochloride (1.00 g, 9.13 mmol) (purchased from

Matrix) and N,N-diisopropylethylamine (4.77 mL, 27.4 mmol) in tetrahydrofuran (100 mL) at 0 °C was added cyclopropanesulfonyl chloride (0.930 mL, 9.13 mmol) and the reaction was stirred for 16 hours. Water was added and the product was extracted with ethyl acetate. The combined extracts were washed with 1N HCl, saturated sodium bicarbonate, and brine, dried over sodium sulfate, decanted and concentrated to afford a yellow oil used without further purification (1.04 g, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (p, 1H), 4.14-4.07 (m, 2H), 3.93-3.86 (m, 2H), 2.69 (br s, 1H), 2.42-2.32 (m, 1H), 1.20-1.11 (m, 2H), 1.06-0.98 (m, 2H).

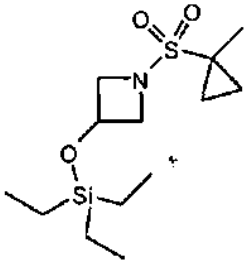
Step 2. 1-(cyclopropylsulfonyl)-3-[(triethylsilyl)oxy]azetidine



To a solution of 1-(cyclopropylsulfonyl)azetidin-3-ol (1.04 g, 5.87 mmol) and triethylamine (3.11 mL, 22.3 mmol) in tetrahydrofuran (20 mL) was added 4-dimethylaminopyridine (0.090 g, 0.73 mmol) followed by chlorotriethylsilane (1.00 M in THF, 8.0 mL, 8.0 mmol). The reaction was stirred at room temperature for 16 hours. To the reaction was added saturated sodium bicarbonate solution and the product was extracted with a 1:1 mix of ethyl acetate : hexanes three times. The combined organic extracts were washed with dilute HCl and brine, then dried over sodium sulfate, decanted and concentrated. Flash column chromatography, eluting with a gradient of 0-50% ethyl acetate in hexanes afforded desired product (1.0 g, 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.56 (p, 1H), 4.05-3.98 (m, 2H), 3.90-3.83 (m, 2H), 2.41-2.32 (m, 1H), 1.20-1.12 (m, 2H), 1.05-0.96 (m, 2H), 0.93 (t, 9H), 0.57 (q, 6H).

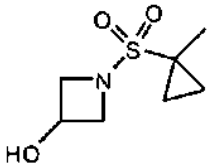
Step 3. 1-[(1-methylcyclopropyl)sulfonyl]-3-[(triethylsilyl)oxy]azetidine



To a solution of 1-(cyclopropylsulfonyl)-3-[(triethylsilyl)oxy]azetidine (1.0 g, 3.4 mmol) in tetrahydrofuran (20 mL) at -78 °C was added 2.50 M of n-butyllithium in hexane (1.37 mL, 3.43 mmol) dropwise. After stirring at this temperature for 1 hour, methyl iodide (0.224 mL, 3.60 mmol) was added. After 30 minutes, the reaction temperature was raised to 0 °C and stirred for 50 minutes. The reaction was quenched by the addition of saturated sodium bicarbonate, followed by brine and the product was extracted with ethyl acetate. The extracts were dried over sodium sulfate, decanted and concentrated. Flash column chromatography eluting with a gradient of 0-30% ethyl acetate in hexanes afforded product (890 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (p, 1H), 4.00-3.94 (m, 2H), 3.92-3.86 (m, 2H), 1.49 (s, 3H), 1.35-1.29 (m, 2H), 0.93 (t, 9H), 0.73 (dt, 2H), 0.57 (q, 6H).

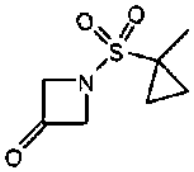
Step 4. 1-[(1-methylcyclopropyl)sulfonyl]azetidin-3-ol



A solution of 1-[(1-methylcyclopropyl)sulfonyl]-3-[(triethylsilyl)oxy]azetidine (0.125 g, 0.41 mmol) in tetrahydrofuran (3 mL), water (1 mL) and acetic acid (1 mL) was stirred at room temperature for four hours. The mixture was neutralized by pouring into a solution of sodium bicarbonate. The product was extracted with ethyl acetate, the extracts were washed with brine, dried over sodium sulfate, decanted and concentrated to afford product, used without further purification (64 mg, 82%).

^{1}H NMR (300 MHz, CD_3OD): δ 4.56-4.47 (m, 1H), 4.02-3.95 (m, 2H), 3.83-3.75 (m, 2H), 1.47 (s, 3H), 1.26-1.19 (m, 2H), 0.84-0.77 (m, 2H).

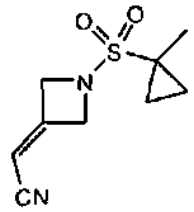
Step 5. 1-[(1-methylcyclopropyl)sulfonyl]azetidin-3-one



To a solution of oxalyl chloride (59 µL, 0.69 mmol) in methylene chloride (1.5 mL) at -78 °C was added dimethyl sulfoxide (0.10 mL, 1.5 mmol) slowly dropwise. The reaction was stirred for 15 minutes following complete addition. A solution of 1-[(1-methylcyclopropyl)-sulfonyl]azetidin-3-ol (64 mg, 0.33 mmol) in methylene chloride (1.0 mL) was added dropwise and the reaction mixture was stirred for 45 min at -60 °C. Triethylamine (0.28 mL, 2.0 mmol) was added dropwise and the reaction was stirred for 15 minutes and the bath was removed and the solution allowed to warm to ambient temperature. The solvent was removed *in vacuo* and ethyl acetate was added. The solution was washed sequentially with saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate, decanted and concentrated. The crude product was used without further purification in Step 6.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (d, 2H), 3.93 (d, 2H), 1.58 (s, 3H), 1.44-1.38 (m, 2H), 0.87 (dt, 2H).

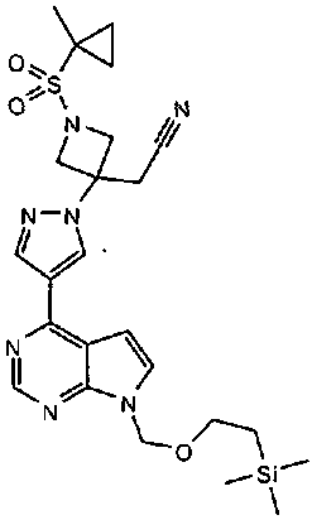
Step 6. 1-[(1-methylcyclopropyl)sulfonyl]azetidin-3-ylideneacetonitrile



To a mixture of sodium hydride (60% dispersion in mineral oil, 17 mg, 0.42 mmol) in tetrahydrofuran (2 mL) at 0 °C was added diethyl cyanomethylphosphonate (70 µL, 0.43 mmol) dropwise. The mixture was then allowed to reach room temperature and stir for a further 45 minutes. A solution of 1-[(1-methylcyclopropyl)sulfonyl]azetidin-3-one (prepared in Step 5) in tetrahydrofuran (1.0 mL) was added and the mixture was allowed to stir at ambient temperature for 16 hours. Into the reaction was added water and solid NaCl, and the product was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated to afford product (71 mg, 100%), used without further purification in Step 7.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.44-5.39 (m, 1H), 4.76-4.71 (m, 2H), 4.69-4.64 (m, 2H), 1.49 (s, 3H), 1.36-1.30 (m, 2H), 0.80 (dt, 2H).

Step 7. 1-[(1-methylcyclopropyl)sulfonyl]-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile



To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.108 g, 0.344 mmol) and 1-[(1-methylcyclopropyl)sulfonyl]azetidin-3-ylideneacetonitrile (71 mg, 0.33 mmol) in acetonitrile (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (51 µL, 0.34 mmol). After a reaction time of 1.5 hours, the acetonitrile was removed *in vacuo* and the residue was partitioned between ethyl acetate and 1N HCl. The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. Flash column chromatography, eluting with a gradient of 0-80% ethyl acetate in hexanes afforded product (135 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.46 (s, 1H), 8.35 (s, 1H), 7.42 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.62 (d, 2H), 4.22 (d, 2H), 3.59-3.50 (m, 2H), 3.42 (s, 2H), 1.55 (s, 3H), 1.42-1.36 (m, 2H), 0.96-0.89 (m, 2H), 0.85 (dt, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 528.1.

Step 8. 1-[(1-methylcyclopropyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt

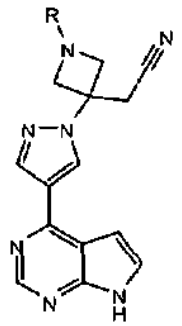
A solution of 1-[(1-methylcyclopropyl)sulfonyl]-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile (44 mg, 0.083 mmol) in methylene chloride (10 mL) and trifluoroacetic acid (5

mL) was stirred for 2 hours. The solvents were removed *in vacuo*. The residue was stirred with 14.50 M of ammonium hydroxide solution (3 mL) in methanol (10 mL) for 16 hours. Solvents were removed *in vacuo* and the residue was purified by preparative HPLC-MS (SunFire C18 column, eluting with a gradient of H_2O and MeCN containing 0.1% TFA) to afford product as the trifluoroacetate salt (0.02 g, 50%).

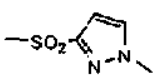
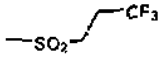
^{1}H NMR (300 MHz, d_6-dmso): δ 12.56 (br s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 7.77 (dd, 1H), 7.21 (dd, 1H), 4.58 (d, 2H), 4.23 (d, 2H), 3.71 (s, 2H), 1.46 (s, 3H), 1.22-1.16 (m, 2H), 0.93-0.87 (m, 2H); LCMS $(M+H)^+$: 398.1.

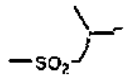
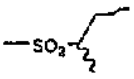
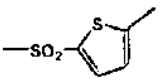
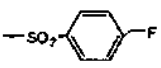
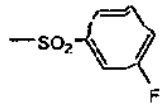
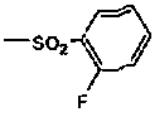
Acid chlorides, isocyanates or chloroformates were used in place of sulfonyl chlorides in either the method of Example 1 or Example 2 to afford amides (Ex. Nos. 22, 24, 26-30 & 33 of Table 1), ureas (Ex. No. 38 of Table 1) or carbamates (Ex. Nos. 35-37 of Table 1), respectively, as products. Additionally, triethylamine and diisopropylethylamine were used interchangeably. Some amides in Table 1 were prepared by an alternative method illustrated in Example 3, by coupling the amine of Example 2, Step 1 with carboxylic acids.

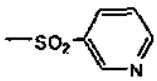
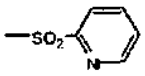
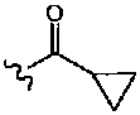
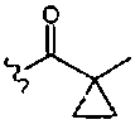
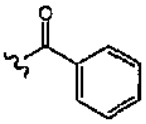
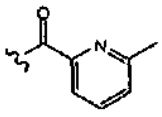
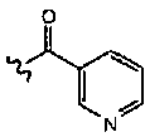
Table 1

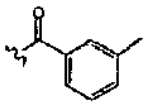
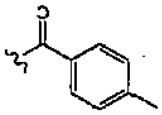
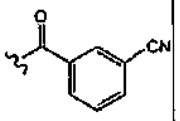
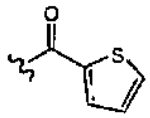
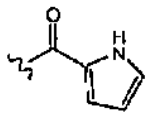


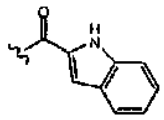
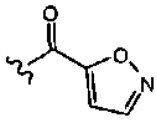
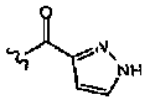
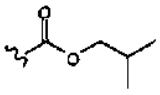
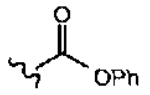
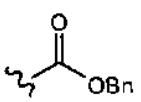
Ex. No.	-R	Name	MS $(M+H)^+$	^{1}H NMR (δ)	Method of Preparation
5	$-SO_2Me$	{1-(methylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	358.1	(400 MHz, d_6-dmso): 12.35 (br s, 1H), 8.99 (s, 1H), 8.77 (s, 1H), 8.52 (s, 1H), 7.70 (t, 1H), 7.16 (dd, 1H), 4.62 (d, 2H), 4.28 (d, 2H), 3.70 (s, 2H), 3.02 (br s, 3H).	Ex. # 1
6	$-SO_2Ph$	{1-(phenylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	420.1	(400 MHz, d_6-dmso): 12.55 (br s, 1H), 8.80 (s, 1H), 8.78 (s, 1H), 8.34 (s, 1H), 7.88-7.83 (m, 2H), 7.79-7.74 (m, 1H), 7.66-7.56 (m, 3H), 7.15-7.11 (m, 1H), 4.40 (d, 2H),	Ex. # 2

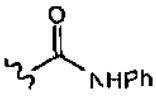
				4.23 (d, 2H), 3.55 (s, 2H).	
7	$-SO_2{}^iPr$	{1-(isopropylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	386.1	(300 MHz, d_6-dmso): 12.16 (br s, 1H), 8.93 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (t, 1H), 7.09 (d, 1H), 4.59 (d, 2H), 4.21 (d, 2H), 3.71 (s, 2H), 3.41-3.29 (m, 1H), 1.26 (d, 6H).	Ex. # 2
8	$-SO_2{}^nPr$	{1-(propylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	386.1	(300 MHz, d_6-dmso): 12.17 (br s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (dd, 1H), 7.09 (dd, 1H), 4.60 (d, 2H), 4.24 (d, 2H), 3.69 (s, 2H), 3.26-3.18 (m, 2H), 1.79-1.65 (m, 2H), 0.99 (t, 3H).	Ex. # 2
9	$-SO_2{}^nBu$	{1-(butylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	400.1	(300 MHz, d_6-dmso): 12.17 (br s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (dd, 1H), 7.09 (dd, 1H), 4.60 (d, 2H), 4.24 (d, 2H), 3.69 (s, 2H), 3.28-3.20 (m, 2H), 1.73-1.61 (m, 2H), 1.47-1.33 (m, 2H), 0.89 (t, 3H).	Ex. # 2
10	$-SO_2{}^tBu$	{1-(tert-butylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	400.1	(400 MHz, d_6-dmso): 12.48 (br s, 1H), 8.99 (s, 1H), 8.80 (s, 1H), 8.54 (s, 1H), 7.74 (s, 1H), 7.21-7.16 (m, 1H), 4.61 (d, 2H), 4.20 (d, 2H), 3.73 (s, 2H), 1.32 (s, 9H).	Ex. # 4
11	$-SO_2NMe_2$	3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3 -d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-sulfonamide trifluoroacetic acid salt	387.1	(400 MHz, d_6-dmso): 12.59 (br s, 1H), 9.03 (s, 1H), 8.84 (s, 1H), 8.56 (s, 1H), 7.80-7.76 (m, 1H), 7.24-7.20 (m, 1H), 4.53 (d, 2H), 4.20 (d, 2H), 3.70 (s, 2H), 2.79 (s, 6H).	Ex. # 2
12		{1-[(1-methyl-1H-pyrazol-3-yl)sulfonyl]-3-[4-(7H- pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]az etidin-3-yl}acetonitrile trifluoroacetic acid salt	424.1	(400 MHz, d_6-dmso): 12.56 (br s, 1H), 8.83 (s, 1H), 8.82 (s, 1H), 8.44 (s, 1H), 7.88 (d, 1H), 7.77 (t, 1H), 7.19-7.15 (m, 1H), 6.79 (d, 1H), 4.53 (d, 2H), 4.28 (d, 2H), 3.77 (s, 3H), 3.52 (s, 2H).	Ex. # 2
13		{3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-1-[(3,3,3-trifluoropropyl)sulfonyl]azetidin-3-yl}acetonitrile	440.1	(300 MHz, d_6-dmso): 12.17 (br s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.49 (s, 1H), 7.63 (dd, 1H), 7.09 (dd, 1H), 4.68 (d, 2H), 4.31 (d, 2H), 3.72 (s,	

				2H), 3.63-3.55 (m, 2H), 2.85-2.67 (m, 2H).	
14		{1-(isobutylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	400.1	(300 MHz, d_6-dmso): 12.17 (br s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (dd, 1H), 7.09 (dd, 1H), 4.60 (d, 2H), 4.24 (d, 2H), 3.68 (s, 2H), 3.16 (d, 2H), 2.22-2.06 (m, 1H), 1.05 (d, 6H).	Ex. # 2
15		{1-(sec-butylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	400.1	(300 MHz, d_6-dmso): 12.16 (br s, 1H), 8.93 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (dd, 1H), 7.08 (dd, 1H), 4.58 (d, 2H), 4.20 (d, 2H), 3.70 (s, 2H), 3.21-3.08 (m, 1H), 1.98-1.82 (m, 1H), 1.55-1.37 (m, 1H), 1.26 (d, 3H), 0.95 (t, 3H).	Ex. # 2
16		{1-[(5-methyl-2-thienyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	440.1	(400 MHz, d_6-dmso): 12.59 (br s, 1H), 8.82 (s, 2H), 8.41 (s, 1H), 7.78 (t, 1H), 7.59 (d, 1H), 7.17 (dd, 1H), 6.39 (dd, 1H), 4.45 (d, 2H), 4.30 (d, 2H), 3.56 (s, 2H), 2.30 (s, 3H).	Ex. # 2
17		{1-[(4-fluorophenyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	438.1	(400 MHz, d_6-dmso): 12.60 (br s, 1H), 8.83 (s, 1H), 8.78 (s, 1H), 8.38 (s, 1H), 7.97-7.91 (m, 2H), 7.80-7.77 (m, 1H), 7.44-7.38 (m, 2H), 7.18-7.14 (m, 1H), 4.42 (d, 2H), 4.25 (d, 2H), 3.57 (s, 2H).	Ex. # 2
18		{1-[(3-fluorophenyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	438.1	(400 MHz, d_6-dmso): 12.50 (br s, 1H), 8.79 (s, 1H), 8.78 (s, 1H), 8.34 (s, 1H), 7.78-7.68 (m, 3H), 7.64 (dt, 1H), 7.53-7.46 (m, 1H), 7.14-7.11 (m, 1H), 4.48 (d, 2H), 4.28 (d, 2H), 3.58 (s, 2H).	Ex. # 2
19		{1-[(2-fluorophenyl)sulfonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	438.1	(400 MHz, d_6-dmso): 12.65 (br s, 1H), 8.94 (s, 1H), 8.84 (s, 1H), 8.41 (s, 1H), 7.86 (dt, 1H), 7.80 (dd, 1H), 7.75-7.68 (m, 1H), 7.46 (dd, 1H), 7.43 (dd, 1H), 7.20-7.17 (m, 1H), 4.56 (d, 2H), 4.35 (d, 2H), 3.64 (s, 2H).	Ex. # 2

20		{1-(pyridin-3-ylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	421.1	(400 MHz, d_6-dmso):12.75 (br s, 1H), 9.01 (d, 1H), 8.86 (s, 2H), 8.80 (dd, 1H), 8.35 (s, 1H), 8.29 (dq, 1H), 7.83 (dd, 1H), 7.63 (ddd, 1H), 7.19 (dd, 1H), 4.49 (d, 2H), 4.32 (d, 2H), 3.62 (s, 2H).	Ex. # 2
21		{1-(pyridin-2-ylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	421.1	(400 MHz, d_6-dmso): 12.66 (br s, 1H), 9.02 (d, 1H), 8.85 (s, 1H), 8.84 (s, 1H), 8.81 (dd, 1H), 8.34 (s, 1H), 8.29 (dt, 1H), 7.82-7.78 (m, 1H), 7.63 (dd, 1H), 7.19-7.15 (m, 1H), 4.49 (d, 2H), 4.31 (d, 2H), 3.62 (s, 2H).	Ex. # 2
22		{1-(cyclopropylcarbonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	348.1	(400 MHz, d_6-dmso): 12.59 (br s, 1H), 9.05 (s, 1H), 8.83 (s, 1H), 8.56 (s, 1H), 7.79-7.75 (m, 1H), 7.25-7.22 (m, 1H), 4.92 (d, 1H), 4.65 (d, 1H), 4.50 (d, 1H), 4.25 (d, 1H), 3.75 (s, 2H), 1.67-1.60 (m, 1H), 0.83-0.71 (m, 4H).	Ex. # 2
23		1-[(1-methylcyclopropyl)carbonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-ylacetonitrile trifluoroacetic acid salt	362.2	(300 MHz, d_6-dmso): 12.82 (br s, 1H), 9.10 (s, 1H), 8.91 (s, 1H), 8.59 (s, 1H), 7.86 (s, 1H), 7.31 (s, 1H), 5.07-4.07 (br, 4H), 3.72 (s, 2H), 1.28 (s, 3H), 0.98 (s, 2H), 0.54 (s, 2H).	Ex. # 3
24		{1-benzoyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azeticin-3-yl}acetonitrile trifluoroacetic acid salt	384.1	(400 MHz, d_6-dmso): 12.59 (br s, 1H), 9.07 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 7.78 (t, 1H), 7.74-7.69 (m, 2H), 7.60-7.47 (m, 3H), 7.26-7.22 (m, 1H), 5.05 (d, 1H), 4.68 (d, 2H), 4.46 (d, 1H), 3.74 (s, 2H).	Ex. # 2
25		{1-[(6-methylpyridin-2-yl)carbonyl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile	399.2	(300 MHz, d_6-dmso): 12.23 (br s, 1H), 9.00 (s, 1H), 8.73 (s, 1H), 8.49 (s, 1H), 7.91-7.79 (m, 2H), 7.65 (dd, 1H), 7.44 (dd, 1H), 7.13 (dd, 1H), 5.25 (d, 1H), 5.02 (d, 1H), 4.76 (d, 1H), 4.46 (d, 1H), 3.78 (s, 2H), 2.55 (s, 3H).	Ex. # 3
26		{1-(pyridin-3-ylcarbonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimicin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitri e	385.1	(300 MHz, d_5-dmso): 12.16 (br s, 1H), 8.98 (s, 1H), 8.90 (s, 1H), 8.74 (d, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 8.11 (d, 1H), 7.65-7.60 (m, 1H),	Ex. # 2

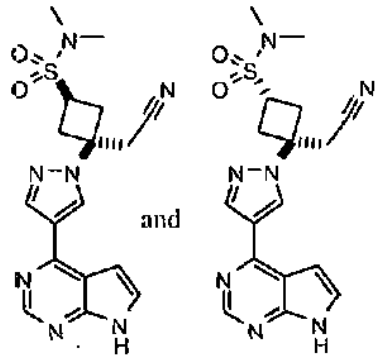
				7.57-7.50 (m, 1H), 7.12-7.07 (m, 1H), 5.13 (d, 1H), 4.76-4.72 (m, 2H), 4.46 (d, 1H), 3.73 (s, 2H).	
27		{1-(3-methylbenzoyl)-3-[4-(7H-pyrrolo[2,3-d]pyrim idin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	398.2	(400 MHz, d_6-dmso): 12.67 (br s, 1H), 9.09 (s, 1H), 8.86 (s, 1H), 8.57 (s, 1H). 7.80 (t, 1H), 7.54-7.48 (m, 2H), 7.39-7.35 (m, 2H), 7.26 (dd, 1H), 5.03 (d, 1H), 4.68 (d, 2H), 4.45 (d, 1H), 3.74 (s, 2H), 2.37 (s, 3H).	Ex. # 2
28		{1-(4-methylbenzoyl)-3-[4-(7H-pyrrolo[2,3-d]pyrim idin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	398.2	(400 MHz, d_6-dmso): 12.62 (br s, 1H), 9.08 (s, 1H), 8.85 (s, 1H), 8.56 (s, 1H), 7.79 (t, 1H), 7.62 (d, 2H), 7.30 (d, 2H), 7.24 (dd, 1H). 5.04 (d, 1H), 4.73-4.63 (m, 2H), 4.44 (d, 1H), 3.74 (s, 2H), 2.37 (s, 3H).	Ex. # 2
29		3-({3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimi din-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}carbonyl)benzonitrile trifluoroacetic acid salt	409.2	(400 MHz, d_6-dmso): 12.52 (br s, 1H), 9.06 (s, 1H), 8.82 (s, 1H), 8.54 (s, 1H), 8.16 (t, 1H), 8.06-8.01 (m, 2H), 7.77-7.74 (m, 1H), 7.72 (t, 1H), 7.24-7.19 (m, 1H), 5.11 (d, 1H), 4.72 (d, 1H), 4.71 (d, 1H), 4.47 (d, 1H), 3.74 (s, 2H).	Ex. # 2
30		[3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-1-(2-thienylcarbonyl)azetidin-3-yl]acetonitrile trifluoroacetic acid salt	390.1	(400 MHz, d_6-dmso): 12.64 (br s, 1H), 9.11 (s, 1H), 8.85 (s, 1H), 8.58 (s, 1H), 7.89 (dd, minor rotamer 1H), 7.88 (dd, major rotamer, 1H), 7.81-7.77 (m, 1H), 7.73 (dd, minor rotamer, 1H), 7.62 (dd, major rotamer, 1H), 7.27-7.25 (m, 1H), 7.22 (dd, major rotamer, 1H), 7.18 (dd, minor rotamer, 1H), 5.23-5.14 (br d, 1H), 4.87 (br d, 1H), 4.69 (br d, 1H), 4.46 (br d, 1H), 3.79 (s, 2H).	Ex. # 2
31		[3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-1-(1H-pyrrol-2-ylcarbonyl)azetidin-3-yl]acetonitrile trifluoroacetic acid salt	373.2	(400 MHz, d_6-dmso): 13.07 (br s, 1H), 11.69 (br s, 1H), 9.21 (s, 1H), 8.99 (s, 1H), 8.66 (s, 1H), 7.96 (s, 1H), 7.41 (s, 1H), 6.96 (s, 1H), 6.59 (s, 1H), 6.20-6.17 (m, 1H), 5.15-4.35 (br, 4H), 3.78 (s, 2H).	Ex. # 3 Modification A

32		{1-(1H-indol-2-ylcarbonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidir-3-yl}a cetonitrile trifluoroacetic acid salt	423.1	(400 MHz, d_6-dmso): 12.91 (br s, 1H), 11.75 (d, 1H), 9.20 (s, 1H), 8.94 (s, 1H), 8.64 (s, 1H), 7.92-7.87 (m, 1H), 7.65 (d, 1H), 7.46 (d, 1H), 7.38-7.34 (m, 1H), 7.25-7.20 (m, 1H), 7.10-7.05 (m, 1H), 6.98 (d, 1H), 5.26 (d, 1H), 4.96 (d, 1H), 4.73 (d, 1H), 4.53 (d, 1H), 3.82 (s, 2H).	Ex. # 3
33		{1-(isoxazol-5-ylcarbonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile trifluoroacetic acid salt	375.0	(400 MHz, d_6-dmso): 12.50 (br s, 1H), 9.09 (s, 1H), 8.83 (d, major rotamer 1H), 8.80 (d, minor rotamer, 1H), 8.81 (s, 1H), 8.55 (s, 1H), 7.76-7.73 (m, 1H), 7.24-7.20 (m, 1H), 7.19 (d, minor rotamer, 1H), 7.15 (d, major rotamer, 1H), 5.22 (d, 1H), 4.91 (d, 1H), 4.73 (d, 1H), 4.48 (d, 1H), 3.79 (s, 2H).	Ex. # 2
34		{1-(1H-pyrazol-3-ylcarbonyl)-3-[4-(7H-pyrrolo[2,3 -d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl }acetonitrile trifluoroacetic acid salt	374.2	(400 MHz, d_6-dmso): 12.77 (br s, 1H), 9.14 (s, 1H), 8.89 (s, 1H), 8.59 (s, 1H), 7.87-7.82 (m, 2H), 7.33-7.29 (m, 1H), 6.71 (d, 1H), 5.11 (d, 1H), 4.91 (d, 1H), 4.68 (d, 1H), 4.44 (d, 1H), 3.78 (s, 2H)	Ex. # 3 Modification A
35		isobutyl 3-(cyanomethyl) -3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol- -yl]azetidine-1-carboxylate trifluoroacetic acid salt	380.1	(400 MHz, d_6-dmso): 12.53 (br s, 1H), 9.02 (s, 1H), 8.82 (s, 1H), 8.53 (s, 1H), 7.78-7.74 (m, 1H), 7.23-7.20 (m, 1H), 4.57 (br s, 2H), 4.30 (br s, 2H), 3.80 (d, 2H), 3.71 (s, 2H), 1.87 (sept, 1H), 0.89 (d, 6H).	Ex. # 2
36		phenyl 3-(cyanomethyl) -3-[4-(7H-pyrrolo[2,3-d]pyrim din-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxy ate trifluoroacetic acid salt	400.1	(400 MHz, d_6-dmso): 12.52 (br s, 1H), 9.08 (s, 1H), 8.83 (s, 1H), 8.57 (s, 1H), 7.79-7.75 (m, 1H), 7.44-7.37 (m, 2H), 7.28-7.22 (m, 2H), 7.20-7.12 (m, 2H), 4.85 (br m, 1H), 4.66 (br m, 1H), 4.56 (br m, 1H), 4.39 (br m, 1H), 3.79 (s, 2H).	Ex. # 2
37		benzyl 3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate trifluoroacetic acid sal:	414.2	(400 MHz, d_6-dmso): 12.56 (br s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.54 (s, 1H), 7.79-7.75 (br m, 1H), 7.40-7.30 (m, 5H), 7.24-7.21 (br m, 1H), 5.10 (s, 2H), 4.60 (br,	Ex. # 2

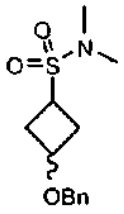
				2H), 4.34 (br, 2H), 3.72 (s, 2H).	
38		3-(cyanomethyl)-N-phenyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxamide trifluoroacetic acid salt	399.2	(400 MHz, d_6-dmso): 12.61 (br s, 1H), 9.06 (s, 1H), 8.85 (s, 1H), 8.75 (s, 1H), 8.57 (s, 1H), 7.79 (br t, 1H), 7.53-7.48 (m, 2H), 7.29-7.22 (m, 3H), 6.95 (t, 1H), 4.61 (d, 2H), 4.36 (d, 2H), 3.75 (s, 2H).	Ex. # 2

Where products in Table 1 are referred to as the free base, they were purified using preparative-HPLC/MS (XBridge C18 column, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH rather than containing 0.1% TFA).

Example 39. cis-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide
and trans-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide



Step 1. cis- and trans-3-(benzyloxy)-N,N-dimethylcyclobutanesulfonamide



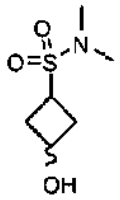
To a solution of methanesulfonamide, N,N-dimethyl- (7.45 g, 60.5 mmol) in tetrahydrofuran (190 mL) at -78 °C was added a solution of 2.50 M of n-butyllithium in

hexane (31 mL, 77.5 mmol) . The reaction was stirred at -78 °C for 45 minutes, was then warmed to 0 °C and stirred for 15 minutes, then was re-cooled to -78 °C. A solution of 2-(benzyloxy)-propane-1,3-diyl bis(4-methylbenzenesulfonate) (prepared as described in Chemical Communications v. 30, pp. 3190-3192 (2006); 29.1 g, 59.3 mmol) in tetrahydrofuran (120 mL) was added dropwise, rapidly. The reaction was stirred at -78 °C for 15 minutes following complete addition, then the bath was removed and the reaction allowed to warm to ambient temperature over 1.5 hours. The solution was re-cooled to -78 °C and 2.50 M of n-butyllithium in hexane (31 mL, 77.5 mmol) was added. After 15 min, the bath was removed and the reaction again allowed to reach ambient temperature and stir for 16 hours. As the reaction was judged incomplete by TLC, it was cooled again to -78 °C and a further portion of 2.50 M of n-butyllithium in hexane (10 mL, 25 mmol) was added. Upon warming to room temperature, the reaction was quenched by the addition of water and the mixture was extracted with three portions of ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate solution followed by brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography, eluting with a gradient of 20-50% ethyl acetate in hexanes afforded desired product. The isomers were characterized separately but were recombined for the subsequent transformation as a mixture of cis and trans isomers (7.06 g, 44%).

Isomer 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 4.42 (s, 2H), 4.41-4.33 (m, 1H), 3.83-3.74 (m, 1H), 2.87 (s, 6H), 2.79-2.71 (m, 2H), 2.47-2.38 (m, 2H).

Isomer 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.44 (s, 2H), 4.02-3.93 (m, 1H), 3.34-3.24 (m, 1H), 2.85 (s, 6H), 2.61-2.46 (m, 4H).

Step 2. cis- and trans-3-hydroxy-N,N-dimethylcyclobutanesulfonamide

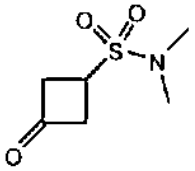


To a mixture of cis- and trans-3-(benzyloxy)-N,N-dimethylcyclobutanesulfonamide (7.06 g, 26.2 mmol) in ethanol (100 mL) was added palladium (2.8 g, 2.6 mmol) (10% on C, wet Degussa type). The mixture was degassed and shaken under 50 psi of hydrogen for 16 hours. The reaction mixture was filtered, and the palladium on carbon was rinsed with ethanol. The filtrate was concentrated to afford a white solid, used without further

purification (4.60 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71-4.63 (m, 1H, minor isomer), 4.22 (p, 1H, major isomer), 3.83-3.74 (m, 1H, minor isomer), 3.37-3.27 (m, 1H, major isomer), 2.87 (s, 6H, minor isomer), 2.86 (s, 6H, major isomer), 2.85-2.77 (m, 2H, minor isomer), 2.76-2.68 (m, 2H, major isomer), 2.48-2.40 (m, 2H, major isomer), 2.40-2.32 (m, 2H, minor isomer).

Step 3. N,N-dimethyl-3-oxocyclobutanesulfonamide



To a solution of Dess-Martin periodinane (14.3 g, 33.7 mmol) in methylene chloride (200 mL) was added cis- and trans-3-hydroxy-N,N-dimethylcyclobutanesulfonamide (5.75 g, 32.1 mol) in methylene chloride (200 mL). The reaction was stirred at ambient temperature for 16 hours. The volume of DCM was reduced to 100 mL *in vacuo*. This solution was filtered through a plug of basic alumina, rinsing with further DCM. The filtrate was evaporated. The resulting yellow sticky solid was extracted by stirring vigorously with several portions of diethyl ether in succession. The extracts were filtered through a plug of solid sodium carbonate and again filtered through another plug of basic alumina, rinsing finally with an additional small portion of ethyl acetate to afford clean product (4 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89-3.80 (m, 1H), 3.68-3.59 (m, 2H), 3.44-3.34 (m, 2H), 2.93 (s, 6H).

Step 4. cis-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide and trans-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide

A mixture of N,N-dimethyl-3-oxocyclobutanesulfonamide (4.0 g, 22 mmol) and (triphenylphosphoranylidene)acetonitrile (6.80 g, 22.6 mmol) in toluene (150 mL) was heated to reflux for 1 hour. The reaction solution was decanted away from insolubles and the solvent removed *in vacuo* to afford crude product, used without further purification in conjugate addition.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31-5.25 (m, 1H), 3.91-3.78 (m, 1H), 3.50-3.10 (m, 4H), 2.89 (s, 6H).

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-

pyrrolo[2,3-d]pyrimidine (7.09 g, 22.5 mmol) and crude 3-(cyanomethylene)-N,N-dimethylcyclobutanesulfonamide (prepared above) in acetonitrile (200 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (3.36 mL, 22.5 mmol). The reaction was stirred for 16 hours. The crude product was purified by flash column chromatography, eluting with a gradient of 0-10% MeOH in DCM (dichloromethane). The product collected from this pre-purification was further purified using preparative-HPLC/MS (XBridge C18 column, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford a mixture of isomers. The cis- and trans- isomers were separated using a portion of this mixture by the following method: Chiral Technologies Chiralcel OJ column, 30 x 250 mm, 5μ packing material, eluting with 60% ethanol in hexanes at a flow rate of 14.5 mL/min and column loading of 65 mg/injection. Peak 1 so obtained was deprotected by stirring with 20% TFA/DCM for 2 hours, followed by evaporation and dissolving the residue in 4 mL MeOH to which 0.25 mL of ethylenediamine was then added. After stirring for 1 hour, the solvents were removed *in vacuo*, the crude product reconstituted and purified by preparative-HPLC/MS (XBridge C18 column, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford cis-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide.

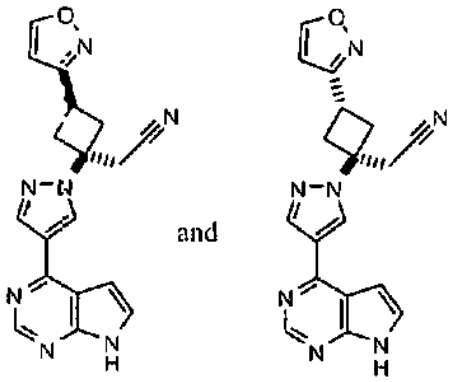
^{1}H NMR (500 MHz, d_6-dmso): δ 12.10 (br s, 1H), 8.78 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 4.25 (p, 1H), 3.59 (s, 2H), 3.14-3.07 (m, 2H), 2.85-2.79 (m, 2H), 3.80 (s, 6H); LCMS: 386.1.

Peak 2 obtained from the separation of isomers was deprotected and purified by the same method as for Peak 1 to afford trans-3-(cyanomethyl)-N,N-dimethyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanesulfonamide.

^{1}H NMR (500 MHz, d_6-dmso): δ 12.10 (br s, 1H), 8.90 (s, 1H), 8.70 (s, 1H), 8.45 (s, 1H), 7.60 (d, 1H), 7.09 (d, 1H), 4.18 (p, 1H), 3.46 (s, 2H), 3.35-3.28 (m, 2H), 2.89-2.82 (m, 2H), 2.79 (s, 6H); LCMS: 386.0.

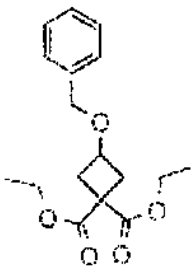
Example 40. cis-3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

and trans -3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



and

Step 1. diethyl 3-(benzyloxy)cyclobutane-1,1-dicarboxylate



To a suspension of sodium hydride (60% dispersion in mineral oil, 4.67 g, 0.117 mol) in 1,4-dioxane (69 mL) was added diethyl malonate (17.7 mL, 0.117 mol) dropwise. The mixture was stirred for 1.5 hours at ambient temperature after complete addition. To this mixture was added [2-bromo-1-(chloromethyl)ethoxy]methylbenzene (prepared according to the procedure found in Organic Letters (2004), 6(11), pp.1853-1856; 32.0 g, 0.121 mol) dropwise and the resulting mixture was stirred for 1 hour at ambient temperature, then heated at reflux for 16 hours. The mixture was cooled briefly in an ice bath and sodium hydride (60% dispersion in mineral oil, 4.67 g, 0.117 mol) was added portionwise. The mixture was heated to reflux for a further 24 hours. Upon cooling to room temperature, the mixture was poured into pH 7 buffer and brine, and the product was extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Flash column chromatography, eluting with a gradient of 5-60% ethyl acetate in hexanes afforded product (26.9 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 4.42 (s, 2H), 4.24-4.10 (m, 5H), 2.83-2.75 (m, 2H), 2.58-2.50 (m, 2H), 1.31-1.24 (m, 6H).

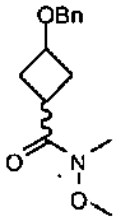
Step 2. cis- and trans-3-(benzyloxy)cyclobutanecarboxylic acid



A solution of diethyl 3-(benzyloxy)cyclobutane-1,1-dicarboxylate (20.0 g, 0.0653 mol) and potassium hydroxide (18 g, 0.32 mol) in ethanol (110 mL) and water (10 mL) was heated to reflux for 2 hours. The basic mixture was washed once with diethyl ether. The ether wash was back extracted with two portions of 1N NaOH. The combined aqueous layers were acidified by the addition of c.HCl and were then extracted with ethyl ether three times. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated to afford the intermediate diacid as a sticky yellow solid which was subsequently azeotroped with toluene. The diacid was heated neat under hyvac (<5 mm Hg) at 190 °C for 1.5 hours to effect decarboxyation to a mixture of cis- and trans- monoacids, used without further purification (13.5 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 10H), 4.44 (s, 2H), 4.43 (s, 2H), 4.31 (p, 1H), 4.02-3.93 (m, 1H), 3.12-3.04 (m, 1H), 2.72-2.62 (m, 1H), 2.59-2.48 (m, 4H), 2.38-2.24 (m, 4H).

Step 3. cis- and trans-3-(benzyloxy)-N-methoxy-N-methylcyclobutanecarboxamide

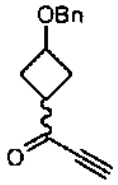


A mixture of 3-(benzyloxy)cyclobutanecarboxylic acid (2.50 g, 12.1 mmol), N,O-dimethylhydroxylamine hydrochloride (1.18 g, 12.1 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (5.9 g, 13 mmol) (Advanced ChemTech) and triethylamine (3.7 mL, 27 mmol) in methylene chloride (80 mL) was stirred at room temperature for 16 hours. The solution was then washed with twice with water, once with brine, dried over sodium sulfate, decanted and concentrated. Flash column chromatography, eluting with a gradient of 20-50% ethyl acetate in hexanes afforded product as a mixture of cis- and trans- isomers (1.7 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 10H), 4.43 (s, 2H), 4.42 (s, 2H), 4.31-4.24 (m,

1H), 4.03-3.95 (m, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 3.47 (br s, 1H), 3.19 (s, 3H), 3.18 (s, 3H), 2.95 (br s, 1H), 2.57-2.48 (m, 2H), 2.47-2.38 (m, 2H), 2.34-2.23 (m, 4H).

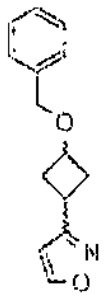
Step 4. cis- and trans-1-[3-(benzyloxy)cyclobutyl]prop-2-yn-1-one



To a solution of 3-(benzyloxy)-N-methoxy-N-methylcyclobutanecarboxamide (1.7 g, 6.8 mmol) in tetrahydrofuran (40 mL) at -78 °C was added 0.5 M of ethynylmagnesium bromide in tetrahydrofuran (14.3 mL, 7.15 mmol) and the reaction was allowed to warm to ambient temperature over a period of 1 hour. The reaction was quenched by the addition of said. NH_4Cl solution and the product was extracted with ethyl acetate. The extracts were dried over sodium sulfate, decanted and concentrated to afford product used without further purification in Step 5.

^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 10H), 4.43 (s, 2H), 4.41 (s, 2H), 4.19-4.09 (m, 1H), 4.06-3.95 (m, 1H), 3.36-3.24 (m, 1H), 3.29 (s, 1H), 3.26 (s, 1H), 2.90-2.79 (m, 1H), 2.67-2.59 (m, 2H), 2.56-2.47 (m, 2H), 2.36-2.26 (m, 4H).

Step 5. cis-3-[3-(benzyloxy)cyclobutyl]isoxazole and trans-3-[3-(benzyloxy)cyclobutyl]isoxazole



To a solution of 1-[3-(benzyloxy)cyclobutyl]prop-2-yn-1-one (prepared in Step 4) in ethanol (40 mL) was added hydroxylamine hydrochloride (0.54 g, 7.7 mmol) followed by sodium carbonate (1.48 g, 14.0 mmol). The reaction was stirred for 16 hours. The reaction

was then heated to reflux for 4 hours and cooled. Into the reaction mixture was added water and ethyl acetate. The layers were separated, and the aqueous layer was extracted with two further portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Flash column chromatography, eluting with a gradient of 15-50% ethyl acetate in hexanes afforded the product as a mixture of cis- and trans- isomers (520 mg, 33% over the two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, 1H), 8.31 (dd, 1H), 7.36-7.26 (m, 10H), 6.30 (d, 1H), 6.21 (d, 1H), 4.47 (s, 2H), 4.45 (s, 2H), 4.38-4.30 (m, 1H), 4.12-4.04 (m, 1H), 3.62-3.53 (m, 1H), 3.23-3.13 (m, 1H), 2.75-2.14 (m, 8H).

Step 6. cis- and trans-3-isoxazol-3-ylcyclobutanol



A mixture of cis- and trans-3-[3-(benzyloxy)cyclobutyl]isoxazole (0.520 g, 2.27 mmol) and 20% palladium hydroxide on carbon (0.14 g, 0.20 mmol) in tetrahydrofuran (30 mL) and acetic acid (8 mL) was degassed and stirred under an atmosphere of hydrogen (provided by a balloon) for 3 hours. The mixture was filtered, neutralized by the addition of NaOH and extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated to afford product as a mixture of cis- and trans- isomers (320 mg, 100%).

^{1}H NMR (400 MHz, CD_3OD): δ 8.55 (dd, 1H), 8.54 (dd, 1H), 6.44 (d, 1H), 6.42 (d, 1H), 4.50-4.41 (m, 1H), 4.26-4.17 (m, 1H), 3.55-3.46 (m, 1H), 3.14-3.03 (m, 1H), 2.73-2.64 (m, 2H), 2.54-2.46 (m, 2H), 2.44-2.35 (m, 2H), 2.13-2.03 (m, 2H).

Step 7. 3-isoxazol-3-ylcyclobutanone

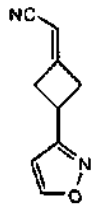


3-Isoxazol-3-ylcyclobutanol (0.316 g, 2.27 mmol), as a mixture of cis- and trans-

isomers, was dissolved in methylene chloride (10 mL) and Dess-Martin periodinane (0.96 g, 2.3 mmol) was added. After stirring for 2 hours, satd. $NaHCO_3$ solution and brine were added, and the mixture was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. Flash column chromatography, eluting with a gradient of 20-50% ethyl acetate in hexanes, afforded product (258 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, 1H), 6.31 (d, 1H), 3.81-3.72 (m, 1H), 3.59-3.48 (m, 2H), 3.46-3.37 (m, 2H).

Step 8. (3-isoxazol-3-ylcyclobutylidene)acetonitrile



Sodium hydride (60% dispersion in mineral oil, 75 mg, 1.88 mmol) was added at once to a solution of diethyl cyanomethylphosphonate (0.33 mL, 2.1 mmol) in tetrahydrofuran (8 mL). After stirring for 5 minutes, a solution of 3-isoxazol-3-ylcyclobutanone (258 mg, 1.88 mmol) in tetrahydrofuran (20 mL) was added. After 2 hours reaction time, the reaction mixture was partitioned between ethyl acetate and brine and the layers separated. The aqueous layer was extracted with two further portions of ethyl acetate and the combined extracts were dried over sodium sulfate, decanted and concentrated. The residue was then azeotroped with toluene and the product was used without further purification in Step 9.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, 1H), 6.28 (d, 1H), 5.27 (p, 1H), 3.81-3.72 (m, 1H), 3.50-3.15 (m, 4H).

Step 9. cis-3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile and trans-3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

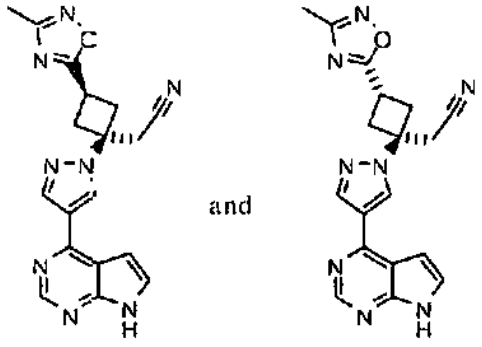
To a solution of (3-isoxazol-3-ylcyclobutylidene)acetonitrile (prepared in Step 8) in acetonitrile (8 mL) was added 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.59 g, 1.9 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (280 µL, 1.9 mmol). The reaction was stirred for 72 hours. The acetonitrile was removed *in*

vacuo. Flash column chromatography, eluting with a gradient of 50-100% ethyl acetate in hexanes, afforded a mixture of cis- and trans- isomers. The mixture was stirred with 20% TFA/DCM (8 mL/32 mL) for 3 hours, and the excess solvents were removed *in vacuo*. The residue was stirred with ethylenediamine (2 mL) in MeOH (40 mL) for 16 hours. Solvents were again removed *in vacuo*. The mixture was purified by preparative-HPLC/MS (XBridge C18 column, mobile phases 20.5-25.5 % of MeCN/H_2O containing 0.1% NH_4OH). Peak 1, cis-3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (185 mg, 28%), Peak 2, trans-3-isoxazol-3-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (85 mg, 13%).

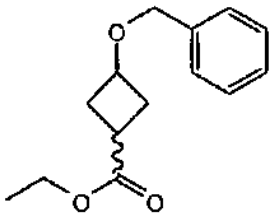
Peak 1, (cis-): ^{1}H NMR (400 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.85 (d, 1H), 8.76 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 6.67 (d, 1H), 3.85 (p, 1H), 3.67 (s, 2H), 3.04-2.95 (m, 2H), 2.89-2.81 (m, 2H); LCMS $(M+H)^+$: 346.1.

Peak 2, (trans-): ^{1}H NMR (400 MHz, d_6-dmso): δ 12.14 (br s, 1H), 8.94 (s, 1H), 8.89 (d, 1H), 8.71 (s, 1H), 8.47 (s, 1H), 7.62 (cd, 1H), 7.11 (dd, 1H), 6.73 (d, 1H), 3.71 (p, 1H), 3.46 (s, 2H), 3.34-3.27 (m, 2H), 2.80-2.71 (m, 2H); LCMS $(M+H)^+$: 346.1.

Example 41. {cis-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetate salt and {trans-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetic acid salt



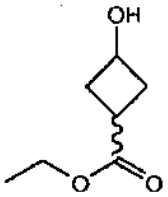
Step 1. cis- and trans-ethyl 3-(benzyloxy)cyclobutanecarboxylate



To a solution of 3-(benzyloxy)cyclobutanecarboxylic acid (5.00 g, 24.2 mmol) (prepared as in Example 6, Step 2) in ethanol (60 mL) was added 0.08 mL c.H_2SO_4. The mixture was heated at gentle reflux for 48 hours. After cooling to room temperature, the solvent was evaporated *in vacuo*. Flash column chromatography, eluting with a gradient of 0-20% ethyl acetate in hexanes afforded desired product as a mixture of cis- and trans- isomers (3.91 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 10H), 4.43 (s, 2H), 4.41 (s, 2H), 4.29 (p, 1H), 4.14 (q, 2H), 4.13 (q, 2H), 3.99-3.91 (m, 1H), 3.07-2.98 (m, 1H), 2.66-2.55 (m, 1H), 2.54-2.44 (m, 4H), 2.34-2.20 (m, 4H), 1.26 (t, 3H), 1.25 (t, 3H).

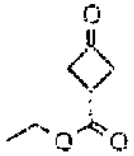
Step 2. cis- and trans-ethyl 3-hydroxycyclobutanecarboxylate



To a solution of cis- and trans-ethyl 3-(benzyloxy)cyclobutanecarboxylate (3.91 g, 16.7 mmol) in ethanol (40 mL) was added palladium (10% on carbon, wet Degussa type) (270 mg, 0.25 mmol). The mixture was degassed and shaken under 50 psi of hydrogen for 16 hours. The reaction mixture was filtered and the solvent removed *in vacuo* to afford product as a mixture of cis- and trans- isomers used without further purification (2.40 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60-4.52 (m, 1H), 4.22-4.12 (m, 1H), 4.14 (q, 2H), 4.13 (q, 2H), 3.04-2.96 (m, 1H), 2.64-2.51 (m, 5H), 2.25-2.11 (m, 4H), 2.02 (br s, 2H), 1.25 (t, 3H) 1.25 (t, 3H).

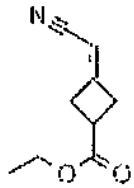
Step 3. ethyl 3-oxocyclobutanecarboxylate



To methylene chloride (100 mL) at -78 °C was added oxalyl chloride (1.79 mL, 21.2 mmol), followed by dimethyl sulfoxide (2.51 mL, 35.3 mmol). After 30 minutes, cis- and trans-ethyl 3-hydroxycyclobutanecarboxylate (2.68 g, 17.6 mol) in methylene chloride (46 mL) was added. The mixture was stirred for 30 minutes at -78 °C. Triethylamine (9.84 mL, 70.6 mmol) was added. The mixture was then allowed to warm to room temperature over 2 hours. Water was added to the reaction mixture, and the layers separated. The organic phase was washed sequentially with 1N HCl, water, saturated sodium bicarbonate solution, brine, dried over sodium sulfate, decanted and concentrated. The product (2.36 g, 94%) was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (q, 2H), 3.45-3.37 (m, 2H), 3.33-3.17 (m, 3H), 1.29 (t, 3H).

Step 4. ethyl 3-(cyanomethylene)cyclobutanecarboxylate

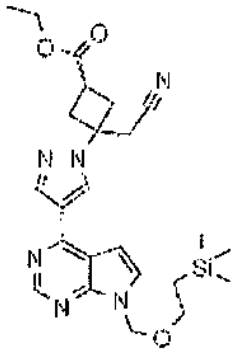


To a suspension of sodium hydride (60% dispersion in mineral oil, 0.730 g, 18.3 mmol) in tetrahydrofuran (100 mL) at 0 °C was added diethyl cyanomethylphosphonate (3.22 mL, 19.9 mmol), dropwise. The cooling bath was removed and the reaction was allowed to reach room temperature and was stirred at this temperature for 45 minutes. The solution was re-cooled to 0 °C and a solution of ethyl 3-oxocyclobutanecarboxylate (2.36 g, 16.6 mmol) in tetrahydrofuran (50 mL) was introduced dropwise. After stirring for 2 hours, water and ethyl ether were added into the reaction. The layers were separated and the aqueous portion extracted with two further portions of ether. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. The residue was azeotroped once with toluene to afford product, used without further purification in Step 5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23-5.20 (m, 1H), 4.18 (q, 2H), 3.25-3.02 (m, 5H), 1.28 (t,

3H).

Step 5. ethyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarboxylate



To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (5.23 g, 16.6 mmol) and ethyl 3-(cyanomethylene)cyclobutanecarboxylate (prepared in Step 4) in acetonitrile (40 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.48 mL, 16.6 mmol). The mixture was stirred for 136 hours at room temperature. The solvent was removed *in vacuo*. Flash column chromatography, eluting with a gradient of 50-90% ethyl acetate in hexanes afforded product as a mixture of cis- and trans- isomers (4.53 g, 52% over the two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.41 (d, 1H), 7.40 (d, 1H), 6.81 (d, 1H), 6.80 (d, 1H), 5.68 (s, 4H), 4.17 (q, 2H), 4.12 (q, 2H), 3.54 (t, 4H), 3.27 (s, 2H), 3.28-2.80 (m, 10H), 3.19 (s, 2H), 1.26 (t, 3H), 1.25 (t, 3H), 0.92 (t, 4H), -0.06 (s, 18H); LCMS $(M+H)^+$: 481.1.

Step 6. {cis-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidn-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetate salt and {trans-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidn-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetate salt

To a solution of cis- and trans-ethyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarboxylate (2 25 g, 3.98 mmol) in tetrahydrofuran (55 mL) and water (18 mL) was added a solution of lithium hydroxide (0.48 g, 20 mmol) in a small amount of water.

The reaction was stirred at room temperature for 4 hours. The reaction mixture was cooled in an ice bath and c.HCl was added to achieve a pH of 5. The product was extracted with three portions of ethyl acetate. The extracts were dried over sodium sulfate, decanted and concentrated to afford the product as a mixture of cis- and trans- isomers, which was used without further purification. LCMS $(M+H)^+$: 453.1.

To a mixture of 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarboxylic acid prepared above (50.0 mg, 0.11 mmol), 1-Hydroxybenzotriazole (3.0 mg, 0.022 mmol), and N-hydroxyethanimidamide (prepared according to the procedure found in J. Org. Chem., 2003, 68(19), pp. 7316-7321) (8.2 mg, 0.11 mmol) in N,N-dimethylformamide (0.5 mL) and N,N-diisopropylethylamine (96 µL, 0.55 mmol) was added O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (42 mg, 0.110 mmol) (Advanced ChemTech) and the mixture was stirred at room temperature for 16 hours. Additional sub-stoichiometric quantities of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and N-hydroxyethanimidamide were added and the reaction was continued for a further 24 hours. The reaction was then heated to 110 °C for 1 hour to complete cyclization. Into the reaction was added saturated sodium bicarbonate solution and the product was extracted with four portions of ethyl acetate. The extracts were dried over sodium sulfate, decanted and concentrated. The crude product mixture was stirred in DCM containing 20% TFA for 2 hours, and the solvents were removed *in vacuo*. The residue was dissolved in 1.5 mL of methanol and 0.3 mL ethylenediamine and was stirred for 2 hours. The reaction mixture was purified by preparative-HPLC/MS (SunFire C18 column, eluting with a gradient of H_2O/MeCN containing 0.1% TFA), which resolved the cis- (6 mg, 10%) and trans- (5 mg, 8%) isomers and afforded each product as the trifluoroacetic acid salt.

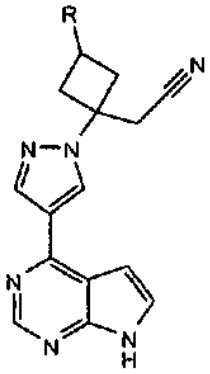
Cis- isomer: ^{1}H NMR (300 MHz, d_6-dmso): δ 12.39 (br s, 1H), 8.86 (s, 1H), 8.77 (s, 1H), 8.48 (s, 1H), 7.86 (br s, 1H), 7.73-7.68 (m, 1H), 7.19-7.14 (m, 1H), 4.12-3.96 (m, 1H), 3.70 (s, 2H), 3.22-3.08 (m, 2H), 2.99-2.85 (m, 2H), 2.31 (s, 3H); LCMS $(M+H)^+$: 361.1.

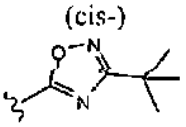
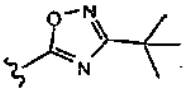
Trans- isomer: ^{1}H NMR (300 MHz, d_6-dmso): δ 12.36 (br s, 1H), 8.99 (s, 1H), 8.77 (s, 1H), 8.52 (s, 1H), 7.90 (br s, 1H), 7.72-7.67 (m, 1H), 7.21-7.17 (m, 1H), 4.03-3.88 (m, 1H), 3.52 (s, 2H), 3.47-3.31 (m, 2H), 2.93-2.84 (m, 2H), 2.36 (s, 3H); LCMS $(M+H)^+$: 361.0.

Additional oxadiazoles were prepared according to Example 41, using different amidoximes (prepared according to the procedure found in J. Org. Chem. 2003, 68(19), pp.

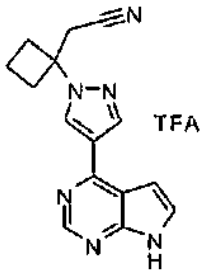
7316-7321) in Step 6, and are found in Table 2.

Table 2



Ex. No.	-R	Name	MS $(M+H)^+$	^{1}H NMR (δ)	Method of Preparation
42a	(cis-) 	{cis-3-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetate salt	403.1	(300 MHz, d_6-dmso): 12.61 (br s, 1H), 8.92 (s, 1H), 8.83 (s, 1H), 8.53 (s, 1H), 7.80-7.74 (m, 1H), 7.25-7.20 (m, 1H), 4.06 (p, 1H), 3.68 (s, 2H), 3.19-3.09 (m, 2H), 3.01-2.90 (m, 2H), 1.27 (s, 9H).	Ex. # 41
42b	(trans-) 	{trans-3-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile trifluoroacetate salt	403.1	(300 MHz, d_6-dmso): 12.54 (br s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 7.79-7.73 (m, 1H), 7.27-7.22 (m, 1H), 3.96 (p, 1H), 3.51 (s, 2H), 3.45-3.33 (m, 2H), 2.98-2.87 (m, 2H), 1.33 (s, 9H).	Ex. # 41

Example 43. 1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile trifluoroacetic acid salt



Step 1. cyclobutylideneacetonitrile.

To a solution of 1.0000 M of potassium tert-butoxide in tetrahydrofuran (19.2 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (3.26 mL, 0.0202

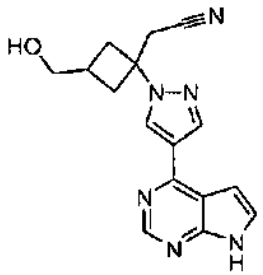
mol) in tetrahydrofuran (24.52 mL, 0.3023 mol). The reaction was warmed to rt and then cooled to 0 °C again. To the reaction mixture was added a solution of cyclobutanone (1.37 mL, 0.0183 mol) in tetrahydrofuran (4.90 mL, 0.0605 mol). The reaction was allowed to warm up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried and evaporated to dryness. The crude mixture was used directly in next step (1.30 g, 76.25%).

Step 2. 1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.030 g, 0.000095 mol) in acetonitrile (0.60 mL, 0.011 mol) was added cyclobutylideneacetonitrile (0.0177 g, 0.000190 mol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0142 mL, 0.0000951 mol). The resulting mixture was stirred at rt overnight. After evaporation to dryness, the residue was purified on silica gel to give the desired Micheal addition product. LCMS (M+H) 409.1.

The crude residue made above was dissolved in 0.2 mL of dichloromethane and treated with 0.4 mL of TFA at rt for 30 min. After evaporation to dryness, the residue was treated with 50 µL of ethylenediamine in 1 mL of methanol at rt for 30 min. The resulting mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA) to give the titled product as TFA salt, LCMS calculated for $C_{15}H_{15}N_6(M+H)^+$: 279.1; Found: 279.0. ^1H NMR (400 MHz, DMSO-d_6): δ 12.68(1H, br s), 8.88 (1H, s), 8.84 (1H, s), 8.51 (1H, s), 7.78 (1H, m), 7.25 (1H, m), 3.49 (2H, s), 2.78 (2H, m), 2.39 (2H, m), 2.06 (1H, m), 1.93 (1H, m) ppm.

Example 44. cis- and trans-3-(hydroxymethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.



Step 1. diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate.

Diisopropyl malonate (72 g, 0.38 mol) was added dropwise, under nitrogen, to a stirred suspension of sodium hydride (17 g, 0.42 mol) in dry N,N-dimethylformamide (140 mL, 1.8 mol) at a rate such that the temperature was maintained below 70 °C. On cessation of hydrogen evolution, 1,3-dibromo-2,2-dimethoxypropane (50 g, 0.2 mol) was added in one portion and the mixture heated at 140 °C for 48 h. The cooled mixture was poured into sat. solution of ammonium chloride (300 mL), extracted with hexane. The organic layer was washed with sat. sodium bicarbonate, brine, dried over sodium sulfate, and evaporated to dryness. The residue was distilled under vacuum (oil pump) to afford the desired cyclobutane compound (31 g, 56.32%). bp 92-94°C/0.01mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02 (2H, sept., J = 6.4 Hz), 3.12 (6H, s), 2.66 (4H, s), 1.11 (12H, d, J = 6.4 Hz) ppm.

Step 2. 3-oxocyclobutanecarboxylic acid.

Diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (31 g, 0.11 mol) was heated with 78 mL of 20% HCl at reflux for 60 h. After cooling, the solution was continuously extracted with ether for 18 h. The ether was removed at a reduced pressure, leaving a yellow oil, which crystallized on standing to give the titled acid (10.4 g, 84.78%).

Step 3. methyl 3-oxocyclobutanecarboxylate.

A solution of N,N'-dicyclohexylcarbodiimide (7.17 g, 0.0347 mol) in methylene chloride (8 mL, 0.1 mol) was added dropwise to a stirred mixture of 3-oxocyclobutanecarboxylic acid (3.6 g, 0.032 mol), methanol (2.6 mL, 0.063 mol) and 4-dimethylaminopyridine (3.08 g, 0.0252 mol) in methylene chloride (20 mL, 0.2 mol). The mixture was stirred at rt for 24 h, then filtered through Celite. The filtrate was washed with 0.5 M HCl and sat. sodium bicarbonate, dried and concentrated to dry. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to give the desired ester (3.26 g, 80.64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 3.43~3.20 (5H, m) ppm.

Step 4. methyl 3-(cyanomethylene)cyclobutanecarboxylate.

To a solution of 1.0000 M of potassium tert-butoxide in tetrahydrofuran (26.7 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (4.53 mL, 0.0280 mol) in tetrahydrofuran (50 mL, 0.6 mol). The reaction was warmed to rt and then cooled at 0 °C again. To the reaction mixture was a solution of methyl 3-oxocyclobutanecarboxylate (3.26 g, 0.0254 mol) in tetrahydrofuran (20 mL, 0.3 mol). The reaction was allowed to warm

up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with ether. The combined organic layers were washed with water, brine, dried and evaporated to dryness. The crude mixture was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to give the desired product (3.12 g, 81.12%). LCMS calculated for $C_8H_{10}NO_2(M+H)^+$: 152.1; Found: 152.3.

Step 5. methyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarboxylate.

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (2.01 g, 0.00637 mol) in acetonitrile (4.081 mL, 0.77 mol) was added methyl 3-(cyanomethylene)cyclobutanecarboxylate (1.93 g, 0.0127 mol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.953 mL, 0.00637 mol). The resulting mixture was stirred at 50 °C overnight. After evaporation to dryness, the residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to give the desired Micheal addition product as a mixture of cis- and trans- isomers (2.12 g, 71.3%). LCMS calculated for $C_{23}H_{31}N_6O_3Si(M+H)^+$: 467.2; Found: 467.4.

Step 6. 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

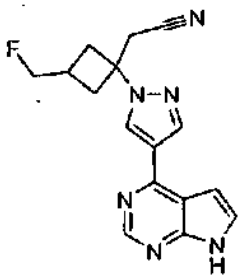
To a mixture of methyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarboxylate (7.0 g, 0.015 mol) in tetrahydrofuran (100 mL, 1 mol) was added lithium tetrahydroborate (0.327 g, 0.0150 mol) at 0 °C. The reaction was then heated at 50 °C for 3 h. To the reaction was added 60 mL of methanol. The resulting mixture was heated at 50 °C for another 15 min, then evaporated to dryness. The residue was treated with 1 N HCl, then neutralized with solid sodium bicarbonate, extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 100% EtOAc, to give the desired product as cis- and trans- mixture (5.85 g, 88.91%). LCMS calculated for $C_{22}H_{31}N_6O_2Si(M+H)^+$: 439.2; Found: 439.4.

Step 7. 3-(hydroxymethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

To 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.030 g, 0.000068 mol) was added

1.5 mL of TFA. The reaction was stirred at rt for 30 min, then evaporated to dryness. The crude mixture was dissolved in 1 mL of methanol and treated with 60 µL of ethylenediamine at rt for 5 h. The resulting mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.766 min, LCMS calculated for $C_{16}H_{17}N_6O(M+H)^+$: 309.1; Found: 309.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.11(1H, br s), 8.67 (1H, s), 8.65 (1H, s), 8.37 (1H, s), 7.58 (1H, d, J = 3.6), 7.02 (1H, d, J = 3.6 Hz), 4.69 (1H, br s), 3.47 (2H, s), 3.41 (2H, br s), 2.53 (2H, m), 2.37 (2H, m) ppm. Second peak retention time 0.805 min, LCMS calculated for $C_{16}H_{17}N_6O(M+H)^+$: 309.1; Found: 309.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.11(1H, br s), 8.80 (1H, s), 8.68 (1H, s), 8.40 (1H, s), 7.58 (1H, d, J = 3.6 Hz), 7.07 (1H, d, J = 3.6 Hz), 4.78 (1H, br t, J = 5.2 Hz), 3.47 (2H, br t, J = 5.2 Hz), 3.36 (2H, s), 2.85 (2H, m), 2.29 (2H, m) ppm.

Example 45. cis- and trans-3-(fluoromethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

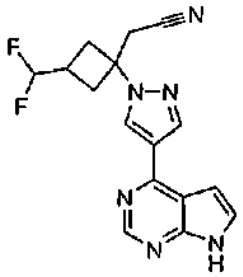


To a mixture of 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.050 g, 0.00011 mol) in methylene chloride (3.10 mL, 0.0483 mol) in a plastic bottle was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ(4)-sulfanyl)ethanamine (63.0 µL, 0.000342 mol) followed by ethanol (1 µL, 0.00002 mol). The reaction was stirred at rt overnight, then evaporated to dryness to yield the fluorinated product. LCMS (M+H) 441.1.

To the residue from above was added 3 mL of TFA. The reaction was stirred at rt for 30 min, then evaporated to dryness. The crude mixture was dissolved in 1 mL of methanol and treated with 60 µL of ethylenediamine at rt for 5 h. The resulting mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing

0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.973 min on analytic LCMS [Waters SunFire HPLC column (C18, 2.1x50 mm, 5 μM), injection volumn 2 μL, flow rate 3 mL/min, gradient from 2 to 80% B in 3 minutes (A = water with 0.025% TFA; B = acetonitrile)], LCMS calculated for $C_{16}H_{16}FN_6(M+H)^+$: 311.1; Found: 311.3. Second peak retention time 1.006 min on analytic LCMS, LCMS calculated for $C_{16}H_{16}FN_6(M+H)^+$: 311.1; Found: 311.3. ^1H NMR (500 MHz, DMSO-d_6): δ 12.09(1H, br s), 8.84 (1H, s), 8.70 (1H, s), 8.43 (1H, s), 7.59 (1H, d, J = 4.0 Hz), 7.08 (1H, d, J = 4.0 Hz), 4.53 (2H, dd, J = 5.5 and 47.5 Hz), 3.38 (2H, s), 2.97 (2H, m), 2.68 (1H, m), 2.39 (2H, m) ppm. ^{19}F NMR (500 MHz, DMSO-d_6) δ -221.84 (td, J = 47.5 and 21.0 Hz) ppm.

Example 46. cis- and trans-3-(difluoromethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.



Step 1. 3-formyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

Dimethyl sulfoxide (0.194 mL, 0.00274 mol) was added to a solution of oxalyl chloride (0.145 mL, 0.00171 mol) in methylene chloride (6.384 mL, 0.09959 mol) at -78 °C. After 10 min, 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.500 g, 0.00114 mol) in methylene chloride (12.77 mL, 0.1992 mol) was added and the resultant mixture was stirred at -78 °C for 30 min. Triethylamine (0.794 mL, 0.00570 mol) was then added and the mixture was stirred for 5 h with the temperature allowed to gradually warm up to rt. After quenching with water, the mixture was extracted with methylene chloride. The organic layers were combined, washed with brine, cried and evaporated to dry. The residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to give the desired aldehyde (430 mg, 86%). LCMS calculated for $C_{22}H_{29}N_6O_2Si(M+H)^+$: 437.2; Found: 437.4.

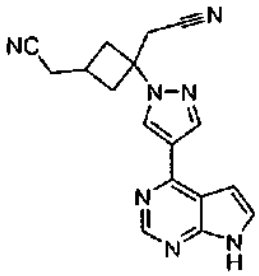
Step 2. 3-(difluoromethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutylacetonitrile.

To a mixture of 3-formyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.285 g, 0.000653 mol) in methylene chloride (6 mL, 0.09 mol) in a plastic bottle was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ(4)-sulfanyl)ethanamine (0.481 mL, 0.00261 mol) followed by ethanol (8 µL, 0.0001 mol). The reaction was stirred at rt overnight, then evaporated to dryness. LCMS (M+H) 459.4.

To the residue made above was added 3 mL of TFA. The reaction was stirred at rt for 30 min, then evaporated to dryness. The crude mixture was dissolved in 3 mL of methanol and treated with ethylenediamine (0.22 mL, 0.0033 mol) at rt for 5 h. The resulting mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.935 min, LCMS calculated for $C_{16}H_{15}F_2N_6(M+H)^+$: 329.1; Found: 329.1. ^1H NMR (500 MHz, DMSO-d_6): δ 12.10(1H, br s), 8.74 (1H, s), 8.69 (1H, s), 8.40 (1H, s), 7.59 (1H, d, J = 3.5 Hz), 7.06 (1H, d, J = 3.5 Hz), 6.20 (1H, td, J = 57.0 and 4.0 Hz), 3.57 (2H, s), 2.98 (1H, m), 2.81 (2H, m), 2.52 (2H, m) ppm. Second peak retention time 0.974 min, LCMS calculated for $C_{16}H_{15}F_2N_6(M+H)^+$: 329.1; Found: 329.1. ^1H NMR (500 MHz, DMSO-d_6): δ 12.10(1H, br s), 8.78 (1H, s), 8.70 (1H, s), 8.44 (1H, s), 7.60 (1H, d, J = 3.5 Hz), 7.09 (1H, d, J = 3.5 Hz), 6.25 (1H, td, J = 57.0 and 4.5 Hz), 3.41 (2H, s), 3.01 (2H, m), 2.90 (1H, m), 2.56 (2H, m) ppm.

Example 47. cis- and trans-2,2'-[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3-diyl]diacetonitrile.



Step 1. 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylmethyl methanesulfonate.

To a mixture of 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.122 g, 0.000278 mol) in methylene chloride (2 mL, 0.04 mol) was added triethylamine (0.0775 mL, 0.000556

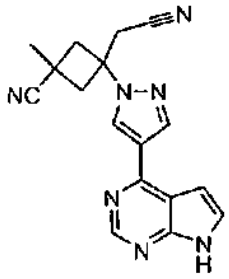
mol) followed by methanesulfonyl chloride (0.0478 g, 0.000417 mol) at 0 °C. The reaction was stirred at rt overnight, quenched with water, extracted with dichloromethane. The organic layers were washed with brine, dried over magnesium sulfate, then evaporated to dryness. The crude mixture was used directly in next step (138 mg, 96.02%). LCMS calculated for $C_{23}H_{33}N_6O_4SSi(M+H)^+$: 517.2; Found: 517.4.

Step 2. 2,2'-[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3-diyl]diacetonitrile.

A mixture of 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylmethyl methanesulfonate (0.138 g, 0.000267 mol) and potassium cyanide (0.0870 g, 0.00134 mol) in N,N-dimethylformamide (1.0 mL, 0.013 mol) was heated at 65 °C overnight. After cooled to rt, the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over magnesium sulfate, then evaporated to dryness. LCMS (M+H) 448.4.

The crude product made above was treated with 1 mL of TFA at rt for 30 min, then evaporated to dryness. The resulting residue was treated with 0.1 mL of ethylenediamine in 1 mL of MeOH at rt overnight. The mixture was applied on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give two isomers at a ratio of 3:2. First peak retention time 0.869 min, LCMS calculated for $C_{17}H_{16}N_7(M+H)^+$: 318.1; Found 318.3. ^1H NMR (500 MHz, DMSO-d_6): δ 12.09(1H, br s), 8.72 (1H, s), 8.69 (1H, s), 8.39 (1H, s), 7.60 (1H, d, J = 3.5 Hz), 7.05 (1H, d, J = 3.5 Hz), 3.52 (2H, s), 2.79 (2H, br s), 2.68 (1H, m), 2.61 (2H, br s), 2.60 (2H, br s) ppm. Second peak retention time 0.919 min, LCMS calculated for $C_{17}H_{16}N_7(M+H)^+$: 318.1; Found 318.3. ^1H NMR (500 MHz, DMSO-d_6): δ 12.09(1H, br s), 8.85 (1H, s), 8.70 (1H, s), 8.43 (1H, s), 7.59 (1H, d, J = 3.5 Hz), 7.08 (1H, d, J = 3.5 Hz), 3.40 (2H, s), 3.07 (2H, m), 2.80 (2H, d, J = 7.0 Hz), 2.70 (1H, m), 2.34 (2H, m) ppm.

Example 48. cis- and trans-3-(cyanomethyl)-1-methyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile.



Step 1. 1-methyl-3-methylenecyclobutanecarbonitrile

To a mixture of 3-methylenecyclobutanecarbonitrile (5.00 g, 0.0537 mol) (from Bepharm Ltd., China) in tetrahydrofuran (200 mL, 2 mol) was added 2.00 M of lithium diisopropylamide in tetrahydrofuran (32.2 mL) at -78 °C. After stirring at -78 °C for 30 min, methyl iodide (4.18 mL, 0.0671 mol) was added. The reaction was stirred at -78 °C for 30 min, then allowed to warm up to rt, quenched with ammonium chloride, then extracted with ether. The combined organic layers were washed with water, brine, dried, and evaporated to dryness. The crude residue was used directly in next step.

Step 2. 1-methyl-3-oxocyclobutanecarbonitrile.

A mixture of water (60 mL, 3 mol) and 1,4-dioxane (200 mL, 2 mol), 1-methyl-3-methylenecyclobutanecarbonitrile (5.75 g, 0.0537 mol), and 0.2 M of osmium tetraoxide in water (1 mL) was stirred for 5 min, during which time the mixture became brown. While the temperature was maintained at room temperature, sodium periodate (24.1 g, 0.113 mol) was added in portions over a period of 30 min. The mixture was stirred overnight. The mixture was extracted with dichloromethane and combined organic layers were dried over $MgSO_4$. After removal of the solvents, the crude product was used directly in next step (5.50 g, 93.92%). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.74 (2H, m), 3.16 (2H, m), 1.75 (3H, s) ppm.

Step 3. 3-(cyanomethylene)-1-methylcyclobutanecarbonitrile.

To a solution of 1.0 M of potassium tert-butoxide in tetrahydrofuran (52.9 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (8.98 mL, 0.0555 mol) in tetrahydrofuran (90 mL, 1 mol). The reaction was warmed to rt and then cooled at 0 °C again. To the reaction mixture was added a solution of 1-methyl-3-oxocyclobutanecarbonitrile (5.50 g, 0.0504 mol) in tetrahydrofuran (40 mL, 0.6 mol). The reaction was allowed to warm up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with ether. The combined organic layers were washed with water,

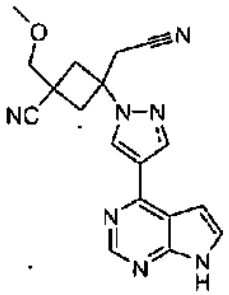
brine, dried and evaporated to dryness. The crude mixture was purified on silica gel, eluting with 0 to 60% EtOAc in hexane, to give the desired product (3.12 g, 46.84%). LCMS calculated for $C_8H_9N_2(M+H)^+$:133.1; Found: 133.1.

Step 4. 3-(cyanomethyl)-1-methyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile.

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.030 g, 0.000095 mol) in acetonitrile (0.5 mL, 0.01 mol) was added 3-(cyanomethylene)-1-methylcyclobutanecarbonitrile (0.0126 g, 0.0000951 mol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0142 mL, 0.0000951 mol). The resulting mixture was stirred at rt overnight, then evaporated to dryness. LCMS (M+H) 448.4.

The crude mixture was treated with 1 mL of TFA (trifluoroacetic acid) at rt for 1 h, and evaporated to dryness. The residue was stirred with 0.050 mL of ethylenediamine in 1 mL of methanol at rt overnight. The reaction mixture was applied on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.916 min, LCMS calculated for $C_{17}H_{16}N_7(M+H)^+$: 318.1; Found 318.4. ^1H NMR (500 MHz, DMSO-d_6): δ 12.10(1H, br s), 8.93 (1H, s), 8.71 (1H, s), 8.46 (1H, s), 7.61 (1H, d, J = 3.5 Hz), 7.08 (1H, d, J = 3.5 Hz), 3.48 (2H, dd, J = 2.0 and 12.5 Hz), 3.45 (2H, s), 2.74 (2H, dd, J = 2.0 and 12.5 Hz), 1.62 (3H, s) ppm. Second peak retention time 0.988 min, LCMS calculated for $C_{17}H_{16}N_7(M+H)^+$: 318.1; Found 318.4. ^1H NMR (500 MHz, DMSO-d_6): δ 12.10(1H, br s), 8.84 (1H, s), 8.70 (1H, s), 8.43 (1H, s), 7.61 (1H, d, J = 3.5 Hz), 7.06 (1H, d, J = 3.5 Hz), 3.52 (2H, s), 3.12 (4H, m), 1.45 (3H, s) ppm.

Example 49. cis- and trans-3-(cyanomethyl)-1-(methoxymethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile.



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Step 1. 1-(methoxymethyl)-3-methylenecyclobutanecarbonitrile

To a mixture of 3-methylenecyclobutanecarbonitrile (1.00 g, 0.0107 mol) in tetrahydrofuran (40 mL, 0.5 mol) was added 2.00 M of lithium diisopropylamide in tetrahydrofuran (6.44 mL) at -78 °C. After stirred at -78 °C for 30 min, to the resulting mixture was added chloromethyl methyl ether (1.02 mL, 0.0134 mol). The reaction was stirred at -78 °C for 30 min, then allowed to warm up to rt, quenched with ammonium chloride, then extracted with ether. The combined organic layers were washed with water, brine, dried, and evaporated to dryness. The crude residue was used directly in next step.

Step 2. 1-(methoxymethyl)-3-oxocyclobutanecarbonitrile.

A mixture of water (2 mL, 0.1 mol) and 1,4-dioxane (7 mL, 0.08 mol), 1-(methoxymethyl)-3-methylenecyclobutanecarbonitrile (0.294 g, 0.00214 mol), and 0.2 M of osmium tetraoxide in water (0.04 mL) was stirred for 5 min, during which time the mixture became brown. While the temperature was maintained at room temperature, sodium periodate (0.963 g, 0.00450 mol) was added in portions over a period of 30 min. The mixture was stirred overnight. The mixture was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$. After removal of the solvents, the crude product was used directly in next step (298 mg, 99.92%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (2H, s), 3.68 (3H, s), 3.58 (2H, m), 3.38 (2H, m) ppm.

Step 3. 3-(cyanomethylene)-1-(methoxymethyl)cyclobutanecarbonitrile

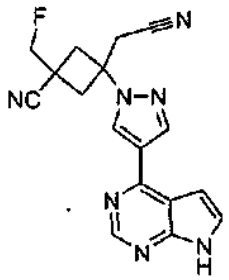
To a solution of 1.0000 M of potassium tert-butoxide in tetrahydrofuran (2.25 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (0.381 mL, 0.00236 mol) in tetrahydrofuran (4 mL, 0.05 mol). The reaction was warmed to rt and then cooled to 0 °C again. To the reaction mixture was added a solution of 1-(methoxymethyl)-3-oxocyclobutanecarbonitrile (0.298 g, 0.00214 mol) in tetrahydrofuran (2 mL, 0.02 mol). The reaction was allowed to warm up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with ether. The combined organic layers were washed with water, brine, dried and evaporated to dryness. The crude mixture was used directly in next step. LCMS calculated for $C_6H_{11}N_2O(M+H)^+$:163.1; Found: 163.1.

Step 4. 3-(cyanomethyl)-1-(methoxymethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile.

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.256 g, 0.000812 mol) in acetonitrile (5 mL, 0.1 mol) was added 3-(cyanomethylene)-1-(methoxymethyl)cyclobutanecarbonitrile (0.166 g, 0.00102 mol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.153 mL, 0.00102 mol). The resulting mixture was stirred at rt overnight, and evaporated to dryness. LCMS (M+H) 478.4.

The crude mixture from above was treated with 1 mL of TFA at rt for 1 h, then evaporated to dryness. The residue was stirred with 0.050 mL of ethylenediamine in 1 mL of methanol at rt overnight. The reaction mixture was applied on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.969 min, LCMS calculated for $C_{18}H_{18}N_7O(M+H)^+$: m/z = 348.2; Found: 348.4. Second peak retention time 0.986 min, LCMS calculated for $C_{18}H_{18}N_7O(M+H)^+$: 348.2; Found: 348.4.

Example 50. cis- and trans-3-(cyanomethyl)-1-(fluoromethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile



Step 1. 1-(hydroxymethyl)-3-methylenecyclobutanecarbonitrile.

To a mixture of 1-(methoxymethyl)-3-methylenecyclobutanecarbonitrile (1.40 g, 0.0102 mol) in methylene chloride (30 mL, 0.4 mol) was added 1.0 M of boron tribromide in methylene chloride (12.8 mL) at -78 °C. The reaction was stirred at rt for 2 h, quenched with aq. sodium bicarbonate, and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated to dryness to give the desired product (1.26 g, 100%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.81 (2H, m), 3.66 (2H, s), 3.10 (2H, m), 2.59 (2H, m) ppm.

Step 2. 1-(fluoromethyl)-3-methylenecyclobutanecarbonitrile

To a mixture of 1-(hydroxymethyl)-3-methylenecyclobutanecarbonitrile (0.252 g, 0.00205 mol) in methylene chloride (20 mL, 0.3 mol) in a plastic bottle was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ(4)-sulfanyl)ethanamine (1.13 mL, 0.00614 mol) followed by ethanol (20 µL, 0.0004 mol). The reaction was stirred at rt overnight, then quenched with aq. sodium bicarbonate, and extracted with dichloromethane. The extracts were combined and washed with water, brine, and dried over magnesium sulfate, and evaporated to dryness. The residue was used directly in next step.

Step 3. 1-(fluoromethyl)-3-oxocyclobutanecarbonitrile.

A mixture of water (2 mL, 0.1 mol) and 1,4-dioxane (6 mL, 0.08 mol), 1-(fluoromethyl)-3-methylenecyclobutanecarbonitrile (0.256 g, 0.00204 mol), and 0.2 M of osmium tetraoxide in water (0.04 mL) was stirred for 5 min, during which time the mixture became brown. While the temperature was maintained at room temperature, sodium periodate (0.919 g, 0.00430 mol) was added in portions over a period of 30 min.The mixture was stirred overnight. The mixture was extracted with EtOAc and combined organic layers were dried over $MgSO_4$. After removal of the solvents, the crude product was used directly in next step.

Step 4. 3-(cyanomethylene)-1-(fluoromethyl)cyclobutanecarbonitrile

To a solution of 1.0 M of potassium tert-butoxide in tetrahydrofuran (2.15 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (0.364 mL, 0.00225 mol) in tetrahydrofuran (4 mL, 3.04 mol). The reaction was warmed to rt and then cooled to 0 °C again. To the reaction mixture was added a solution of 1-(fluoromethyl)-3-oxocyclobutanecarbonitrile (0.260 g, 0.00204 mol) in tetrahydrofuran (2 mL, 0.02 mol). The reaction was allowed to warm up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with ether. The combined organic layers were washed with water then brine, dried, and evaporated to dryness. The crude mixture was used directly in next step.

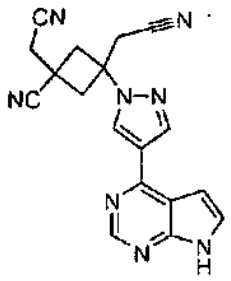
Step 5. 3-(cyanomethyl)-1-(fluoromethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-

pyrrolo[2,3-d]pyrimidine (0.256 g, 0.000812 mol) in acetonitrile (5 mL, 0.1 mol) was added 3-(cyanomethylene)-1-(fluoromethyl)cyclobutanecarbonitrile (0.153 g, 0.00102 mol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.153 mL, 0.00102 mol). The resulting mixture was stirred at rt overnight, evaporated to dry. LCMS (M+H) 465.4.

The crude mixture was treated with 1 mL of TFA at rt for 1 h, and evaporated to dryness. The residue was stirred with 0.050 mL of ethylenediamine in 1 mL of methanol at rt overnight. The reaction mixture was applied on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.939 min, LCMS calculated for $C_{17}H_{15}FN_7(M+H)^+$: 336.1; Found: 336.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.08(1H, br s), 8.97 (1H, s), 8.70 (1H, s), 8.49 (1H, s), 7.61 (1H, d, J = 3.6 Hz), 7.09 (1H, d, J = 3.6 Hz), 4.81 (2H, d, J = 46.4 Hz), 3.48 (2H, s), 3.44 (2H, m), 2.90 (2H, m) ppm. Second peak retention time 0.978 min, LCMS calculated for $C_{17}H_{15}FN_7(M+H)^+$: 336.1; Found: 336.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.08(1H, br s), 8.85 (1H, s), 8.68 (1H, s), 8.43 (1H, s), 7.61 (1H, d, J = 4.4 Hz), 7.06 (1H, d, J = 4.4 Hz), 4.58 (2H, d, J = 46.4 Hz), 3.58 (2H, s), 3.26 (2H, m), 3.09 (2H, m) ppm.

Example 51. cis- and trans-1,3-bis(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile



Step 1. (1-cyano-3-methylenecyclobutyl)methyl methanesulfonate.

To a mixture of 1-(hydroxymethyl)-3-methylenecyclobutanecarbonitrile (0.756 g, 0.00614 mol) in methylene chloride (20 mL, 0.3 mol) was added triethylamine (1.28 mL, 0.00921 mol) followed by methanesulfonyl chloride (0.594 mL, 0.00767 mol) at 0 °C. The reaction was stirred at rt for 1 h, quenched with water, and extracted with dichloromethane. The combined organic layers were washed with water, brine, and then dried over magnesium sulfate and evaporated to dryness. The residue was used directly in next step.

Step 2. 1-(cyanomethyl)-3-methylenecyclobutanecarbonitrile.

A mixture of (1-cyano-3-methylenecyclobutyl)methyl methanesulfonate (0.41 g, 0.0020 mol) and potassium cyanide (0.66 g, 0.010 mol) in N,N-dimethylformamide (5 mL, 0.06 mol) was heated at 65 °C overnight. After diluting with water, the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried and evaporated to dry. The residue was used directly in next step.

Step 3. 1-(cyanomethyl)-3-oxocyclobutanecarbonitrile.

A mixture of water (2 mL, 0.1 mol) and 1,4-dioxane (6 mL, 0.08 mol), 1-(cyanomethyl)-3-methylenecyclobutanecarbonitrile (0.270 g, 0.00204 mol), and 0.2 M of osmium tetraoxide in water (0.04 mL) was stirred for 5 min, during which time the mixture became brown. While the temperature was maintained at room temperature, sodium periodate (0.919 g, 0.00430 mol) was added in portions over a period of 30 min. The mixture was stirred overnight. The mixture was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$. After removal of the solvents, the crude product was used directly in next step.

Step4. 1-(cyanomethyl)-3-(cyanomethylene)cyclobutanecarbonitrile.

To a solution of 1.0 M of potassium tert-butoxide in tetrahydrofuran (2.15 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (0.364 mL, 0.00225 mol) in tetrahydrofuran (4 mL, 0.04 mol). The reaction was warmed to rt and then cooled to 0 °C again. To the reaction mixture was added a solution of 1-(cyanomethyl)-3-oxocyclobutanecarbonitrile (0.274 g, 0.00204 mol) in tetrahydrofuran (2 mL, 0.02 mol). The reaction was allowed to warm up to rt and stirred at rt overnight. After quenching with water, the mixture was extracted with ether. The combined organic layers were washed with water and brine, then dried and evaporated to dryness. The crude mixture was used directly in next step.

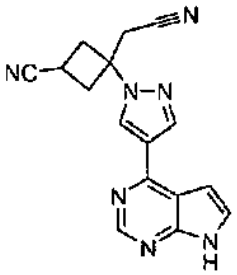
Step 5. 1,3-bis(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile

To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.256 g, 0.000812 mol) in acetonitrile (5 mL, 0.1 mol) was added 1-(cyanomethyl)-3-(cyanomethylene)cyclobutanecarbonitrile (0.161 g, 0.00102 mol),

followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.153 mL, 0.00102 mol). The resulting mixture was stirred at rt overnight, evaporated to dry. LCMS (M+H) 473.4.

The crude mixture was treated with 1 mL of TFA at rt for 1 h, then evaporated to dryness. The residue was stirred with 0.050 mL of ethylenediamine in 1 mL of methanol at rt overnight. The reaction mixture was applied on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired products as free bases. First peak retention time 0.883 min, LCMS calculated for $C_{18}H_{15}N_8(M+H)^+$: 343.1; Found: 343.4. ^1H NMR (400 MHz, DMSO-d_6): δ 12.12(1H, br s), 8.98 (1H, s), 8.70 (1H, s), 8.48 (1H, s), 7.61 (1H, d, J = 4.0 Hz), 7.10 (1H, d, J = 4.0 Hz), 3.56 (2H, d, J = 13.2), 3.46 (2H, s), 3.42 (2H, m), 2.92 (2H, d, J = 13.2 Hz) ppm. Second peak retention time 0.897 min, LCMS calculated for $C_{18}H_{15}N_8(M+H)^+$: 343.1; Found: 343.4. ^1H NMR (400 MHz, DMSO-d_6): δ 12.08(1H, br s), 8.35 (1H, s), 8.69 (1H, s), 8.43 (1H, s), 7.61 (1H, m), 7.07 (1H, m), 3.38 (2H, s), 3.27 (2H, m), 3.14 (2H, m), 2.88 (2H, m) ppm.

Example 52. cis and trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile



Step 1. 3-oxocyclobutanecarbonitrile.

A mixture of water (40 mL, 2 mol) and 1,4-dioxane (100 mL, 1 mol), 3-methylenecyclobutanecarbonitrile (3.30 g, 0.0354 mol) (commercially available from Bepharma Ltd., China), and 0.2 M of osmium tetraoxide in water (0.7 mL) was stirred for 5 min, during which time the mixture became brown. While the temperature was maintained at room temperature, sodium periodate (15.9 g, 0.0744 mol) was added in portions over a period of 30 min. The mixture was stirred for an additional 1.5 h, then extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated to give a solid (2.04 g, 60.54%). ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (4H, m),

3.25 (1H, m) ppm.

Step 2. 3-(cyanomethylene)cyclobutanecarbonitrile

To a solution of 1 M of potassium tert-butoxide in THF (67.4 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (11.4 mL, 0.0706 mol) in tetrahydrofuran (100 mL, 1 mol). The reaction mixture was warmed up to room temperature and cooled to 0 °C again. To the resulting mixture, a solution of 3-oxocyclobutanecarbonitrile (6.10 g, 0.0641 mol) in tetrahydrofuran (20 mL, 0.2 mol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. After quenching with water, the mixture was extracted with EtOAc. The combined organic layers were dried and concentrated. The residue was purified by flash silica gel column, eluting with 0-10% MeOH/dichloromethane to give the titled product (5.40 g, 71.26%). LCMS (M+Na) 141.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 (1H, m), 3.40 (2H, m), 3.14 (3H, m) ppm.

Step 3. 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile

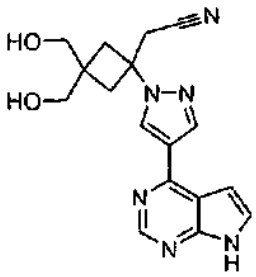
3-(Cyanomethylene)cyclobutanecarbonitrile (120 mg, 0.0010 mol) was combined with 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.1 g, 0.0003 mol) in acetonitrile (2 mL, 0.04 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6 µL, 0.00004 mol) under nitrogen. The mixture was stirred at room temperature over the weekend. After evaporation to dryness, the crude mixture was purified by flash column, eluting with 0 to 10% MeOH in dichloromethane, to give the desired product. LCMS (M+H) 434.4.

Step 4. 3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile.

A 500 mL round bottom flask fitted with stir bar, condenser, and nitrogen inlet, was charged with acetonitrile (16.3 mL, 0.311 mol), water (1.4 mL, 0.078 mol) and 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutanecarbonitrile (1.00 g, 0.00231 mol). The solution was homogeneous. After adding lithium tetrafluoroborate (2.21 g, 0.0231 mol), the resulting mixture was heated to reflux overnight, then charged with 7.2 M of ammonium hydroxide in water (1.2 mL) in portions over a period of 5 minutes at room temperature to adjust pH to 9-

10. The reaction was stirred for 2 h at room temperature. Solid was removed by filtration and the filtrate was diluted with acetonitrile, water, and MeOH: The resultant mixture was purified on Waters XBridge HPLC column (C18, 30x100 mm, 5 μM), with injection volume 5 mL (~50 mg/injection) and flow rate 60 mL/min, at gradient 10-28% B in 12 minutes (A = water with 0.15% NH_4OH; B = acetonitrile with 0.15% NH_4OH), to give the desired products as free bases. First peak retention time 0.826 min at Waters SunFire HPLC column (C18, 2.1x50 mm, 5 μM) with injection volumn 2 μL and flow rate 3 mL/min, at gradient from 2 to 80% B in 3 minutes (A = water with 0.025% TFA; B = acetonitrile). LCMS calculated for $C_{16}H_{14}N_7(M+H)^+$: 304.1; Found 304.3. ^1H NMR (500 MHz, DMSO-d_6): δ 12.10(1H, br s), 8.82 (1H, s), 8.70 (1H, s), 8.44 (1H, s), 7.61 (1H, d, J = 4.0 Hz), 7.08 (1H, d, J = 4.0 Hz), 3.59 (1H, m), 3.57 (2H, s), 3.19 (2H, m), 2.86 (2H, m) ppm. Second peak retention time 0.864 min at the same SunFire column HPLC condition. LCMS calculated for $C_{16}H_{14}N_7(M+H)^+$: 304.1; Found 304.3. ^1H NMR (400 MHz, CD_3OD): δ 8.67 (1H, s), 8.66 (1H, s), 8.40 (1H, s), 7.51 (1H, d, J = 3.6 Hz), 6.99 (1H, d, J = 3.6 Hz), 3.50 (1H, m), 3.42 (2H, s), 3.24 (2H, m), 3.00 (2H, m) ppm.

Example 53. 3,3-bis(hydroxymethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



Step 1. diisopropyl 3-oxocyclobutane-1,1-dicarboxylate.

A mixture of diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (3 g, 0.01 mol) in 20 mL of trifluoroacetic acid-water (95:5) was stirred at 0 °C for 4 h. The reaction was diluted with EtOAc, washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$ and evaporated to give crude product (2.4 g) as yellow oil, which was used directly in the next step. H NMR ($CDCl_3$, 400 MHz) δ 5.07 (2H, h, J = 6.8 Hz), 3.54 (4H, s), 1.23 (12H, d, J = 6.8 Hz) ppm.

Step 2. diisopropyl 3-(cyanomethylene)cyclobutane-1,1-dicarboxylate

To a mixture of 1.0000 M of potassium tert-butoxide in tetrahydrofuran (17 mL) and THF (10 mL) was added dropwise, at 0 °C, diethyl cyanomethylphosphonate (2.7 mL, 0.017 mol). The reaction was warmed to rt and 30 min later cooled to 0 °C again. To the reaction mixture was added a solution of diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (2.7 g, 0.011 mol) in THF (10 mL). The reaction was allowed to warm up to rt gradually and stirred at rt for 2 h. The reaction was quenched with saturated aq. NH_4Cl and the organic solvent was reduced. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated and purified with Combiflash (silica gel, 0-35% EtOAc/Hex) to give the desired product (2.65 g) as light yellow oil.

Step 3. diisopropyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,1-dicarboxylate

Diisopropyl 3-(cyanomethylene)cyclobutane-1,1-dicarboxylate (2.65 g, 0.00999 mol) was combined with 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (1 g, 0.003 mol) in acetonitrile (10 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 mL, 0.003 mol) was added under N_2. The mixture was heated at 50 °C overnight. The reaction was concentrated and purified with Combiflash (silica gel, 0-50% EtOAc/Hex) to give the desired product (0.3 g) as colorless oil. LCMS calculated for $C_{29}H_{41}N_6O_5Si(M+H)^+$: 581.3; Found: 581.4.

Step 4. 3,3-bis(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

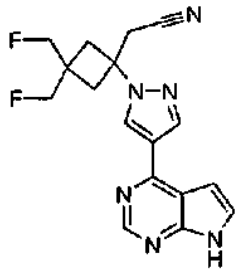
Diisopropyl 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,1-dicarboxylate (0.3 g, 0.5 mmol) was dissolved in tetrahydrofuran (15 mL, 180 mmol) and lithium tetrahydroborate (0.017 g, 0.77 mmol) was added at 0 °C. The reaction was then heated to 50 °C for 30 min. To the reaction was added MeOH (10 mL). The reaction was held at 50 °C for 15 min, then stripped to near dryness. The residue was treated with 1N HCl, then neutralized with solid $NaHCO_3$. The mixture was partitioned between water and EtOAc. The phases were separated and the aq. phase was washed with EtOAc. The combined organic phases were washed with water, then brine, dried over $MgSO_4$, concentrated and purified with Combiflash (silica gel, 0-100% EtOAc/Hex) to give the desired product (0.145 g, 60%) as colorless oil.

LCMS calculated for $C_{23}H_{33}N_6O_3Si(M+H)^+$: 469.2; Found: 469.4.

Step 5. 3,3-bis(hydroxymethyl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

3,3-Bis(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.022 g, 0.000046 mol) was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min and evaporated to dryness. The residue was then mixed with ethylenediamine (0.2 mL, 0.003 mol) in MeOH (1 mL) for 2 h. The reaction was concentrated and purified on prep. LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product as free base. LCMS calculated for $C_{17}H_{19}N_6O_2(M+H)^+$: 339.2; Found: 339.3. ^1H NMR (300 MHz, CD_3OD): δ 8.72 (1H, s), 8.67 (1H, s), 8.39 (1H, s), 7.51 (1H, d, J = 3.3 Hz), 6.97 (1H, d, J = 3.3 Hz), 3.62 (2H, s), 3.46 (2H, s), 3.36 (2H, s), 2.80 (2H, d, J = 13.8 Hz), 2.54 (2H, d, J = 13.8 Hz) ppm.

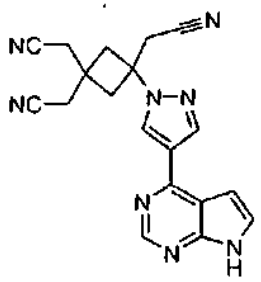
Example 54. 3,3-bis(fluoromethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



A solution of 3,3-bis(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.03 g, 0.00006 mol) in dichloromethane (3 mL), contained in a Teflon bottle equipped with a nitrogen inlet tube and stirring bar, was treated with 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ(4)-sulfanyl)ethanamine (0.06 mL, 0.0004 mol) at rt. Ethanol (0.003 mL, 0.00006 mol) was added, and the mixture was stirred at rt overnight. The resultant mixture was concentrated and purified with prep LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the corresponding fluorinated product, which was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min. After

evaporation to dryness, the resultant residue was mixed with ethylenediamine (0.2 mL, 0.003 mol) in MeOH (1 mL) at rt for 2 h. The reaction was evaporated to dry and the residue was purified with prep. LCMS (pH=10) to give the desired porduct. LCMS calculated for $C_{17}H_{17}F_2N_2$ $(M+H)^+$: 343.1; Found: 343.4. ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (1H, br s), 8.86 (1H, s), 8.49 (1H, s), 8.35 (1H, s), 7.40 (1H, m), 6.82 (1H, m), 4.54 (2H, d, J = 47.7 Hz), 4.38 (2H, d, J = 47.4 Hz), 3.14 (2H, s), 2.96 (2H, d, J = 13.8 Hz), 2.72 (2H, d, J = 13.8 Hz) ppm.

Example 55. 2,2',2''-[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3,3-triyl]triacetonitrile



Step 1. (3,3-dimethoxycyclobutane-1,1-diyl)dimethanol

At 0 °C, to a solution of diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (3.0 g, 0.010 mol) in THF (20 mL) was added 2.0 M of lithium tetrahydroaluminate in tetrahydrofuran (16 mL) slowly with stirring. The mixture was stirred for 2 h, allowing warm up to rt. At 0 °C, to the reaction was added dropwise water (1.2 mL), 15% NaOH solution (1.2 mL) and water (3.6 mL) successively and the resultant mixture was stirred for 20 min at rt. The mixture was filtered and the filtrate was concentration to give the desired product (1.64 g, 89%) as colorless oil which was used directly in the next step without purification.

Step 2. (3,3-dimethoxycyclobutane-1,1-diyl)bis(methylene) dimethanesulfonate

To a mixture of (3,3-dimethoxycyclobutane-1,1-diyl)dimethanol (1.64 g, 0.00931 mol) and triethylamine (7.8 mL, 0.056 mol) in dichloromethane (10 mL) was added methanesulfonyl chloride (2.2 mL, 0.028 mol) dropwise at 0 °C. The resultant mixture was stirred at rt for 1 h. The reaction was diluted with dichloromethane, washed with water and brine, dried over $MgSO_4$ and concentrated to give crude mesylate product (2.95 g, 95.4%) as brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.38 (4H, s), 3.14 (6H, s), 3.02 (6H, s), 2.10 (4H,

s) ppm.

Step 3. 2,2'-(3,3-dimethoxycyclobutane-1,1-diyl)diacetonitrile

To a solution of (3,3-dimethoxycyclobutane-1,1-diyl)bis(methylene) dimethanesulfonate (2.9 g, 0.0037 mol) in DMSO (10 mL) was added potassium cyanide (1.7 g, 0.026 mol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (6.9 g, 0.026 mol). The reaction was stirred at 60 °C over night. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give crude product (2 g) as brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.14 (6H, s), 2.78 (4H, s), 2.11 (4H, s) ppm.

Step 4. 2,2'-(3-oxocyclobutane-1,1-diyl)diacetonitrile

To a mixture of 2,2'-(3,3-dimethoxycyclobutane-1,1-diyl)diacetonitrile (2 g, 0.01 mol) in acetone (5 mL) was added p-toluenesulfonic acid (1 g, 0.006 mol). The mixture was stirred at rt over weekend. The reaction was neutralized with aq. saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give a crude product as brown oil.

Step 5. 2,2',2''-cyclobutane-1,1-diyl-3-ylidenetriacetonitrile

To a solution of 1.0 M of potassium tert-butoxide in tetrahydrofuran (5.1 mL) was added dropwise at 0 °C diethyl cyanomethylphosphonate (0.82 mL, 0.0051 mol). The reaction was warmed to rt and 30 min later cooled to 0 °C again. To the reaction mixture was added a solution of 2,2'-(3-oxocyclobutane-1,1-diyl)diacetonitrile (0.5 g, 0.003 mol) in THF (5 mL). The reaction was allowed to warm up to rt gradually and stirred at rt for 2 h. The reaction was quenched with saturated aq. NH_4Cl, then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a brown oily crude product, which was used directly in the next step.

Step 6. 2,2',2''-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3,3-triyltriacetonitrile

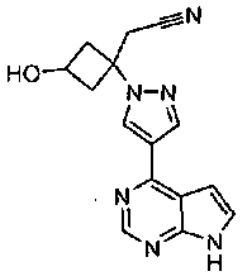
The crude 2,2',2''-cyclobutane-1,1-diyl-3-ylidenetriacetonitrile (1 g, 0.006 mol) was combined with 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.2 g, 0.0006 mol) in acetonitrile (10 mL) and 1,8-diazabicyclo[5.4.0]undec-7-

ene (0.1 mL, 0.001 mol) was added under nitrogen. The mixture was heated at 50 °C over night. The reaction was concentrated and purified with Combiflash (silica gel, 0-100% EtOAc/Hex) to give the desired product as light brown oil. LCMS calculated for $C_{25}H_{31}N_8OSi(M+H)^+$: 487.2; Found: 487.4.

Step 7. 2,2',2''-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3,3-triyltriacetonitrile

2,2',2''-1-[4-(7-[2-(Trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,3,3-triyltriacetonitrile (0.03 g, 0.00006 mol) was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min and then evaporated to dryness. The residue was mixed with ethylenediamine (0.2 mL, 0.003 mol) in MeOH (1 mL) at rt for 1 h. The reaction was evaporated to dryness and the residue was purified with prep. LCMS (pH=10) to give the desired product. LCMS calculated for $C_{19}H_{17}N_8(M+H)^+$: m/z = 357.1; Found: 357.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (1H, br s), 8.79 (1H, s), 8.63 (1H, s), 8.38 (1H, s), 7.55 (1H, d, J = 3.6 Hz), 7.01 (1H, d, J = 3.6 Hz), 3.46 (2H, s), 3.03 (2H, s), 2.97 (2H, d, J = 15.2 Hz), 2.76 (2H, s), 2.57 (2H, d, J = 15.2 Hz) ppm.

Example 56. cis- and trans-3-Hydroxy-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



Step 1. N-methoxy-N-methyl-3-oxocyclobutanecarboxamide

To a mixture of N,O-dimethylhydroxylamine hydrochloride (5.2 g, 0.054 mol), and 3-oxocyclobutanecarboxylic acid (4.0 g, 0.035 mol) in dichloromethane (30 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (10.0 g, 0.052 mol), 1-hydroxybenzotriazole (7.1 g, 0.052 mol) followed by triethylamine (34 mL, 0.24 mol) at 0 °C. The mixture was stirred at rt over night, then quenched with water. The mixture was extracted with EtOAc. The organic layers were dried over $MgSO_4$, concentrated and purified

with Combiflash (silica gel, 0-5% for 30 min followed by 5-20% EtOAc/Hex) to give the desired product (4.3 g, 78%) as light yellow oil. LCMS calculated for $C_7H_{12}NO_3(M+H)^+$: 158.1; Found: 158.3.

Step 2. 3-hydroxy-N-methoxy-N-methylcyclobutanecarboxamide

N-Methoxy-N-methyl-3-oxocyclobutanecarboxamide (1 g, 0.006 mol) was dissolved in methanol (8 mL, 0.2 mol). To the mixture, sodium borohydride (0.2 g, 0.006 mol) was added. The reaction was stirred at rt for 1 h. To the reaction mixture was added 1N aq. HCl to adjust the pH to 2. The mixture was concentrated, then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to give crude product (1.4 g) as light yellow oil. LCMS calculated for $C_7H_{14}NO_3(M+H)^+$: 160.0; Found: 160.3.

Step 3. 3-[tert-butyl(diphenyl)silyl]oxy-N-methoxy-N-methylcyclobutanecarboxamide

Into a solution of 3-hydroxy-N-methoxy-N-methylcyclobutanecarboxamide (0.6 g, 0.004 mol in DMF (10 mL) was added tert-butylchlorodiphenylsilane (3 mL, 0.01 mol), followed by 1H-imidazole (1 g, 0.02 mol). The mixture was stirred at rt over night. The reaction was diluted with dichloromethane and washed with sat. $NaHCO_3$, water and brine. The organic layers were dried over $MgSO_4$, concentrated and purified with Combiflash (silica gel, 0-30% EtOAc/Hex) to give the desired product (0.7 g, 50%) as cis- and trans-isomer mixtures. LCMS calculated for $C_{23}H_{32}NO_3Si(M+H)^+$: 398.2 ; Found: 398.1.

Step 4. 1-(3-[tert-butyl(diphenyl)silyl]oxycyclobutyl)ethanone

A solution of 3-[tert-butyl(diphenyl)silyl]oxy-N-methoxy-N-methylcyclobutanecarboxamide (0.7 g, 0.002 mol) in ether (10 mL) was added into 3.0 M of methylmagnesium iodide in ether (3 mL) slowly under N_2. The reaction was stirred and heated to reflux for 2 h. The mixture was quenched with ice and the ether layer separated. The aq. layer was acidified with 1N HCl and extracted several times with ether. The organic layers were combined, dried over $MgSO_4$, concentrated and purified with Combiflash (silica gel, 0-30% EtOAc/Hex) to give the desired product (0.6 g) as colorless oil. LCMS calculated for $C_{22}H_{29}O_2Si(M+H)^+$: 353.2; Found: 353.3.

Step 5. 3-[tert-butyl(diphenyl)silyl]oxycyclobutyl acetate

To a stirred solution of 1-(3-[tert-butyl(diphenyl)silyl]oxycyclobutyl)ethanone (0.65 g, 0.0018 mol) in dichloromethane (10 mL) at 0 °C was added sodium bicarbonate (0.39 g,

0.0046 mol) and m-chloroperbenzoic acid (1.0 g, 0.0046 mol) with stirring. The reaction was stirred at rt over night. LCMS showed incomplete reaction, another 2.5 eq. of mCPBA and $NaHCO_3$ were added and the reaction was stirred for another day. The reaction was quenched with 20% aq. $Na_2S_2O_3$ solution (50 mL) and stirred for a further 30 min at rt, then extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated and purified on silica gel with Combiflash (silica gel, 0-10% EtOAc/Hex) to give the desired product (0.3 g, 40%) as colorless oil. LCMS calculated for $C_{22}H_{29}O_3Si(M+H)^+$: 369.2; Found: 369.4.

Step 6. 3-[tert-butyl(diphenyl)silyl]oxycyclobutanol

To a solution of 3-[tert-butyl(diphenyl)silyl]oxycyclobutyl acetate (0.27 g, 0.00073 mol) in THF (5 mL) and MeOH (3 mL) was added 1.0 M of lithium hydroxide in water (10 mL). The reaction was stirred at rt for 1 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to give crude alcohol product (0.3 g) as colorless oil, which was directly used in next step without further purification. LCMS calculated for $C_{20}H_{26}O_2NaSi(M+Na)^+$: 349.2; Found: 349.3.

Step 7. 3-[tert-butyl(diphenyl)silyl]oxycyclobutanone

A solution of oxalyl chloride (0.1 mL, 0.001 mol) in dichloromethane (2 mL) under N_2 was cooled to -78 °C. Dimethyl sulfoxide (0.2 mL, 0.002 mol) was added dropwise. On complete addition, the reaction was stirred for 15 min. A solution of crude 3-[tert-butyl(diphenyl)silyl]oxycyclobutanol (0.2 g, 0.0006 mol) in dichloromethane (3 mL) was added dropwise and the reaction mixture was stirred for 45 min at -78 °C. Triethylamine (0.5 mL, 0.004 mol) was added dropwise and the reaction was stirred for 15 minutes. The reaction was then allowed to warm to rt, quenched with water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated to give crude ketone (0.27 g) as yellow oil, which was directly used in the next step without further purification. LCMS calculated for $C_{20}H_{25}O_2Si(M+H)^+$: 325.12; Found: 325.3.

Step 8. (3-[tert-butyl(diphenyl)silyl]oxycyclobutylidene)acetonitrile

To 1.0 M of potassium tert-butoxide in tetrahydrofuran (1.2 mL) was added dropwise, at 0 °C, diethyl cyanomethylphosphonate (0.19 mL, 0.0012 mol). The reaction was warmed to rt and 30 min later cooled to 0 °C again. To the reaction mixture was added a solution of

3-[tert-butyl(diphenyl)silyl]oxycyclobutanone (0.25 g, 0.00077 mol) in THF (5 mL). The reaction was allowed to warm up to rt gradually and stirred at rt for 2 h. The reaction was quenched with saturated aq. NH4Cl, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated. The resultant residue was purified with Combiflash (silica gel, 0-20% EtOAc/Hex) to give the desired product (0.2 g) as colorless oil. LCMS calculated for $C_{22}H_{26}NOSi(M+H)^+$: 348.1 Found: 348.3.

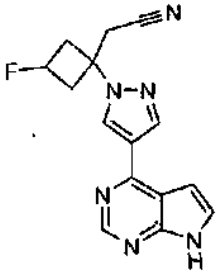
Step 9. {3-Hydroxy-1-[4-(1H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

(3-[tert-Butyl(diphenyl)silyl]oxycyclobutylidene)acetonitrile (0.15 g, 0.00043 mol) was combined with 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.14 g, 0.00043 mol) in acetonitrile (5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.064 mL, 0.00043 mol) was added under nitrogen. The mixture was heated to 50 °C over night. LCMS showed a peak with m/z of 425.4, indicating a de-silyl reaction occurred simultaneously during the Micheal addition. The reaction was concentrated and purified on combiflash (silica gel, 0-100% EtOAc/Hex) to yield the desired produt. LCMS (M+H) 425.4.

Step 10. 3-hydroxy-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

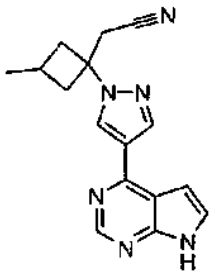
3-Hydroxy-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.020 g, 0.000046 mol) was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min and evaporated to dry. The resultant residue was mixed with ethylenediamine (0.2 mL, 0.003 mol) in MeOH (1 mL) for 2 h. The reaction was concentrated and purified on prep. LCMS (pH=10) to give 2 isomers of the desired products. First peak retention time 0.714 min, LCMS calculated for $C_{15}H_{15}N_6O(M+H)^+$: 295.1; Found: 295.3. Second peak retention time 0.750 min, LCMS calculated for $C_{15}H_{15}N_6O(M+H)^+$: 295.1; Found: 295.3. ^1H NMR (400 MHz, CD_3OD): δ 8.67 (1H, s), 8.66 (1H, s), 8.38 (1H, s), 7.51 (1H, d, J = 3.6 Hz), 6.98 (1H, d, J = 3.6 Hz), 4.37 (1H, s), 3.34 (2H, s), 3.22 (2H, m), 2.48 (2H, m) ppm.

Example 57. 3-fluoro-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



A solution of 3-hydroxy-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.01 g, 0.00003 mol) (a mixture of cis/trans isomers) in dichloromethane (3 mL), contained in a Teflon bottle equipped with a nitrogen inlet tube and stirring bar, was treated with 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ(4)-sulfanyl)ethanamine (0.03 mL, 0.0002 mol) at rt. Ethanol (0.002 mL, 0.00003 mol) was added, and the mixture was stirred at rt over weekend. The reaction was evaporated to dry and the residue was purified with prep. HPLC (pH=10) to give a mixture of two isomers. LCMS calculated for $C_{15}H_{14}FN_6(M+H)^+$: 297.1; Found: 297.3.

Example 58. 3-methyl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile



Step 1. 3-(bromomethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

To an ice-cooled mixture of 3-(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (1.0 g 0.0023 mol) and carbon tetrabromide (1.1 g, 0.0034 mol) in DMF (7 mL) was added triphenylphosphine (0.90 g, 0.0034 mol) and the mixture was stirred at this temp. for 30 min. To the resulting dark brown solution was added saturated aq. $NaHCO_3$ (5 mL) followed by water (5 mL) and the mixture was extracted with

dichloromethane. The organic layers were combined, washed with water, dried over Na_2SO_4, concentrated and purified with combiflash (silica gel, 0-40% EtOAc/Hex) to give the desired product (1.0 g, 87%) as light yellow solid. LCMS calculated for $C_{22}H_{30}BrN_6OSi(M+H)^+$: 501.1; Found: 501.3.

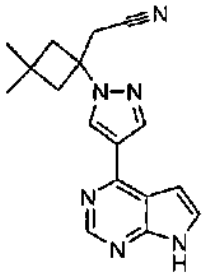
Step 2. 3-methyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

3-(Bromomethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.65 g, 0.0013 mol) was reacted with sodium tetrahydroborate (0.096 g, 0.0026 mol) in DMF (5.2 mL) (~0.5 M) at rt under nitrogen for 3h. The reaction was quenched with water and extracted with dichloromethane. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give a yellow oil, the desired product as cis- and trans-isomer mixtures. LCMS calculated for $C_{22}H_{31}N_6OSi(M+H)^+$: 423.2; Found: 423.4.

Step 3. 3-methyl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

To a mixture of 3-methyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.5 g, 0.001 mol) in acetonitrile (8.07 mL, 0.154 mol) and water (0.70 mL, 0.039 mol) was added lithium tetrafluoroborate (1.10 g, 0.0114 mol). The solution was warmed to reflux at 100 °C over 5 days. Charged 7.2 M of ammonium hydroxide in water (0.59 mL) in portions over a period of 5 minutes at rt adjusting pH to 9-10. The reaction mixture was stirred for 2 h at rt. The reaction was filtered and the filtrate was diluted with acetonitrile, water and MeOH and purified with prep. HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the first isomer with retention time 1.057 min, LCMS calculated for $C_{16}H_{17}N_6(M+H)^+$: 293.2; Found: 293.3. ^1H NMR (500 MHz, $CDCl_3$): δ 10.07(1H, br s), 8.88 (1H, s), 8.45 (1H, s), 8.34 (1H, s), 7.43 (1H, d, J = 3.5 Hz), 6.85 (1H, d, J = 3.5 Hz), 3.16 (2H, s), 2.77 (2H, m), 2.55 (1H m), 2.43 (2H, m), 1.24 (3H, d, J = 6.5 Hz) ppm; then the second isomer with retention time 1.107 min; LCMS calculated for $C_{16}H_{17}N_6(M+H)^+$: 293.2; Found: 293.3. ^1H NMR (500 MHz, $CDCl_3$): δ 10.21(1H, br s), 8.89 (1H, s), 8.61 (1H, s), 8.37 (1H, s), 7.44 (1H, d, J = 3.5 Hz), 6.86 (1H, d, J = 3.5 Hz), 3.07 (2H, s), 3.05 (2H, m), 2.61 (1H, m), 2.26 (2H, m), 1.25 (3H, d, J = 7.0 Hz) ppm.

Example 59. 3,3-dimethyl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.



Step 1. 3-(cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,1-diylbis(methylene) dimethanesulfonate.

To a mixture of 3,3-bis(hydroxymethyl)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.06 g, 0.0001 mol) and triethylamine (0.1 mL, 0.0008 mol) in dichloromethane (3 mL) was added methanesulfonyl chloride (0.03 mL, 0.0004 mol) slowly. The resultant mixture was stirred at rt for 30 min. The reaction was diluted with dichloromethane, washed with water and brine, dried over $MgSO_4$, concentrated. The residue was purified on Combiflash (silica gel, 0-100% EtOAc/Hex) to give the desired product (60 mg, 75%) as white solid. LCMS calculated for $C_{25}H_{37}N_6O_7S_2Si(M+H)^+$: 625.2; Found: 625.3.

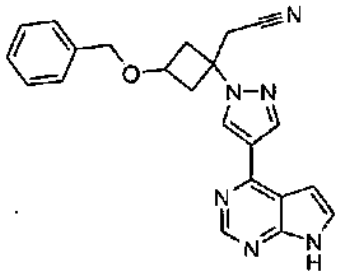
Step 2. 3,3-dimethyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile

3-(Cyanomethyl)-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutane-1,1-diylbis(methylene) dimethanesulfonate (0.06 g, 0.0001 mol) was reacted with sodium tetrahydroborate (0.02 g, 0.0004 mol) in DMF (0.8 mL) (~0.5 M) at 65 °C under nitrogen for 2h. The reaction was quenched with water, and extracted with dichloromethane. The organic layers were washed with water, dried over $MgSO_4$, concentrated. The residue was purified with Combiflash (silica gel, 0-60% EtOAc/Hex) to give the desired prouct. LCMS calculated for $C_{23}H_{33}N_6OSi(M+H)^+$: 437.2; Found: 437.4.

Step 3. 3,3-dimethyl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

3,3-Dimethyl-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.020 g, 0.000046 mol) was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min and then evaporated to dry. The residue was then shaked with ethylenediamine (0.2 mL, 0.003 mol) in MeOH (1 mL) for 2 h. The reaction was concentrated and purified on prep HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{17}H_{19}N_6(MHH)^+$: 307.2; Found: 307.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.10 (1H, br s), 8.76 (1H, s), 8.67 (1H, s), 8.40 (1H, s), 7.58 (1H, d, J = 3.6 Hz), 7.05 (1H, d, J = 3.6 Hz), 3.35 (2H, s), 2.75 (2H, d, J = 14 Hz), 2.33 (2H, d, J = 14.0 Hz), 1.22 (3H, s), 1.02 (3H, s) ppm.

Example 60. cis- and trans-3-(benzyloxy)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.



Step 1. [2-bromo-1-(bromomethyl)ethoxy]methylbenzene

1-Bromo-2,3-epoxypropane (28 mL, 0.33 mol) and benzyl bromide (39 mL, 0.33 mol) was mixed with mercury(II) chloride (0.04 g, 0.0002 mol). The mixture was heated slowly to 155-160 °C and stirred over night. The reaction mixture was then cooled to room temperature, purified with Combiflash (silica gel, 100% hexanes) to give the desired product (63 g, 62%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (5H, m), 4.71 (2H, s), 3.82 (1H, t, J = 4.8 Hz), 3.60 (4H, d, J = 4.8 Hz) ppm.

Step 2. ([3-(methylsulfinyl)-3-(methylthio)cyclobutyl]oxymethyl)benzene.

2.5 M of n-butyllithium in hexane (19 mL) was added to a solution of (methylsulfinyl)(methylthio)methane (5.0 g, 0.040 mol) in THF (10 mL) dropwise at -10 °C

and the mixture was stirred for 3 h. To the resultant solution was added dropwise [2-bromo-1-(bromomethyl)ethoxy]methylbenzene (4.9 g, 0.016 mol) at -70 °C over 30 min. The mixture was stirred at this temperature for 3 h and then at rt over night. The reaction was diluted with dichloromethane and washed with water. The aqueous phases were extracted with dichloromethane. The organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated and purified with Combiflash (silica gel, 0-55% EtOAc/Hex) to give the desired product (2.4 g, 56%) as brown oil. LCMS (M+Na) 293.3. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (5H, m), 4.45 (2H, s), 4.33 (1H, m), 2.75 (2H, m), 2.65 (2H, m), 2.41 (3H, s), 2.12 (3H, s) ppm.

Step 3. 3-(benzyloxy)cyclobutanone.

([3-(methylsulfinyl)-3-(methylthio)cyclobutyl]oxymethyl)benzene (2.4 g, 0.0089 mol) was dissolved in Et_2O (40 mL) and 35% perchloric acid (1.8 mL) was added. The resulting mixture was stirred at rt overnight. To the reaction mixture was added solid $NaHCO_3$ and $MgSO_4$ and stirred for a while. The insoluble solid was filtered off. The filtrate was concentrated and purified with combiflash (silica gel, 100% dichloromethane) to give the desired product (0.7 g) as light yellow oil. LCMS calculated for $C_{11}H_{13}O_2(M+H)^+$: 177.1. Found: 177.3.

Step 4. [3-(benzyloxy)cyclobutylidene]acetonitrile.

To a mixture of 1.0000 M of potassium tert-butoxide in tetrahydrofuran (0.68 mL) and THF (5 mL) was added, at 0 °C, diethyl cyanomethylphosphonate (0.11 mL, 0.00068 mol) dropwise. The reaction was warmed to rt and 30 min later cooled to 0 °C again. To the reaction mixture was added a solution of 3-(benzyloxy)cyclobutanone (0.1 g, 0.0006 mol) in THF (5 mL). The reaction was stirred over night, allowing warmed up to rt. The reaction was quenched with saturated aq. NH_4Cl solution, extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The crude product was used directly in next step without further purification.

Step 5. 3-(benzyloxy)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

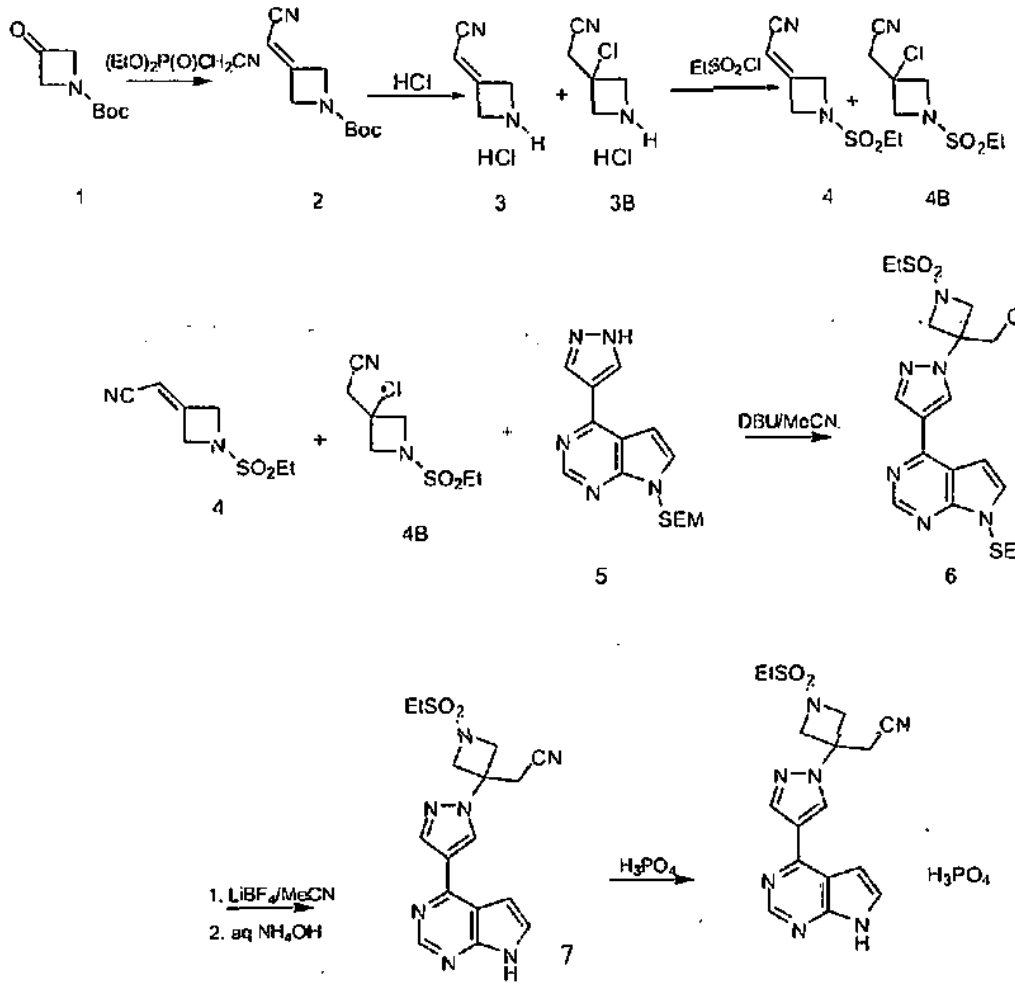
To a mixture of [3-(benzyloxy)cyclobutylidene]acetonitrile (0.1 g, 0.0005 mol) and 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidine (0.1 g,

0.0003 mol) in acetonitrile (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.05 mL, 0.0003 mol) under nitrogen. The mixture was heated at 50 °C overnight, then concentrated under reduced pressure. The residue was purified with combiflash (silica gel, 0-55% EtOAc/Hex) to give the desired product as cis- and trans-isomer mixture. LCMS calculated for $C_{28}H_{35}N_6O_2Si(M+H)^+$: 515.3 Found: 515.4.

Step 6. 3-(benzyloxy)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile.

3-(Benzyloxy)-1-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutylacetonitrile (0.024 g, 0.000046 mol) was treated with trifluoroacetic acid (0.5 mL, 0.006 mol) at rt for 30 min, then evaporated to dry. The residue was dissolved in MeOH (1 mL) and treated with ethylenediamine (0.2 mL, 0.003 mol) at rt for 2 h. The reaction mixture was concentrated in vacuo and the resulting residue purified on prep. HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give 2 isomers of the desired products. First peak retention time 1.406 min; LCMS calculated for $C_{22}H_{21}N_6O(M+H)^+$: 385.2; Found: 385.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.10 (1H, br s), 8.71 (1H, s), 8.67 (1H, s), 8.38 (1H, s), 7.58 (1H, d, J = 3.6 Hz), 7.33 (4H, m), 7.29 (1H, m), 7.05 (1H, d, J = 3.6 Hz), 4.43 (2H, s), 4.23 (1H, m), 3.43 (2H, s), 2.78 (2H, m), 2.74 (2H, m) ppm. Second peak retention time 1.474 min, LCMS calculated for $C_{22}H_{21}N_6O(M+H)^+$: 385.2; Found: 385.3. ^1H NMR (400 MHz, DMSO-d_6): δ 12.10 (1H, br s), 8.79 (1H, s), 8.67 (1H, s), 8.39 (1H, s), 7.59 (1H, d, J = 3.6 Hz), 7.34 (4H, m), 7.29 (1H, m), 7.06 (1H, d, J = 3.6 Hz), 4.44 (2H, s), 4.14 (1H, m), 3.44 (2H, s), 3.16 (2H, m), 2.44 (2H, m) ppm.

Example 61. Large scale preparation of {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile phosphoric acid salt



Step. 1 tert-Butyl 3-(cyanomethylene)azetidine-1-carboxylate (2).

Diethyl cyanomethyl phosphonate (745 g, 4.20 mol, 1.20 eqiv) and anhydrous THF (9 L) was added to a four-neck flask equipped with thermowell, addition funnel and nitrogen protection tube. The solution was cooled with an ice-methanol bath to -14 °C and a 1.0 M solution of *t*-BuOK in THF (3.85 L, 3.85 mol, 1.1 equiv) was added over 20 min keeping the temperature <-5 °C. The mixture was stirred for 3 hr at -10 °C and a solution of 1-*tert*-butoxycarbonyl-3-azetidinone (1, 600 g, 3.50 mol) in THF (2 L) was added over 2 hr while keeping the reaction temperature < -5 °C. The reaction mixture was stirred at -5 to -10 °C over 1 hr and then slowly warmed up to room temperature and stirred at room temperature for overnight. The reaction mixture was then diluted with water (4.5 L) and saturated brine (4.5 L) and extracted with ethyl acetate (2 x 9 L). The combined organic layers were combined and washed with brine (6 L), dried over anhydrous Na_2SO_4. The organic solvent was

removed under reduced pressure, diluted with dichloromethane (4 L) and adsorbed onto silica gel (1.5 kg). The product was purified by flash column chromatography (SiO_2, 3.5 kg × 2), each column was eluted with (8 L of heptane, 8 L of 5% AcOEt/heptane, 12 L of 10% AcOEt/heptane, 40 L of 25% AcOEt/heptane) to give the pure *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (2, 414.7 g, 679.8 g theoretical, 61% yield) as white solid. For 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 4.62 (m, 2H), 4.72 (m, 2H), 5.41 (m, 1H).

Step 2. 2-(1-(Ethylsulfonyl)azetidin-3-ylidene)acetonitrile (4).

tert-Butyl 3-(cyanomethylene)azetidine-1-carboxylate (2, 1000 g, 5.2 mol) was diluted with acetonitrile (7 L) and 3 N aqueous HCl (7 L). This resulting reaction mixture was stirred at room temperature for 18 h. When TLC showed the reaction was deemed complete, the reaction mixture was concentrated under reduced pressure. The residual solids were then suspended in acetonitrile (12 L) and cooled to 5°C. Diisopropyethyl amine (2.7 L, 15. 6 mol, 3 equiv) was slowly added to the suspension while keeping the temperature < 15°C. The homogeneous solution was allowed to cool to 5°C and ethanesulfonyl chloride (730 mL, 7.73 mol, 1.5 equiv) was added over 1 h while keeping the reaction temperature < 15°C. The resulting solution was allowed to slowly warm to room temperature and stirred at room temperature for overnight. The additional amount of ethanesulfonyl chloride (100 ml, 1.05 mol, 0.2 equiv) was added and the reaction mixture was stirred for an additional 2 h at room temperature. After the reaction was deemed complete, the reaction mixture was concentrated under reduced pressure to a volume of about 4 L. This solution was then placed in a 50 L separatory funnel, diluted with dichloromethane (10 L) and washed with half saturated brine (10 L). The aqueous phase was extracted with dichloromethane (5 L). The combined organic layers were dried over sodium sulphate and absorbed onto silica gel (1 Kg) under reduced pressure. The material was then loaded onto a silica gel column (2.5 Kg) and eluted with 20 % ethyl acetate in heptane (40 L), 40 % ethyl acetate in heptane (80 L) and finally 60 % ethyl acetate in heptane (40 L) to afford pure 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (4, 567 g, 968.4 g theoretical, 58.6 % yield) as a off-white solid. For 4: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H), 3.05 (q, 2H), 4.72 (m, 2H), 4.79 (m, 2H), 5.41 (m, 1H); MS: *m/z* calcd. 187.05; found: 187.1.

Step 3. 2-(1-(Ethylsulfonyl)azetidin-3-ylidene)acetonitrile (4) and 2-(3-chloro-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (4B).

tert-Butyl 3-(cyanomethylene)azetidine-1-carboxylate (2, 82 g, 0.42 mol) was added to THF (850 mL) and the resulting solution was cooled to 0°C before a 4 M HCl solution in 1,4-dioxane (850 mL, 3.38 mol, 8.0 equiv) was added over 1 h while keeping the temperature < 5°C. The resulting reaction mixture was slowly warmed to room temperature and stirred at room temperature for 18 h. When the reaction was deemed complete, the reaction mixture was concentrated under reduced pressure and the residue was placed under high vacuum for an additional 3 h before being treated with THF (900 mL) and diisopropylethylamine (183 mL, 1.06 mol, 2.5 equiv) at room temperature. The resulting solution was then cooled to 0°C and ethanesulfonyl chloride (56 mL, 0.59 mol, 1.4 equiv) was added while keeping the reaction temperature < 5°C. The ice bath was removed and the reaction was stirred at room temperature for 18 h. When TLC indicated the reaction was complete, the reaction mixture was diluted with ethyl acetate (1 L) and washed with saturated brine (1 L). The aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure. The residue was diluted with dichloromethane and absorbed onto silica gel (150 g). This mixture was purified by column chromatography (1.5 Kg silica gel) eluting with heptane (4 L), 10 % EtOAc in heptane (4 L), 20 % EtOAc in heptane (8L), 30 % EtOAc in heptane (12 L), and finally with 40 % EtOAc in heptane (12 L) to afford 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (4) and 2-(3-chloro-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (4B) as a off-white solid (58.1 g, 68% yield), which was found to be an approximately one to one mixture of compound **4** and **4B**. For **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H), 3.05 (q, 2H), 4.72 (m, 2H), 4.79 (m, 2H), 5.41 (m, 1H); MS: *m/z* calcd. 187.05; found: 187.1. For **4B**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H), 3.05 (q, 2H), 3.1 (s, 2H), 4.15 (d, 2H), 4.37 (d, 2H); MS: *m/z* calcd. 222.9; found: 222.9.

Step 4. 2-(1-(Ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitrile (6).

To a solution of 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (4) and 2-(3-chloro-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (4B) obtained from the previous reaction as an approximate one to one mixture (4 and 4B, 184 g, 919 mmol, 1.2 equiv) and 4-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5, 241 g,

766 mmol) in acetonitrile (6 L) was added DBU (137 mL, 919 mmol, 1.2 equiv) dropwise over 30 min at room temperature. The resulting reaction mixture was stirred overnight at room temperature. When the reaction was deemed complete, the solvent was removed under reduced pressure. The resulting solid was dissolved in 6 L of ethyl acetate and 2 L of acetonitrile at 40°C and the solution was washed with a mixture of brine (3 L) and water (1 L). The aqueous layer was extracted with ethyl acetate (3 x 1.6 L). The combined organic layers were washed with brine (1.6 L) and the solvent was removed under reduced pressure. Toluene (2 L) was added to the residue and the azeotropic distillation was repeated under reduced pressure. The residue was triturated with MTBE (1.5 L, methyl t-butyl ether) and the solids were collected by filtration. The brown solid was dissolved completely in ethyl acetate (3 L) at 50°C before the solution was treated with charcoal (30 g) and silica gel (30 g). The resulting mixture was stirred at 45 °C for 1 h before being filtered hot through celite. The solvent was removed under reduced pressure and the residue was triturated with MTBE (3 L). The solids were collected by filtration and washed with MTBE (1 L). The solids were then completely dissolved in isopropanol (8.8 L) at 70°C, and the resulting solution was gradually cooled down to room temperature with stirring for overnight. The solids were collected by filtration, washed with isopropanol (1.3 L) and heptane (2 x 490 mL), and dried in an oven overnight to afford 2-(1-(ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (6, 327 g, 384.3 g theoretical, 85% yield) as an off-white solid. For 6: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.99 (m, 2H), 1.49 (t, 3H), 3.15 (q, 2H), 3.49 (s, 2H), 3.60 (m, 2H), 4.30 (d, 2H), 4.70 (d, 2H), 5.76 (s, 2 H), 6.83 (s, 1H), 7.50 (s, 1H), 8.40 (s, 1H), 8.50 (s, 1H), 8.90 (s, 1H); MS: *m/z* calcd. 502.20; found: 502.3

Step 5. 2-(3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (7).

To a solution of 2-(1-(ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (6, 327 g, 655 mmol) in acetonitrile (3 L) and water (300 mL) was added $LiBF_4$ (614 g, 6.55 mol, 10.0 equiv). The resulting reaction mixture was stirred at 75°C for overnight. The reaction mixture was cooled to 0°C before a solution of ammonium hydroxide (NH_4OH, 570 mL) in water (2.2 L) was added slowly to keep the temperature below 10°C (pH 9-10). The mixture was stirred at room temperature for overnight. When the reaction was deemed complete, water (10 L)

was added and the resulting mixture was vigorously stirred for 3 h at room temperature. The solids were collected by filtration, washed with water (6.7 L) and heptane (6.7 L), and dried in vacuum oven at 45°C over the weekend. The dried solid was then dissolved in 20 % MeOH in dichloromethane (12 L), and was purified by column chromatography on 1.3 Kg of silica gel eluting with a 20 % MeOH in dichloromethane solution (18L) to afford 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (7, 204 g, 243.3 g theoretical, 83.8% yield) as an off-white solid. For 7: ^{1}H NMR (300 MHz, *d6*-DMSO) δ 1.25 (t, 3H), 3.25 (q, 2H), 3.75 (s, 2H), 4.25 (d, 2H), 4.65 (d, 2H), 7.10 (d, 1H), 7.65 (dd, 1H), 8.50 (s, 1H), 8.70 (s, 1H), 8.95 (s, 1H), 12.2 (bs, 1H); MS: *m/z* calcd. 372.12; found: 372.0.

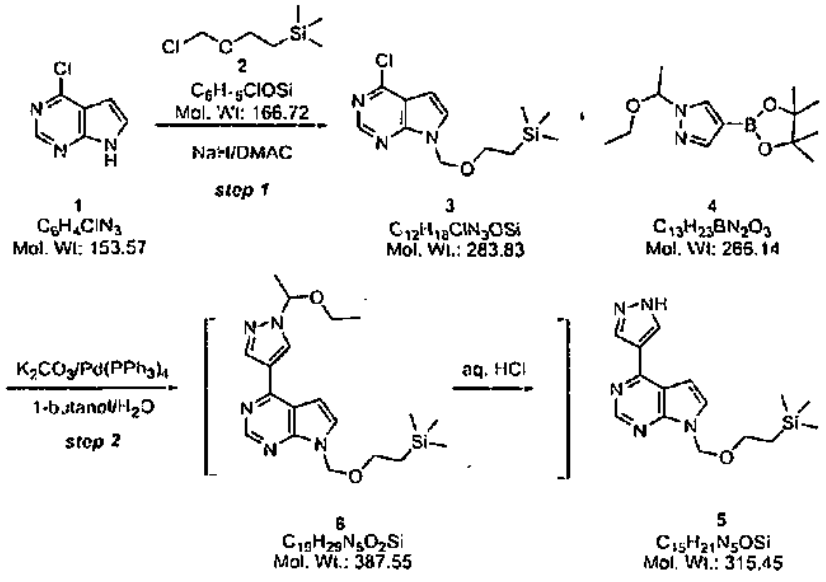
Step 6. 2-(3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile phosphoric acid salt.

To a solution of 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (7, 204 g, 550 mmol) in acetonitrile (5.1 L) and ethanol (1.6 L) was added a solution of phosphoric acid (67.4 g, 688 mmol, 1.25 equiv) in ethanol (800 mL) slowly over 30 min at 70°C. The resulting reaction mixture was stirred at 70°C for 2 h before being gradually cooled to room temperature with stirring for overnight. The solids were collected by filtration, washed with acetonitrile (160 mL) and dried in vacuum oven at 45°C for 6 h to afford 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile phosphoric acid salt (240 g, 258.2 g theoretical, 93% yield) as a white solid. For final product: ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.25 (t, 3H), 3.25 (q, 2H), 3.75 (s, 2H), 4.20 (d, 2H), 4.61 (d, 2H), 7.10 (d, 1H), 7.60 (dd, 1H), 8.50 (s, 1H), 8.70 (s, 1H), 8.95 (s, 1H), 12.2 (bs, 1H); MS: *m/z* calcd. 372.12; found: 372.0.

Example 62. 4-Chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3).

To a flask equipped with a nitrogen inlet, an addition funnel, a thermowell, and the mechanical stirrer was added 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (1, 600 g, 3.91 mol) and *N*,*N*-dimethylacetimide (DMAC, 9.6 L) at room temperature. The mixture was cooled to 0 - 5 °C in an ice/brine bath before solid sodium hydride (NaH, 60 wt%, 174 g, 4.35 mol, 1.1 equiv) was added in portions at 0 - 5 °C. The reaction mixture went to a dark solution during

15 minutes. Trimethylsilylethoxymethyl chloride (2, SEM-Cl, 763 mL, 4.31 mol, 1.1 equiv) was then added slowly via an addition funnel at a rate that the internal reaction temperature did not exceed 5 °C. The reaction mixture was then stirred at 0 - 5 °C for 30 minutes. When the reaction was deemed complete determined by TLC and HPLC, the reaction mixture was quenched by water (1 L). The mixture was then diluted with water (12 L) and MTBE (8 L). The two layers were separated and the aqueous layer was extracted with MTBE (8 L). The combined organic layers were washed with water (2 x 4 L) and brine (4 L) and dried over sodium sulfate (Na_2SO_4). The solvents were removed under reduced pressure. The residue was then dissolved in heptane (2 L), filtered and loaded onto a silica gel (SiO_2, 3.5 Kg) column eluting with heptane (6 L), 95% heptane/ethyl acetate (12 L), 90% heptane/ethyl acetate (10 L), and finally 80% heptane/ethyl acetate (10 L). The fractions containing the pure desired product were combined and concentrated under reduced pressure to give 4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3, 987 g, 1109.8 g theoretical, 88.9% yield) as a pale yellow oil which partially solidified to an oily solid on standing at room temperature. For 3: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.67 (s, 1H), 7.87 (d, 1H, J = 3.8 Hz), 6.71 (d, 1H, J = 3.6 Hz), 5.63 (s, 2H), 3.50 (t, 2H, J = 7.9 Hz), 0.80 (t, 2H, J = 8.1 Hz), 1.24 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 151.3, 150.8, 150.7, 131.5, 116.9, 99.3, 72.9, 65.8, 17.1, -1.48 ppm; $C_{12}H_{18}ClN_3OSi$ (MW 283.83), LCMS (EI) *m/e* 284/286 (M^+ + 1).



Example 63. 4-(1*H*-Pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5).

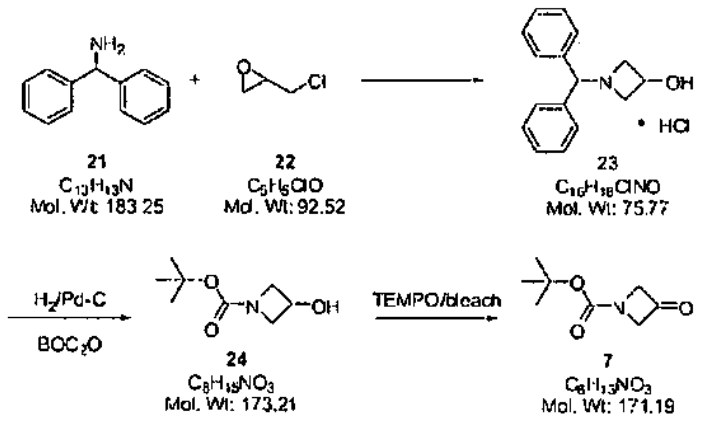
To a reactor equipped with the overhead stirrer, a condenser, a thermowell, and a nitrogen inlet was charged water (H_2O, 9.0 L), solid potassium carbonate (K_2CO_3, 4461 g, 32.28 mol, 2.42 equiv), 4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3, 3597 g, 12.67 mol), 1-(1-ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (4, 3550 g, 13.34 mol, 1.05 equiv), and 1-butanol (27 L) at room temperature. The resulting reaction mixture was degassed three times backfilling with nitrogen each time before being treated with tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 46 g, 0.040 mol, 0.003 equiv) at room temperature. The resulting reaction mixture was heated to gentle reflux (about 90 °C) for 1 - 4 hours. When the reaction was deemed complete determined by HPLC, the reaction mixture was gradually cooled down to room temperature before being filtered through a Celite bed. The Celite bed was washed with ethyl acetate (2 x 2 L) before the filtrates and washing solution were combined. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (12 L). The combined organic layers were concentrated under reduced pressure to remove solvents, and the crude 4-(1-(1-ethoxyethyl)-1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (6) was directly charged back to the reactor with tetrahydrofuran (THF, 4.2 L) for the subsequent acid-promoted de-protection reaction without further purification.

To a suspension of crude 4-(1-(1-ethoxyethyl)-1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (6), made as described above, in tetrahydrofuran (THF, 4.2 L) in the reactor was charged water (H_2O, 20.8 L), and a 10% aqueous HCl solution (16.2 L, 45.89 mol, 3.44 equiv) at room temperature. The resulting reaction mixture was stirred at 16 – 30 °C for 2 – 5 h. When the reaction was deemed complete by HPLC analysis, the reaction mixture was treated with a 30% aqueous sodium hydroxide (NaOH) solution (4 L, 50.42 mol, 3.78 equiv) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 – 2 h. The solids were collected by filtration and washed with water (2 x 5 L). The wet cake was charged back to the reactor with acetonitrile (21.6 L), and resulting suspension was heated to gentle reflux for 1 – 2 h. The clear solution was then gradually cooled down to room temperature with stirring, and solids were precipitated out from the solution with cooling. The mixture was stirred at room temperature for an additional 1 – 2 h. The solids were collected by filtration, washed with acetonitrile (2 x 3.5 L), and dried in oven under reduced pressure at 45 – 55 °C to constant

weight to afford 4-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5, 3281.7 g, 3996.8 g theoretical, 82.1% yield) as white crystalline solids (99.5 area% by HPLC). For 5: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.41 (br. s, 1H), 8.74 (s, 1H), 8.67 (br. s, 1H), 8.35 (br. s, 1H), 7.72 (d, 1H, J = 3.7 Hz), 7.10 (d, 1H, J = 3.7 Hz), 5.61 (s, 2H), 3.51 (t, 2H, J = 8.2 Hz), 0.81 (t, 2H, J = 8.2 Hz), 0.13 (s, 9H) ppm; $C_{15}H_{21}N_5OSi$ (MW, 315.45), LCMS (EI) *m/e* 316 (M^+ + H).

Example 64. 1-Benzhydrylazetidin-3-ol hydrochloride (23).

A solution of diphenylmethanamine (21, 2737 g, 15.0 mol, 1.04 equiv) in methanol (MeOH, 6 L) was treated with 2-(chloromethyl)oxirane (22, 1330 g, 14.5 mol) from an addition funnel at room temperature. During the initial addition a slight endotherm was noticed. The resulting reaction mixture was stirred at room temperature for 3 days before being warmed to reflux for an additional 3 days. When TLC showed that the reaction was deemed complete, the reaction mixture was first cooled down to room temperature and then to 0 - 5 °C in an ice bath. The solids were collected by filtration and washed with acetone (4 L) to give the first crop of the crude desired product (23, 1516 g).The filtrate was concentrated under reduced pressure and the resulting semisolid was diluted with acetone (1 L). This solid was then collected by filtration to give the second crop of the crude desired product (23, 221 g). The crude product, 1-benzhydrylazetidin-3-ol hydrochloride (23, 1737 g, 3998.7 g theoretical, 43.4 % yield), was found to be sufficiently pure to be used in the subsequent reaction without further purification. For 23: ^{1}HNMR (DMSO-d_6, 300 MHz), δ 12.28 (br. d, 1H), 7.7 (m, 5H), 7.49 (m, 5H), 6.38 (d, 1H), 4.72 (br. s, 1H), 4.46 (m, 1H), 4.12 (m, 2H), 3.85 (m, 2H) ppm; $C_{16}H_{18}ClNO$ (free base of 23, $C_{16}H_{17}NO$ MW, 239.31), LCMS (EI) *m/e* 240 (M^+ + H).



Example 65. ***tert*-Butyl 3-hydroxyazetidine-1-carboxylate (24).**

A suspension of 1-benzhydrylazetidin-3-ol hydrochloride (**23**, 625 g, 2.27 mol) in a 10 % solution of aqueous sodium carbonate (Na_2CO_3, 5 L) and dichloromethane (CH_2Cl_2, 5 L) was stirred at room temperature until all solids were dissolved. The two layers were separated, and the aqueous layer was extracted with dichloromethane (CH_2Cl_2, 2 L). The combined organics extracts were dried over sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. This resulting crude free base of **23** was then dissolved in THF (6 L) and the solution was placed into a large Parr bomb. Di-*tert*-butyl dicarbonate (BOC_2O, 545 g, 2.5 mol, 1.1 equiv) and 20 % palladium (Pd) on carbon (125 g, 50 % wet) were added to the Parr bomb. The vessel was charged to 30 psi with hydrogen gas (H_2) and stirred under steady hydrogen atmosphere (vessel was recharged three times to maintain the pressure at 30 psi) at room temperature for 18 h. When HPLC showed that the reaction was complete (when no more hydrogen was taken up), the reaction mixture was filtered through a Celite pad and the Celite pad was washed with THF (4 L). The filtrates were concentrated under reduced pressure to remove the solvent and the residue was loaded onto a Biotage 150 column with a minimum amount of dichloromethane (CH_2Cl_2). The column was eluted with 20 – 50 % ethyl acetate in heptane and the fractions containing the pure desired product (**24**) were collected and combined. The solvents were removed under reduced pressure to afford *tert*-butyl 3-hydroxyazetidine-1-carboxylate (**24**, 357 g, 393.2 g theoretical, 90.8% yield) as colorless oil, which solidified upon standing at room temperature in vacuum. For **24**: ^{1}HNMR ($CDCl_3$, 300 MHz), δ 4.56 (m 1H), 4.13 (m, 2H), 3.81 (m, 2H), 1.43 (s, 9H) ppm.

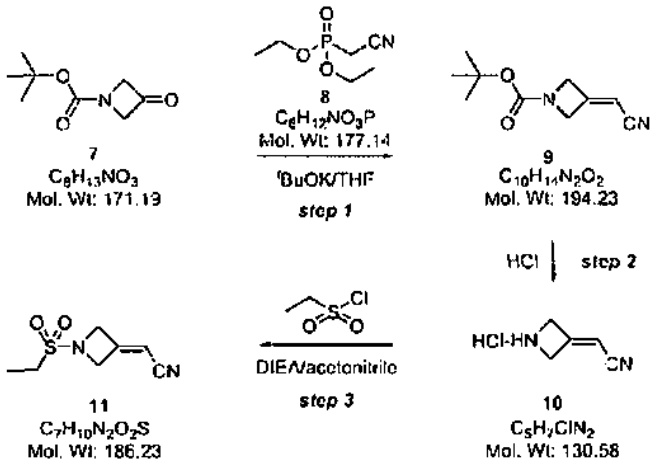
Example 66. ***tert*-Butyl 3-oxoazetidine-1-carboxylate (7).**

A solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (**24**, 50 g, 289 mmol) in ethyl acetate (400 mL) was cooled to 0 °C. The resulting solution was then treated with solid TEMPO (0.5 g, 3.2 mmol, 0.011 equiv) and a solution of potassium bromide (KBr, 3.9 g, 33.2 mmol, 0.115 equiv) in water (60 mL) at 0 – 5 °C. While keeping the reaction temperature between 0 - 5 °C a solution of saturated aqueous sodium bicarbonate ($NaHCO_3$, 450 mL) and an aqueous sodium hypochlorite solution (NaClO, 10 - 13 % available chlorine, 450 mL) were added. Once the solution of sodium hypochlorite was added, the color of the reaction mixture was changed immediately. When additional amount of sodium hypochlorite solution was added, the color of the reaction mixture was gradually faded. When TLC showed that all of the starting material was consumed, the color of the reaction mixture was

no longer changed. The reaction mixture was then diluted with ethyl acetate (EtOAc, 500 mL) and two layers were separated. The organic layer was washed with water (500 mL) and the saturated aqueous sodium chloride solution (500 mL) and dried over sodium sulfate (Na_2SO_4). The solvent was then removed under reduced pressure to give the crude product, *tert*-butyl 3-oxoazetidine-1-carbcxylate (7, 48 g, 49.47 g theoretical, 97% yield), which was found to be sufficiently pure and was used directly in the subsequent reaction without further purification. For crude 7: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 4.65 (s, 4H), 1.42 (s, 9H) ppm.

Example 67. ***tert*-Butyl 3-(cyanomethylene)azetidine-1-carboxylate (9).**

Diethyl cyanomethyl phosphonate (8, 745 g, 4.20 mol, 1.20 equiv) and anhydrous tetrahydrofuran (THF, 9 L) was added to a four-neck flask equipped with a thermowell, an addition funnel and the nitrogen protection tube at room temperature. The solution was cooled with an ice-methanol bath to -14 °C and a 1.0 M solution of potassium *tert*-butoxide (*t*-BuOK) in anhydrous tetrahydrofuran (THF, 3.85 L, 3.85 mol, 1.1 equiv) was added over 20 min while keeping the reaction temperature below -5 °C. The resulting reaction mixture was stirred for 3 h at -10 °C and a solution of 1-*tert*-butoxycarbonyl-3-azetidinone (7, 600 g, 3.50 mol) in anhydrous tetrahydrofuran (THF, 2 L) was added over 2 h while keeping the internal temperature below -5 °C. The reaction mixture was stirred at -5 to -10 °C over 1 h and then slowly warmed up to room temperature and stirred at room temperature for overnight. The reaction mixture was then diluted with water (4.5 L) and saturated aqueous sodium chloride solution (NaCl, 4.5 L) and extracted with ethyl acetate (EtOAc, 2 x 9 L). The combined organic layers were washed with brine (6 L) and dried over anhydrous sodium sulfate (Na_2SO_4). The organic solvent was removed under reduced pressure and the residue was diluted with dichloromethane (CH_2Cl_2, 4 L) before being absorbed onto silica gel (SiO_2, 1.5 Kg). The crude product, which was absorbed on silica gel, was purified by flash column chromatography (SiO_2, 3.5 Kg, 0 – 25% EtOAc/hexanes gradient elution) to afford *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (9, 414.7 g, 679.8 g theoretical, 61% yield) as white solid. For 9: ^{1}H NMR ($CDCl_3$, 300MHz), δ 5.40 (m, 1H), 4.70 (m, 2H), 4.61 (m, 2H), 1.46 (s, 9H) ppm; $C_{10}H_{14}N_2O_2$ (MW, 194.23), LCMS (EI) *m/e* 217 (M^+ + Na).



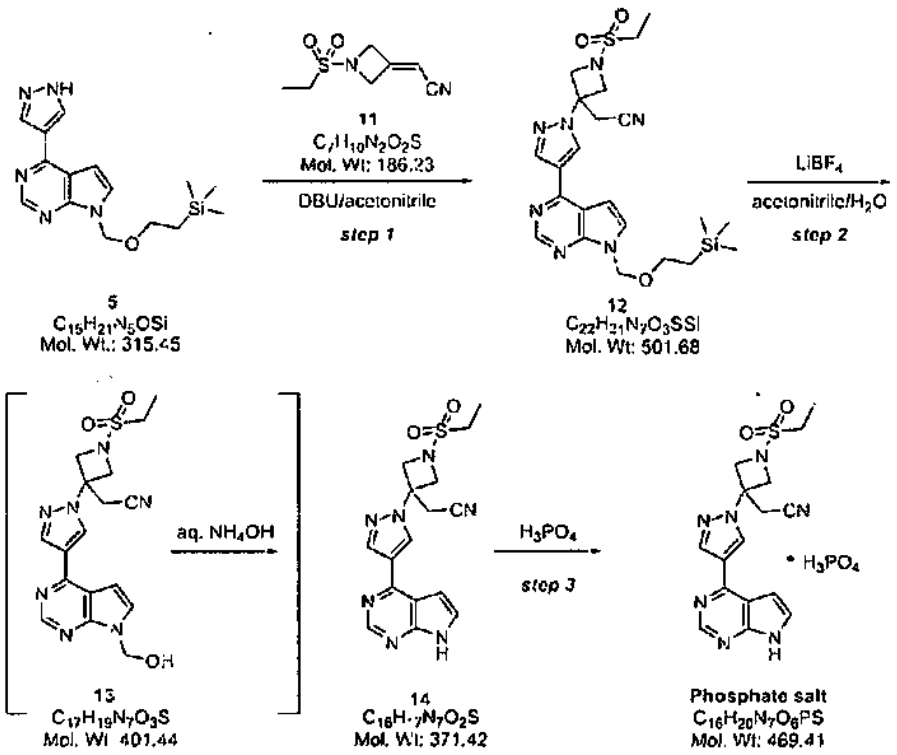
Example 68. 2-(1-(Ethylsulfonyl)azetidin-3-ylidene)acetonitrile (11).

A solution of *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (9, 1000g, 5.2 mol) in acetonitrile (7 L) and a 3 N aqueous HCl solution (7 L) was stirred at room temperature for 18 h. When HPLC showed that all the starting material (9) was consumed, the reaction mixture was concentrated under reduced pressure to dryness. The residue, which contains the crude desired deprotection product (10), was then suspended in acetonitrile (12 L) and the resulting suspension was cooled to 0 - 5 °C. Diisopropyethylamine (DIEA, 3.14 L, 18.03 mol, 3.5 equiv) was then slowly added while keeping the internal temperature below 5 °C. The resulting homogeneous solution was allowed to cool down to 0 °C and ethane sulfonyl chloride ($EtSO_2Cl$, 730 mL, 7.73 mol, 1.5 equiv) was added over 1 h while keeping the internal temperature below 5 °C. The resulting reaction mixture was allowed to gradually warm to room temperature and stirred at room temperature for overnight. When HPLC showed that the reaction was complete, the reaction mixture was concentrated under reduced pressure to a volume of approximately 2 L. The bath temperature of the rotary evaporator is set to not exceed 45 °C. The concentrated residue was then diluted with dichloromethane (CH_2Cl_2, 10 L) and the resulting dichloromethane solution was washed with aqueous sodium chloride solution (10 L). The aqueous phase was back extracted with dichloromethane (CH_2Cl_2, 5 L). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4) and the residue was absorbed onto silica gel (SiO_2, 1 Kg) under reduced pressure. The bath temperature of the rotary evaporator was set to not exceed 45 °C. The material was then loaded onto a silica gel column (SiO_2, 2.5 Kg) and eluted with 20 – 60 % ethyl acetate in heptane to afford 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (11, 882 g, 968.4 g theoretical, 91 % yield) as off-white solids. For 11: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.46 (m,

1H), 4.77 (m, 2H), 4.70 (m, 2H), 3.05 (q, 2H), 1.39 (t, 3H) ppm; $C_7H_{10}N_2O_2S$ (MW, 186.23), LCMS (EI) *m/e* 187 ($M^+ + H$).

Example 69. 2-(1-(Ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (12).

Method A. To a suspension of 4-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5, 440 g, 1.395 mol) and 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (11, 312.4 g, 1.68 mol, 1.2 equiv) in acetonitrile (4.4 L) was added DBU (249.8 mL, 1.67 mol, 1.2 equiv) drop wise to keep the reaction temperature between 15 – 25 °C. After adding DBU, the reaction mixture became homogeneous, but a precipitate appeared in 30 min. The reaction mixture was stirred for 3 h at room temperature. When HPLC showed that the reaction was deemed complete, the reaction mixture was quenched with water (11 L). The resulting mixture was stirred at room temperature for additional 30 min and then filtered. The solid cake was washed with water (4 L), MTBE (2 L) and dried in vacuum oven at 35 °C for 24 h to afford crude 2-(1-(ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (12, 681 g, 699.8 g theoretical, 97.3 % yield) as white solids, which was found to be sufficiently pure for the subsequent reaction without further purification. For 12: ^{1}HNMR ($CDCl_3$, 300 MHz), δ 8.86 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 7.43 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.65 (d, 2H), 4.27 (d, 2H), 3.55 (s, 2H), 3.4 (t, 2H), 3.07 (m, 2H), 1.42 (m, 3H), 0.92 (m, 2H), -0.05 (s, 9H) ppm; $C_{22}H_{31}N_7O_3SSi$ (MW, 501.68), LCMS (EI) *m/e* 502 ($M^+ + H$).



Example 70. 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14).

Method A. To a solution of 2-(1-(ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (**12**, 400 g, 797 mmol) in acetonitrile (3.6 L) and water (360 mL) was added solid lithium tetrafluoroborate ($LiBF_4$, 747.5 g, 7.97 mol, 10.0 equiv) at room temperature. The resulting reaction mixture was warmed to 80 °C and stirred at 80 °C for overnight. When HPLC showed the first stage of deprotection was complete, which afforded the corresponding hydroxymethyl intermediate **13**, the reaction mixture was cooled down to room temperature gradually and subsequently to 0 °C. A solution of ammonium hydroxide (28 – 30% aqueous NH_4OH, 680 mL) in water (2.7 L) was added slowly to the reaction mixture to adjust pH to 9-10 while keeping the internal temperature below 10 °C. The resulting mixture was stirred at room temperature for overnight. When HPLC showed that the second stage of deprotection was complete, the reaction mixture was added into water (10 L), and the resulting mixture was vigorously stirred at room temperature for 3 h. The solids were collected by filtration, washed with water (8 L) and heptane (8 L), and dried in convection oven at 35 °C over the weekend. The dried solids were dissolved in 20 % MeOH in dichloromethane (16 L) before

being purified by column chromatography on 1.6 Kg of silica gel (SiO_2). The column was eluted with a 20 % MeOH in dichloromethane solution (CH_2Cl_2, 18 L) to give 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14, 239.5 g, 296.1 g theoretical, 80.9% yield) as off-white solids. For 14: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.15 (s, 1H), 8.94 (s, 1H), 8.72 (s, 1H), 8.49 (s, 1H), 7.63 (d, 1H), 7.09 (d, 1H), 4.62 (d, 2H), 4.25 (d, 2H), 3.71 (s, 2H), 3.24 (q, 2H), 1.26 (t, 3H) ppm; $C_{16}H_{17}N_7O_2S$ (MW, 371.42), LCMS (EI) *m/e* 372 (M^+ + H).

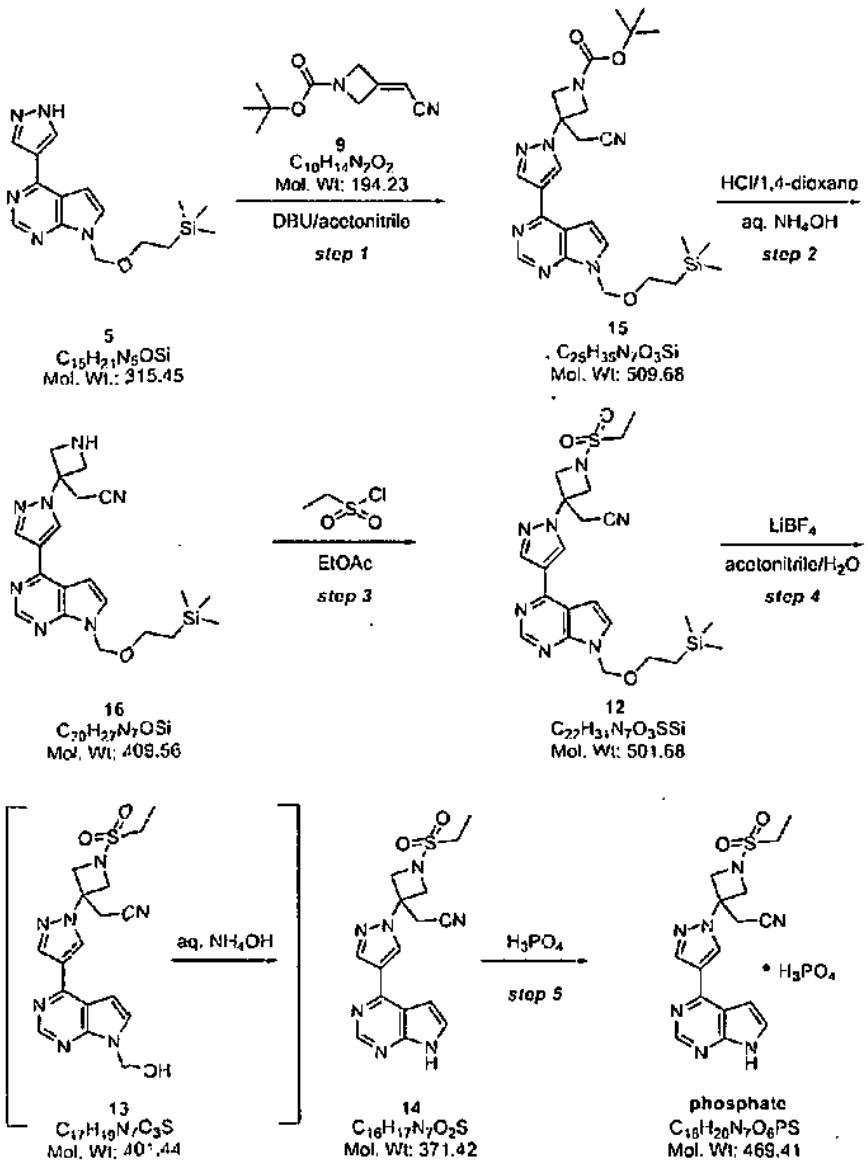
Example 71. 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile phosphate salt.

To a solution of 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14, 471.2 g, 1268.6 mmol) in acetonitrile (10.86 L) and ethanol (3.75 L) was added an 85 % aqueous solution of phosphoric acid (H_3PO_4, 191.6 g, 1661.7 mmol, 1.31 equiv) in ethanol (EtOH, 1.68 L) slowly over 50 min at 70 °C. The resulting reaction mixture was cooled down to room temperature slowly and stirred at room temperature for overnight. The solids were collected by filtration and washed with acetonitrile (500 mL). The resulting wet cake was then suspended in ethanol (EtOH, 7.0 L) before being treated with an aqueous 85 % solution of phosphoric acid (H_3PO_4, 95.1 g, 824.6 mmol, 0.65 equiv) in ethanol (EtOH, 1.23 L) at room temperature. The resulting mixture was then warmed to reflux and stirred at reflux for 1 h before being cooled down to room temperature slowly and stirred at room temperature for overnight. The solids were collected by filtration, washed with ethanol (2 L) and heptane/ethanol (v/v 2/1, 2.1 L), and dried in vacuum oven at 40 °C for overnight to afford 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile phosphate salt (534.8 g, 595.5 g theoretical, 89.8% yield) as white crystalline solids. **For phosphate salt**: mp: 187 °C; elemental analysis for $C_{16}H_{20}N_7O_6PS$, Calcd: C, 40.94; H, 4.29; N, 20.89; P, 6.60; S, 6.83; Found: C, 40.65; H, 4.22; N, 20.71; P, 6.53; S, 6.95; FTIR (νmax, cm^{-1}): 3123 (-CH-), 2254 (CN), 1627 and 1441 (heteroaromatic C=N), 1600 and 1559 (heteroaromatic C=C), 1312 (-SO_2-); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.19 (s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.62 (dd, 1H, J = 3.5, 2.3 Hz), 7.08 (dd, 1H, J = 3.6, 1.5 Hz), 4.60 (d, 2H, J = 9.3, 9.2 Hz), 4.23 (d, 2H, J = 9.3, 9.2 Hz), 3.69 (s, 2H), 3.23 (q, 2H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.3 Hz) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.3, 150.9, 149.4, 140.0, 129.7, 127.1, 122.2,

116.8, 113.1, 100.1, 58.6, 56.1, 43.3, 26.9, 7.5 ppm; $C_{16}H_{17}N_7O_2S$ (free base, MW, 371.42), LCMS (EI) *m/e* 372 (M^+ + H).

Example 72. tert-Butyl 3-(cyanomethyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidine-1-carboxylate (15).

To a suspension of *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (**9**, 417.2 g, 2.15 mol, 1.05 equiv) and 4-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**5**, 645 g, 2.04 mol) in acetonitrile (4.9 L) was added DBU (30.5 mL, 0.204 mol, 0.1 equiv) drop wise at room temperature. The resulting reaction mixture was then stirred at room temperature for 3 h. After about 1 h, a clear, brown solution was obtained. When LCMS showed that no starting material remained, silica gel (SiO_2, 1 Kg) was added and the mixture was concentrated to dryness under reduced pressure. This material, which contains the crude desired product (**15**), was then loaded onto a pre-packed silica column (SiO_2, 2.5 Kg) and the column was eluted with 60 – 80% of ethyl acetate/heptane. The fractions containing the pure desired product (**15**) were combined and concentrated under reduced pressure to give the desired product as thick oil which was then stirred in heptane at room temperature until crystallization occurred. The solids were collected by filtration and washed with heptane to afford *tert*-butyl 3-(cyanomethyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidine-1-carboxylate (**15**, 1014.9 g, 1039.7 g theoretical, 97.6% yield) as white solids. For **15**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.93 (s, 1H), 8.77 (s, 1H), 8.47 (s, 1H), 7.80 (d, 1H, J = 3.8 Hz), 7.20 (d, 1H, J = 3.7 Hz), 5.63 (s, 2H), 4.50 (d, 2H, J = 9.3 Hz), 4.21 (d, 2H, J = 9.3 Hz), 3.66 (s, 2H), 3.52 (t, 2H, J = 7.8 Hz), 1.40 (s, 9H), 0.82 (t, 2H, J = 8.1 Hz), -0.12 (s, 9H) ppm; $C_{25}H_{35}N_7O_3Si$ (MW, 509.68), LCMS (EI) *m/e* 510 (M^+ + H) and 532 (M^+ + Na).



Example 73. 2-(3-(4-(7-((2-(Trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (16).

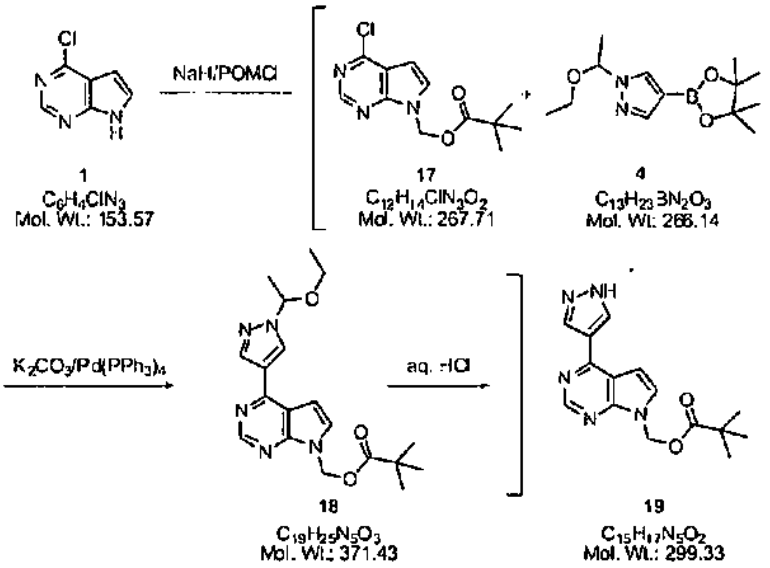
To a solution of *tert*-butyl 3-(cyanomethyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidine-1-carboxylate (15, 389.6 g, 0.765 mol) in dichloromethane (CH_2Cl_2, 7 L) was added a solution of hydrogen chloride (HCl) in dioxane (4 M, 1.15 L, 4.6 mol, 6.0 equiv) drop wise at room temperature. The resulting reaction mixture was stirred at room temperature for 48 h. When LCMS showed that all of the starting material had been consumed, the reaction mixture was transferred in portions to a 22 L separation funnel containing aqueous ammonium hydroxide (NH_4OH, about 4% v/v, 2.5 L). Gas was evolved but the funnel stayed

cool to the touch. Ice cubes were periodically added as a precaution. Once all of the reaction mixture was added, stirring was continued for about 15 min. The pH of the aqueous layer was found to be close to 11. The two layers were separated and the organic layer was washed with brine (2 L), dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure to a minimum volume. Heptane (about 3 L) was added to the residue and the resulting suspension was concentrated to dryness under reduced pressure to give crude 2-(3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (**16**, 268.2 g, 313.3 g theoretical, 85.6% yield) as an orange oil which was used directly for the subsequent reaction without further purification. For crude **16**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 7.47 (d, 1H), 6.87 (d, 1H), 5.74 (s, 2H), 4.36 (d, 2H), 3.95 (d, 2H), 3.77 (s, 2H), 3.62 (t, 2H), 1.9 (br. s, 1H), 0.99 (t, 2 H), 0.01 (s, 9H) ppm; $C_{20}H_{27}N_7OSi$ (MW, 409.56), LCMS (EI) *m/e* 410 (M^+ + H).

Example 75. 2-(1-(Ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (12).

Method B. To a solution of crude 2-(3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (**16**, 423.7 g, 1.03 mol) in ethyl acetate (EtOAc, 6.5 L) at 0 - 5 °C was added a solution of ethane sulfonyl chloride ($EtSO_2Cl$, 117 mL, 1.23 mol, 1.2 equiv) in ethyl acetate (110 mL) drop wise. The resulting reaction mixture was allowed to warm gradually to room temperature and stirred at room temperature for overnight. When LCMS analysis showed that no starting material remained and the reaction mixture was transferred to a 22 L separation funnel and washed with water (4 L), brine (2 L) and saturated aqueous sodium bicarbonate solution ($NaHCO_3$, 2 L). The combined aqueous layer was back extracted with ethyl acetate (EtOAc, 2 L). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified on silica gel eluted with dichloromethane/ethyl acetate (100/0 to 0/100). The fractions containing the pure desired product (**12**) were combined and concentrated under reduced pressure to a minimum volume before being treated with heptane at room temperature. The solids were collected by filtration and washed with heptane to afford 2-(1-(ethylsulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl)acetonitrile (**12**, 397 g, 516.7 g theoretical, 76.8% yield) as white solids, which was found

to be identical to the material prepared by method A in every comparable aspect . For **12**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 8.86 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 7.43 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.65 (d, 2H), 4.27 (d, 2H), 3.55 (s, 2H), 3.4 (t, 2H), 3.07 (m, 2H), 1.42 (m, 3H), 0.92 (m, 2H), -0.05 (s, 9H) ppm; $C_{22}H_{31}N_7O_3SSi$ (MW, 501.68), LCMS (EI) *m/e* 502 ($M^+ + H$).



Example 76. [4-(1*H*-Pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]methyl pivalate (19). To a oven dried 3 L 4-neck round bottom flask equipped with a stirring bar, a septa, a thermocouple, a 500 mL addition funnel and the nitrogen inlet was charged solid sodium hydride (NaH, 60 wt% in mineral oil, 32.82 g, 0.82 mol, 1.20 equiv) and anhydrous 1,2-dimethoxyethane (DME, 500 mL, 4.8 mol) and the resulting mixture was cooled to 0 - 3 °C. To a oven dried 1 L round bottom flask was charged 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**, 105.0 g, 0.684 mol) and 1,2-dimethoxyethane (DME, 750 mL, 7.2 mol) and the resulting slurry was then portion wise added to the suspension of sodium hydride in DME via large bore canula over 30 minutes at 5 – 12 °C. The resulting reaction mixture was heterogeneous. Following the addition, the cold bath was removed and the mixture was gradually warmed to room temperature and allowed to stir at room temperature for 1 hour before being cooled to 0 – 5 °C. Chloromethyl pivalate (pivaloyloxymethyl chloride, POM-Cl, 112 ml, 0.752 mol, 1.1 equiv) was then added drop wise into the reaction mixture over 30 minutes with stirring at 0 – 5 °C. The addition of chloromethyl pivalate was mildly exothermic and the reaction temperature went up to as high as 14 °C. After addition of chloromethyl pivalate, the cooling bath was removed and the reaction mixture was allowed to return to room temperature and

stirred at room temperature for 90 min. When the reaction was deemed complete after confirmed by HPLC, the reaction mixture was carefully quenched with water (100 mL) and this quenched reaction mixture, which contains crude POM-protected chlorodeazapurine (17), was used directly in the subsequent Suzuki coupling reaction without further work-up and purification.

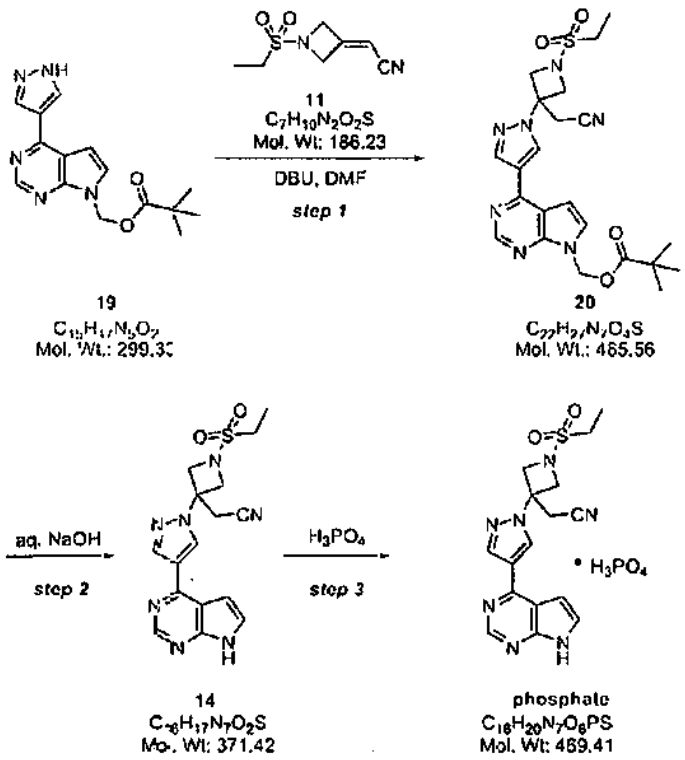
To the quenched reaction mixture, which contains crude POM-protected chlorodeazapurine (17) made as described above, was added 1-(1-ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) –1*H*-pyrazole (4, 200 g, 0.75 mol, 1.10 equiv) and solid potassium carbonate (K_2CO_3, 189 g, 1.37 mol, 2.0 equiv) at room temperature. The resulting mixture was degassed by passing a stream of nitrogen through the solution for 15 minutes before being treated with tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 7.9 g, 0.68 mmol, 0.01 equiv) and the resulting reaction mixture was heated at reflux (about 82 °C) for 10 hours. When the reaction was deemed complete by TLC (1:1 hexanes/ethyl acetate) and LCMS, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (2 L) and water (1 L). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (500 mL). The combined organic layers were washed with water (2 x 1 L) and brine (1 L) before being concentrated under reduced pressure to afford crude {4-[1-(1-ethoxyethyl)-1*H*-pyrazol-4-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]methyl pivalate (18) as a pale-yellow oil, which was directly used in the subsequent de-protection reaction without further purification.

A solution of crude 18 in THF (1 L, 12.3mol) was treated with a 4 N aqueous HCl solution (500 mL) at room temperature. The resulting reaction mixture was subsequently stirred at room temperature for 5 h. When the reaction was deemed complete, the reaction mixture was cooled to 0 – 5 °C before the pH was adjusted to 9 -10 with a 1 M aqueous sodium hydroxide (NaOH) solution (2 L). The mixture was then concentrated under reduced pressure to remove most of the THF and the resulting suspension was stirred at room temperature for 2 h. The solids were collected by filtration, washed with water (3 x 500 mL), and dried in vacuum oven to afford [4-(1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]methyl pivalate (19, 157.5 g, 204.43 g theoretical, 77% yield for three steps) as off-white solids, which was found to be sufficiently pure (> 98 area% by HPLC) to do the subsequent reaction without further purification. For 19: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.42 (br s, 1H), 8.76 (s, 1H), 8.67 (s, 1H), 8.33 (s, 1H), 7.68 (d, 1H, J = 3.8 Hz), 7.11 (d, 1H, J = 3.8 Hz), 6.21 (s, 2H), 1.06 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.74, 152.31,

152.09, 151.91, 139.52, 130.39, 120.51, 113.93, 101.91, 67.26, 38.98, 27.26 ppm; $C_{15}H_{17}N_5O_2$ (MW, 299.33), LCMS (EI) *m/e* 300 (M^+ + H).

Example 77. (4-(1-(3-(Cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl pivalate (20).

To a suspension of [4-(1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]methyl pivalate (19, 10.0 g, 33.4 mmol) and 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile (11, 6.22 g, 33.4 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (DMF, 20 mL) was added DBU (254 mg, 1.67 mmol, 0.05 equiv) drop wise to keep the reaction temperature between 15 – 25 °C. After adding DBU, the reaction mixture became homogeneous within 90 min. The reaction mixture was stirred for 3 h at room temperature. When HPLC showed that the reaction was deemed complete, the reaction mixture was quenched with water (120 mL) and acetonitrile (80 mL). The resulting mixture was stirred at room temperature for an additional 30 min. The solids were collected by filtration, washed with a mixture of acetonitrile and water (2/3 by volume, 2 x 20 mL), and dried in vacuum oven at 40 - 45 °C for 24 h to afford crude (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl pivalate (**20**, 14.5 g, 16.2 g theoretical, 89.5 % yield) as white solids, which was found to be sufficiently pure (> 98.0% by HPLC) for the subsequent reaction without further purification. For **20**: ^{1}HNMR ($CDCl_3$, 300 MHz), δ 8.87 (s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 7.51 (d, 1H, J = 3.6 Hz), 6.76 (d, 1H, J = 3.6 Hz), 6.26 (s, 2H), 4.64 (d, 2H, J = 9.6 Hz), 4.25 (d, 2H, J = 9.6 Hz), 3.41 (s, 2H), 3.09 (q, 2H, J = 7.6 Hz), 1.42 (t, 3H, J = 7.6 Hz), 1.17 (s, 9H) ppm; $C_{22}H_{27}N_7O_4S$ (MW, 485.56), LCMS (EI) *m/e* 486 (M^+ + H).



Example 78. 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14).

Method B. A suspension of (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl pivalate (**20**, 1.0 g, 2.06 mmol) in methanol (MeOH, 5 mL) and tetrahydrofuran (THF, 20 mL) was treated with a 1 M aqueous sodium hydroxide solution (NaOH, 2.3 mL, 2.3 mmol, 1.12 equiv) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 – 3 h. When HPLC showed that the reaction was deemed complete, the reaction mixture was quenched with water (10 mL) and a 1 N aqueous HCl solution (0.2 mL) to adjust pH to 7 – 7.5 at room temperature. The resulting mixture was stirred at room temperature for 30 min before the solids were collected by filtration. The solids were washed with a mixture of acetonitrile and water (2/3 by volume, 2 x 4 mL) and dried in vacuum at 40 - 45 °C for 24 h to afford crude 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14, 658 mg, 765 mg theoretical, 86% yield) as off-white solids, which was found to be identical to the material prepared by Method A. For crude 14: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.15 (s, 1H), 8.94 (s, 1H), 8.72 (s, 1H), 8.49 (s, 1H), 7.63 (d, 1H), 7.09 (d,

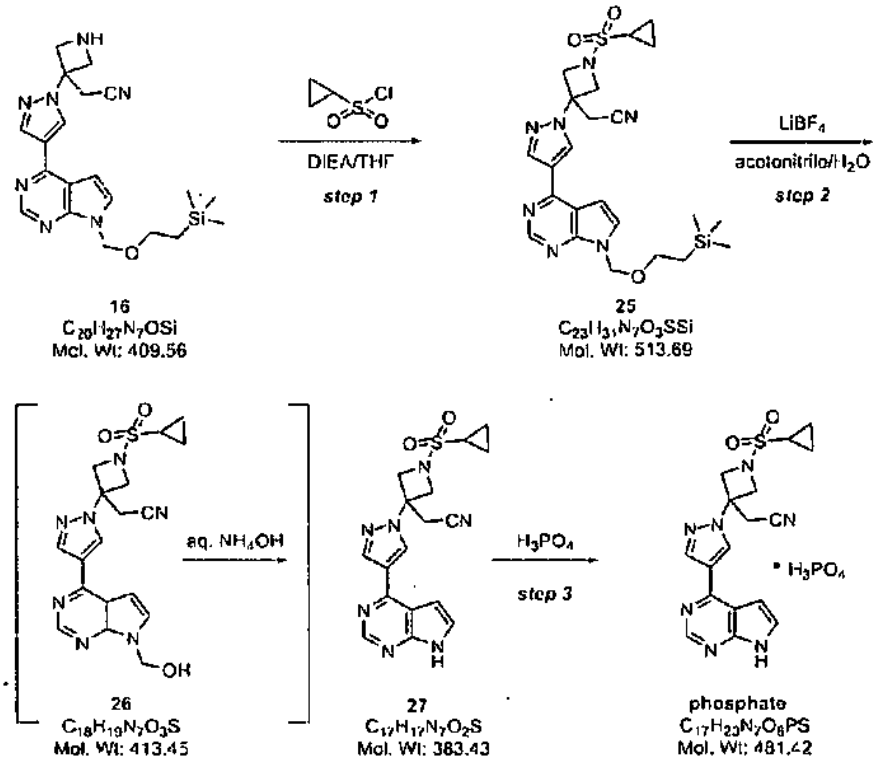
1H), 4.62 (d, 2H), 4.25 (d, 2H), 3.71 (s, 2H), 3.24 (q, 2H), 1.26 (t, 3H) ppm; $C_{16}H_{17}N_7O_2S$ (MW, 371.42). LCMS (EI) *m/e* 372 ($M^+ + H$).

Method C. Alternatively, a suspension of (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (20, 10.0 g, 20.6 mmol) and lithium hydroxide monohydrate (2.59 g, 61.8 mmol) in acetonitrile (CH_3CN 40 mL) and isopropyl alcohol (10 mL) was heated at 45 – 50 °C for 6 hours. When HPLC showed that the reaction was deemed complete, the reaction mixture was cooled to room temperature and 1M hydrochloric acid aqueous solution (41 mL) as added to adjust the pH to 6 – 7 at temperature below 25 °C. After the acid addition, the mixture was stirred at room temperature for 1 h and the precipitates were isolated by filtration. The wet cake was washed with water (50 mL) and dried in vacuum oven at 50 °C to give crude 2-(3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (14, 6.0 g, 7.65 g theoretical, 78% yield) as off-white solids, which was found to be identical to the material prepared by Method A.

Example 79. {1-(Cyclopropylsulfonyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile (25).

To a oven dried 2 L round bottom flask equipped with the overhead stirring, a nitrogen inlet, a septa and a thermocouple was charged anhydrous tetrahydrofuran (THF, 800 mL); {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile (16, 38.6 g, 94.2 mmol) and *N,N*-diisopropylethylamine (DIEA, 22.0 mL, 126 mmol, 1.34 eqeiv) at room temperature. The resulting solution was then cooled to 0 – 5 °C before being charged with cyclopropanesulfonyl chloride (14.3 mL, 134 mmol, 1.42 eeuiv) portion wise over eight minutes via syringe at 0 – 5 °C. After 10 minutes, the ice bath was removed and the reaction mixture was allowed to warm gradually to room temperature. When HPLC showed that the reaction was complete after 22 h, the reaction mixture was concentrated under reduced pressure to remove about 400 mL of solvent. The residue was treated with ethyl acetate (EtOAc, 500 mL) and the resulting solution was washed with 20% aqueous sodium chloride solution (NaCl, 300 mL). The aqueous layer was back extracted with ethyl acetate (EtOAc, 150 mL). The combined organic fractions were dried over magnesium sulfate ($MgSO_4$) and concentrated under reduced pressure to yield the crude product (25) as an amber oil. The crude product was then purified by flash column chromatography (SiO_2, 50% to 70% ethyl acetate/hexane gradient elution) to afford {1-(cyclopropylsulfonyl)-3-[4-(7-{[2-

(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile (25, 39.4 g, 48.4 g theoretical, 81.4% yield) as a light yellow oil, which solidified upon standing at room temperature in vacuum. For 25: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.98 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 7.81 (d, 1H, J = 3.8 Hz), 7.20 (d, 1H, J = 3.6 Hz), 5.63 (s, 2H), 4.66 (d, 2H, J = 9.5 Hz), 4.28 (d, 2H, J = 9.3 Hz), 3.69 (s, 2H), 3.52 (t, 2H, J = 7.8 Hz), 2.84 (m, 1H), 1.01 (m, 4H), 0.82 (t, 2H, J = 8.4 Hz), -0.12 (s, 9H) ppm; $C_{23}H_{31}N_7O_3SSi$ (MW, 513.69), LCMS (EI) *m/e* 514 (M^+ + H) and 536 (M^+ + Na).



Example 80. 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(cyclopropylsulfonyl)azetidin-3-yl)acetonitrile (27).

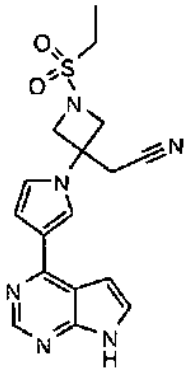
To a 500 mL round bottom flask equipped with a stir bar, a condenser, a thermocouple and a nitrogen inlet was charged {1-(cyclopropylsulfonyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile (25, 17.5 g, 34.1 mmol), acetonitrile (254 mL) and water (23.9 mL) at room temperature. The resulting reaction mixture was charged with solid lithium tetrfluoroborate ($LiBF_4$, 32.6 g, 341 mmol, 10.0 equiv) in one portion at room temperature. The resulting reaction mixture was warmed to reflux and stirred at reflux for 21 h. When HPLC showed that the first stage of deprotection reaction was complete, which produced the corresponding

hydroxymethyl intermediate 26, the reaction mixture was allowed to gradually cool to room temperature before the solution pH was adjusted to 9 - 10 with a 20% aqueous NH_4OH solution (45 mL) at room temperature. The resulting reaction mixture was then stirred at room temperature for overnight. When HPLC showed that the second stage of deprotection reaction was complete, the reaction mixture was filtered through a Celite pad and the Celite pad was washed with ethyl acetate (EtOAc, 50 mL). The filtrates were then diluted with a 20% aqueous sodium chloride solution (NaCl, 200 mL) and ethyl acetate (EtOAc, 200 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (EtOAc, 200 mL). The combined organic fractions were washed with 1 M aqueous sodium bicarbonate solution ($NaHCO_3$, 200 mL) and water (200 mL). The combined aqueous solution was back extracted with ethyl acetate (EtOAc, 100 mL). The combined organic fractions were then dried over magnesium sulfate ($MgSO_4$) and concentrated under reduced pressure to give the crude product (27) as light yellow solids. The crude solids were then treated with acetonitrile (200 mL) and the resulting suspension was warmed to 60 °C for 15 minutes before being cooled down to room temperature and stirred at room temperature for 60 minutes. The solids were collected by filtration and washed with a small volume of acetonitrile to give the first crop of the desired product (27, 6.9 g). The combined filtrates were then concentrated to afford yellow solids, which was treated with acetonitrile (100 mL) and warmed to 60 °C for 30 minutes. The suspension was cooled down to room temperature and stirred at room temperature for 60 minutes. The solids were collected by filtration and washed with a small volume of acetonitrile to give the second crop of the desired product (27, 3.0 g). The filtrate was then concentrated and the residue was purified by flash column chromatography (SiO_2, 50% ethyl acetate/acetonitrile elution) to give the third crop of the desired product (27, 1.4 g). This reaction afforded 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(cyclopropylsulfonyl)azetidin-3-yl)acetonitrile (27, 11.3 g, 13.07 g theoretical, 86.5% overall yield) as off-white solids. For 27: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.16 (br. s, 1H), 8.95 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.62 (dd, 1H, J = 3.6, 2.3 Hz), 7.08 (dd, 1H, J = 3.5, 1.4 Hz), 4.66 (d, 2H, J = 9.4 Hz), 4.28 (d, 2H, J = 9.4 Hz), 3.69 (s, 2H), 2.84 (m, 1H), 1.01 (m, 4H) ppm; $C_{17}H_{17}N_7O_2S$ (MW, 383.43), LCMS (EI) *m/e* 384 (M^+ + H).

Example 81. 2-(3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(cyclopropylsulfonyl)azetidin-3-yl)acetonitrile phosphoric acid salt.

To a 1 L round bottom flask equipped with a stir bar, an addition funnel, a nitrogen inlet and a condenser was charged 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(cyclopropylsulfonyl)azetidin-3-yl)acetonitrile (27, 11.3 g, 29.5 mmol) and acetonitrile (275 mL) at room temperature. The resulting mixture was warmed to 70 °C before being charged with ethanol (EtOH, 150 mL) in three portions at 70 °C. The resulting homogeneous solution was filtered into a clean 1 L round bottom flask equipped with the overhead stirring, an addition funnel, a nitrogen inlet and a condenser. The mixture was then warmed to 67 °C producing a homogeneous solution again. A solution of phosphoric acid (H_3PO_4, 3.03 g, 30.9 mmol, 1.05 equiv) in ethanol (EtOH, 30 mL) was then charged drop wise to the solution over ten minutes at 67 °C. The solution was still homogeneous after the end of the addition of phosphoric acid ethanol solution. The resulting reaction mixture was stirred at 67 °C for 10 minutes before being gradually cooled down to room temperature and stirred at room temperature for 19 h. The solids were collected by filtration and washed with acetonitrile (2 x 40 mL). The wet cake was partially dried under high vacuum and then transferred to a 75 °C vacuum oven and dried to constant weight to afford 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(cyclopropylsulfonyl)azetidin-3-yl)acetonitrile phosphate (12.0 g, 14.2 g theoretical, 84.5% yield) as white solids. For **Phosphate**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.13 (br. s, 1H), 9.20 (br. s, 3H), 8.94 (s, 1H), 8.70 (s, 1H), 8.47 (s, 1H), 7.61 (dd, 1H, J = 3.4, 2.3 Hz), 7.07 (dd, 1H, J = 3.6, 1.6 Hz), 4.65 (d, 2H, J = 9.1 Hz), 4.28 (d, 2H, J = 9.7 Hz), 3.68 (s, 2H), 2.82 (m, 1H), 1.01 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 152.9, 151.6, 150.0, 140.6, 130.3, 127.7, 122.9, 117.3, 113.8, 100.7, 59.7, 57.1, 27.6, 25.4, 4.9 ppm; $C_{17}H_{20}N_7O_6PS$ (MW, 481.42; $C_{17}H_{17}N_7O_2S$ for free base, MW, 383.43), LCMS (EI) *m/e* 384 (M^+ + H).

Example 82: {1-(Ethylsulfonyl)-3-[3-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrrol-1-yl]azetidin-3-yl}acetonitrile



~~146~~ 147

Step 1. 4-(1H-pyrrol-3-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 4-chloro-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (12.9 g, 45.4 mmol) (prepared as in WO 2007/070514, Ex.65) and [1-(triisopropylsilyl)-1H-pyrrol-3-yl]boronic acid (Frontier Scientific) (10.4 g, 38.9 mmol) and sodium carbonate (4.36 g, 41.2 mmol) in 1,2-dimethoxyethane (100 mL) and water (35 mL) was degassed by purging with a stream of nitrogen for 20 minutes. Tetrakis(triphenylphosphine)palladium(0) (2.25 g, 1.94 mmol) was then added and the reaction was heated to reflux for 9 hours. As the coupling reaction proceeded, the TIPS protecting group was also slowly removed. The solvent was removed by rotary evaporation and the product was purified by flash column chromatography, eluting with a gradient from 10-50% ethyl acetate in hexanes to afford the desired product (7 g, 57%).

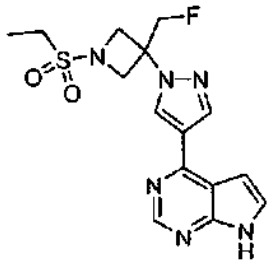
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (br s, 1H), 8.84 (s, 1H), 7.73-7.69 (m, 1H), 7.33 (d, 1H), 7.04-7.00 (m, 1H), 6.94 (dd, 1H), 6.85 (d, 1H), 5.66 (s, 2H), 3.55 (m, 2H), 0.92 (m, 2H), -0.06 (s, 9H). LCMS (M+H)+: 315.2.

Step 2.

A solution of 4-(1H-pyrrol-3-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (0.100 g, 0.318 mmol) and [1-(ethylsulfonyl)azetidin-3-ylidene]acetonitrile (0.118 g, 0.636 mmol, prepared as in Example 68) in acetonitrile (1 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (24 µL, 0.16 mmol). The mixture was stirred for 4 hours. The solvent was evaporated. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution, then extracted with two further portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was stirred with 25% TFA / DCM (8 mL) overnight. The solvents were evaporated. The product was then stirred with ethylenediamine (0.3 mL) in methanol (5 mL). Preparative HPLC-MS (eluting with a gradient of methanol and water containing 0.15% NH_4OH) was used to purify the product.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.54 (dd, 1H), 7.27 (d, 1H), 6.95 (dd, 1H), 6.82 (dd, 1H), 6.74 (d, 1H), 4.49 (d, 2H), 4.15 (d, 2H), 3.24 (s, 2H), 3.02 (q, 2H), 1.33 (t, 3H); LCMS (M+H)+: 371.1.

Example 83: 4-{1-[1-(Ethylsulfonyl)-3-(fluoromethyl)azetidin-3-yl]-1H-pyrazol-4-yl}-7H-pyrrolo[2,3-d]pyrimidine trifluoroacetic acid salt



·TFA

Step 1. tert-butyl 3-[fluoro(phenylsulfonyl)methylene]azetidine-1-carboxylate

To a mixture of fluoromethyl phenyl sulfone (0.50 g, 2.9 mmol) and phosphorochloridic acid, diethyl ester (0.415 mL, 2.87 mmol) in tetrahydrofuran (6 mL, 70 mmol) was added 1.000 M of lithium hexamethyldisilazide in tetrahydrofuran (6.2 mL, 6.2 mmol) dropwise at -78 °C. After the mixture was stirred at -78 °C for 1 h, a solution of tert-butyl 3-oxoazetidine-1-carboxylate (0.378 g, 2.21 mmol) in tetrahydrofuran (1.3 mL, 16 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred for 2 h at rt. The reaction was poured into an ice-cold mixture of EtOAc and sat. ammonium chloride. The organic layer was separated and the aq. layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to give the desired product (560 mg, 77.5%). LCMS calculated for $C_{15}H_{18}FNO_4SNa(M+Na)^+$: m/z = 350.1; Found (M+Na) 350.3.

Step 2. tert-butyl 3-[[fluoro(phenylsulfonyl)methyl]-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

A mixture of 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (0.40 g, 1.3 mmol), tert-butyl 3-[fluoro(phenylsulfonyl)methylene]azetidine-1-carboxylate (0.56 g, 1.7 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.182 mL, 1.22 mmol) in acetonitrile (6 mL, 100 mmol) was stirred at rt for 3 h. After evaporation to dryness, the residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to give the desired product (820 mg, 100%). LCMS calculated for $C_{30}H_{40}FN_6O_5SSi(M+H)^+$: m/z = 643.3; Found: 643.4. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.92 (1H, s), 8.55 (1H, s), 8.32 (1H, s), 7.87 (2H, m), 7.68 (1H, m), 7.55 (2H, m), 7.47 (1H, d, J = 3.6 Hz), 6.84 (1H, d, J = 3.6 Hz), 5.77 (1H, d, J = 45.6 Hz), 5.74 (2H, s), 4.93

(1H, d, J = 10.2 Hz), 4.73~4.58 (3H, m), 3.60 (2H, t, J = 8.1 Hz), 1.51 (9H, s), 0.98 (3H, t, J = 8.1 Hz), 0.07 (9H, s) ppm. ^{19}F NMR ($CDCl_3$, 300 MHz) δ -181.84 (1F, d, J = 48.6 Hz) ppm.

Step 3. tert-butyl 3-(fluoromethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

To a mixture of tert-butyl 3-[fluoro(phenylsulfonyl)methyl]-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (0.312 g, 0.485 mmol) and disodium hydrogen phosphate (1.38 g, 9.71 mmol) in methanol (7.5 mL, 180 mmol) was added sodium mercury amalgam (2.17 g, 9.71 mmol), under nigtrogen, at -20 °C. The reaction was stirred at -20 to 0 °C for 1 h, diluted with EtOAc, then quenched with sat. ammonium chloride. The mixture was filtered through Celite and the solid collected was treated with elemental sulfur powder to destroy the mercury residue. The filtrate layers were separated and the organic layers were washed with brine, dried over sodium sulfate and evaporated. The residue was purified on silica gel, eluting with 0 to 80% EtOAc in hexane, to give the desired product (120 mg, 49.2%). LCMS calculated for $C_{24}H_{36}FN_6O_3Si(M+H)^+$: m/z = 503.3; Found: 503.2.

Step 4. 4-{1-[1-(ethylsulfonyl)-3-(fluoromethyl)azetidin-3-yl]-1H-pyrazol-4-yl}-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine

tert-Butyl 3-(fluoromethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (0.120 g, 0.239 mmol) was treated with 4.00 M of hydrogen chloride in 1,4-dioxane (1.0 mL, 4.0 mmol) at rt for 1h, then evaporated to dryness under reduced pressured. LCMS (M+H) 403.4. To the resultant crude HCl salt in acetonitrile (4 mL, 80 mmol) was added triethylamine (0.0998 mL, 0.716 mmol) followed by ethanesulfonyl chloride (0.0317 mL, 0.334 mmol). The mixture was stirred at rt for 30 min. After quenching with aq. sodium bicarbonate, the mixture was extracted with dichloromethane. The combined organic layers were washed with water, brine and dried over sodium sulfate, evaporated to dry. The residue was used directly in next step. LCMS calculated for $C_{21}H_{32}FN_6O_3SSi(M+H)^+$: m/z = 495.2; Found: 495.4.

Step 5. 4-{1-[1-(ethylsulfonyl)-3-(fluoromethyl)azetidin-3-yl]-1H-pyrazol-4-yl}-7H-pyrrolo[2,3-d]pyrimidine

4-{1-[1-(Ethylsulfonyl)-3-(fluoromethyl)azetidin-3-yl]-1H-pyrazol-4-yl}-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (0.060 g, 0.12 mmol) was treated with 2 mL of TFA at rt for 30 min. The reaction mixture was evaporated to dryness. LCMS (M+H) 395.3. The resulting residue was dissolved in 3 mL of methanol and treated with ethylenediamine (0.0811 mL, 1.21 mmol) at rt for 30 min. The mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetone/water containing 0.2% TFA) to give the desired product as TFA salt. LCMS calculated for $C_{15}H_{18}FN_6O_2S(M+H)^+$ (free base): m/z = 365.1; Found: 365.3. ^1H NMR (DMSO-d_6, 300 MHz) δ 12.57 (1H, br s), 8.94 (1H, s), 8.81 (1H, s), 8.53 (1H, s), 7.75 (1H, br s), 7.21 (1H, br s), 5.03 (2H, d, J = 46.8 Hz), 4.53 (1H, dd, J = 9.0 and 2.7 Hz), 4.24 (1H, d, J = 9.0 Hz), 3.25 (2H, q, J = 7.2 Hz), 1.23 (3H, t, J = 7.2 Hz) ppm. ^{19}F NMR (DMSO-d_6, 300 MHz) δ -74.98 (3F, s), -225.56 (1F, t, J = 48.3 Hz) ppm.

Example A: *In vitro* JAK Kinase Assay

Compounds herein were tested for inhibitory activity of JAK targets according to the following *in vitro* assay described in Park *et al.*, *Analytical Biochemistry* 1999, *269*, 94-104. The catalytic domains of human JAK1 (a.a. 837-1142), JAK2 (a.a. 828-1132) and JAK3 (a.a. 781-1124) with an N-terminal His tag were expressed using baculovirus in insect cells and purified. The catalytic activity of JAK1, JAK2 or JAK3 was assayed by measuring the phosphorylation of a biotinylated peptide. The phosphorylated peptide was detected by homogenous time resolved fluorescence (HTRF). IC_{50}s of compounds were measured for each kinase in the reactions that contain the enzyme, ATP and 500 nM peptide in 50 mM Tris (pH 7.8) buffer with 100 mM NaCl, 5 mM DTT, and 0.1 mg/mL (0.01%) BSA. The ATP concentration in the reactions was 90 μM for Jak1, 30 μM for Jak2 and 3 μM for Jak3. Reactions were carried out at room temperature for 1 hr and then stopped with 20 μL 45 mM EDTA, 300 nM SA-APC, 6 nM Eu-Py20 in assay buffer (Perkin Elmer, Boston, MA). Binding to the Europium labeled antibody took place for 40 minutes and HTRF signal was measured on a Fusion plate reader (Perkin Elmer, Boston, MA). The compounds of Examples 1-60, 82, and 83 were found to have IC_{50} values less than 60 nM for at least one of JAK1, JAK2, and JAK3.

Example B: Cellular Assays

One or more compounds herein were tested for inhibitory activity of JAK targets according to at least one of the following cellular assays.

Cancer cell lines dependent on cytokines and hence JAK/STAT signal transduction, for growth, were plated at 6000 cells per well (96 well plate format) in RPMI 1640, 10% FBS, and 1 nG/mL of appropriate cytokine. Compounds were added to the cells in DMSO/media (final concentration 0.2% DMSO) and incubated for 72 hours at 37 °C, 5% CO_2. The effect of compound on cell viability was assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) followed by TopCount (Perkin Elmer, Boston, MA) quantitation. Potential off-target effects of compounds were measured in parallel using a non-JAK driven cell line with the same assay readout. All experiments were performed in duplicate.

The above cell lines can also be used to examine the effects of compounds on phosphorylation of JAK kinases or potential downstream substrates such as STAT proteins, Akt, Shp2, or Erk. These experiments can be performed following an overnight cytokine starvation, followed by a brief preincubation with compound (2 hours or less) and cytokine stimulation of approximately 1 hour or less. Proteins are then extracted from cells and analyzed by techniques familiar to those schooled in the art including Western blotting or ELISAs using antibodies that can differentiate between phosphorylated and total protein. These experiments can utilize normal or cancer cells to investigate the activity of compounds on tumor cell survival biology or on mediators of inflammatory disease. For example, with regards to the latter, cytokines such as IL-6, IL-12, IL-23, or IFN can be used to stimulate JAK activation resulting in phosphorylation of STAT protein(s) and potentially in transcriptional profiles (assessed by array or qPCR technology) or production and/or secretion of proteins, such as IL-17. The ability of compounds to inhibit these cytokine mediated effects can be measured using techniques common to those schooled in the art.

Compounds herein can also be tested in cellular models designed to evaluate their potency and activity against mutant JAKs, for example, the JAK2V617F mutation found in myeloid proliferative disorders. These experiments often utilize cytokine dependent cells of hematological lineage (e.g. BaF/3) into which the wild-type or mutant JAK kinases are ectopically expressed (James, C., *et al. Nature* 434:1144-1148; Staerk, J., *et al.* JBC 280:41893-41899). Endpoints include the effects of compounds on cell survival, proliferation, and phosphorylated JAK, STAT, Akt, or Erk proteins.

Certain compounds herein have been or can be evaluated for their activity inhibiting T-cell proliferation. Such as assay can be considered a second cytokine (*i.e.* JAK) driven

proliferation assay and also a simplistic assay of immune suppression or inhibition of immune activation. The following is a brief outline of how such experiments can be performed. Peripheral blood mononuclear cells (PBMCs) are prepared from human whole blood samples using Ficoll Hypaque separation method and T-cells (fraction 2000) can be obtained from PBMCs by elutriation. Freshly isolated human T-cells can be maintained in culture medium (RPMI 1640 supplemented with10% fetal bovine serum, 100 U/ml penicillin, 100 µg/ml streptomycin) at a density of 2 x 10^6 cells/ml at 37 °C for up to 2 days. For IL-2 stimulated cell proliferation analysis, T-cells are first treated with Phytohemagglutinin (PHA) at a final concentration of 10 µg/mL for 72h. After washing once with PBS, 6000 cells/well are plated in 96-well plates and treated with compounds at different concentrations in the culture medium in the presence of 100 U/mL human IL-2 (ProSpec-Tany TechnoGene; Rehovot, Israel). The plates are incubated at 37 °C for 72h and the proliferation index is assessed using CellTiter-Glo Luminescent reagents following the manufactory suggested protocol (Promega; Madison, WI).

Example C: *In vivo* anti-tumor efficacy

Compounds herein can be evaluated in human tumor xenograft models in immune compromised mice. For example, a tumorigenic variant of the INA-6 plasmacytoma cell line can be used to inoculate SCID mice subcutaneously (Burger, R., *et al. Hematol* J. 2:42-53, 2001). Tumor bearing animals can then be randomized into drug or vehicle treatment groups and different doses of compounds can be administered by any number of the usual routes including oral, i.p., or continuous infusion using implantable pumps. Tumor growth is followed over time using calipers. Further, tumor samples can be harvested at any time after the initiation of treatment for analysis as described above (Example B) to evaluate compound effects on JAK activity and downstream signaling pathways. In addition, selectivity of the compound(s) can be assessed using xenograft tumor models that are driven by other know kinases (*e.g.* Ber-Abl) such as the K562 tumor model.

Example D: Murine Skin Contact Delayed Hypersensitivity Response Test

Compounds herein can also be tested for their efficacies (of inhibiting JAK targets) in the T-cell driven murine delayed hypersensitivity test model. The murine skin contact delayed-type hypersensitivity (DTH) response is considered to be a valid model of clinical contact dermatitis, and other T-lymphocyte mediated immune disorders of the skin, such as psoriasis (*Immunol Today*. 1998 Jan;19(1):37-44). Murine DTH shares multiple

characteristics with psoriasis, including the immune infiltrate, the accompanying increase in inflammatory cytokines, and keratinocyte hyperproliferation. Furthermore, many classes of agents that are efficacious in treating psoriasis in the clinic are also effective inhibitors of the DTH response in mice (Agents Actions. 1993 Jan;38(1-2):116-21).

On Day 0 and 1, Balb/c mice are sensitized with a topical application, to their shaved abdomen with the antigen 2,4,dinitro-fluorobenzene (DNFB). On day 5, ears are measured for thickness using an engineer's micrometer. This measurement is recorded and used as a baseline. Both of the animals' ears are then challenged by a topical application of DNFB in a total of 20 μL (10 μL on the internal pinna and 10 μL on the external pinna) at a concentration of 0.2%. Twenty-four to seventy-two hours after the challenge, ears are measured again. Treatment with the test compounds was given throughout the sensitization and challenge phases (day -1 to day 7) or prior to and throughout the challenge phase (usually afternoon of day 4 to day 7). Treatment of the test compounds (in different concentration) was administered either systemically or topically (topical application of the treatment to the ears). Efficacies of the test compounds are indicated by a reduction in ear swelling comparing to the situation without the treatment. Compounds causing a reduction of 20% or more were considered efficacious. In some experiments, the mice are challenged but not sensitized (negative control).

The inhibitive effect (inhibiting activation of the JAK-STAT pathways) of the test compounds can be confirmed by immunohistochemical analysis. Activation of the JAK-STAT pathway(s) results in the formation and translocation of functional transcription factors. Further, the influx of immune cells and the increased proliferation of keratinocytes should also provide unique expression profile changes in the ear that can be investigated and quantified. Formalin fixed and paraffin embedded ear sections (harvested after the challenge phase in the DTH model) are subjected to immunohistochemical analysis using an antibody that specifically interacts with phosphorylated STAT3 (clone 58E12, Cell Signaling Technologies). The mouse ears are treated with test compounds, vehicle, or dexamethasone (a clinically efficacious treatment for psoriasis), or without any treatment, in the DTH model for comparisons. Test compounds and the dexamethasone can produce similar transcriptional changes both qualitatively and quantitatively, and both the test compounds and dexamethasone can reduce the number of infiltrating cells. Both systemically and topical administration of the test compounds can produce inhibitive effects, *i.e.*, reduction in the number of infiltrating cells and inhibition of the transcriptional changes.

Example E: *In vivo* anti-inflammatory activity

Compounds herein can be evaluated in rodent or non-rodent models designed to replicate a single or complex inflammation response. For instance, rodent models of arthritis can be used to evaluate the therapeutic potential of compounds dosed preventatively or therapeutically. These models include but are not limited to mouse or rat collagen-induced arthritis, rat adjuvant-induced arthritis, and collagen antibody-induced arthritis. Autoimmune diseases including, but not limited to, multiple sclerosis, type I-diabetes mellitus, uveoretinitis, thyroditis, myasthenia gravis, immunoglobulin nephropathies, myocarditis, airway sensitization (asthma), lupus, or colitis may also be used to evaluate the therapeutic potential of compounds herein. These models are well established in the research community and are familiar to those schooled in the art (Current Protocols in Immunology, Vol 3., Coligan, J.E. *et al*, Wiley Press.; *Methods in Molecular Biology*. Vol. 225, Inflammation Protocols., Winyard, P.G. and Willoughby, D.A., Humana Press, 2003.).

Example F: Animal Models for the Treatment of Dry Eye, Uveitis, and Conjunctivitis

Compounds may be evaluated in one or more preclinical models of dry eye known to those schooled in the art including, but not limited to, the rabbit concanavalin A (ConA) lacrimal gland model, the scopolamine mouse model (subcutaneous or transdermal), the Botulinumn mouse lacrimal gland model, or any of a number of spontaneous rodent auto-immune models that result in ocular gland dysfunction (e.g. NOD-SCID, MRL/lpr, or NZB/NZW) (Barabino et al., Experimental Eye Research 2004, 79, 613-621 and Schrader et al., Developmental Opthalmology, Karger 2008, 41, 298-312, each of which is incorporated herein by reference in its entirety). Endpoints in these models may include histopathology of the ocular glands and eye (cornea, etc.) and possibly the classic Schirmer test or modified versions thereof (Barabino et al.) which measure tear production. Activity may be assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists.

Compounds may be evaluated in one or more preclinical models of uveitis known to those schooled in the art. These include, but are not limited to, models of experimental autoimmune uveitis (EAU) and endotoxin induced uveitis (EIU). EAU experiements may be performed in the rabbit, rat, or mouse and may involve passive or activate immunization. For instance, any of a number or retinal antigens may be used to sensitize animals to a relevant immunogen after which animals may be challenged ocularly with the same antigen. The EIU model is more acute and involves local or systemic administration of lipopolysaccaride at

sublethal doses. Endpoints for both the EIU and EAU models may include fundoscopic exam, histopathology amongst others. These models are reviewed by Smith et al. (Immunology and Cell Biology 1998, 76, 497-512, which is incorporated herein by reference in its entirety). Activity is assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Some models listed above may also develop scleritis/episcleritis, chorioditis, cyclitis, or iritis and are therefore useful in investigating the potential activity of compounds for the therapeutic treatment of these diseases.

Compounds may also be evaluated in one or more preclinical models of conjunctivitis known those schooled in the art. These include, but are not limited to, rodent models utilizing guinea-pig, rat, or mouse. The guinea-pig models include those utilizing active or passive immunization and/or immune challenge protocols with antigens such as ovalbumin or ragweed (reviewed in Groneberg, D.A., et al., Allergy 2003, 58, 1101-1113, which is incorporated herein by reference in its entirety). Rat and mouse models are similar in general design to those in the guinea-pig (also reviewed by Groneberg). Activity may be assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Endpoints for such studies may include, for example, histological, immunological, biochemical, or molecular analysis of ocular tissues such as the conjunctiva.

Example G: Comparative Data

Table 3 below provides potency data for the compound of Example 1 compared with other JAK inhibitors described in US Pat. App. Pub. No. 2007/0135461.

Table 3

Compound	JAK2 IC_{50} (nM)	JAK1 IC_{50} (nM)	INA-6 IC_{50} (nM)
Example 1	0.3	1.1	148
Example 82	0.3	1.3	NA
Example 83	1.5	5.5	NA
Comparative 1	1.4	7.6	1138
Comparative 2	1.2	2.2	505
Comparative 3	22	93	1900
Comparative 4	2.4	6.3	431
Comparative 5	3.7	1	2250

The JAK1 and JAK2 data in Table 3 was obtained using the *in vitro* assay procedures described in Example A above. The INA-6 data in Table 3 was obtained using the cellular assay procedure of Example B above, where the cancer cells used were INA-6 cells (Burger et al., *The Hematology Journal* (2001), 2, 42-53). Comparative 1 corresponds to the compound {1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclopentyl}acetonitrile; Comparative 2 corresponds to the compound {1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclopentyl}acetonitrile; Comparative 3 corresponds to the compound 3-{1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclopentyl}propanenitrile; Comparative 4 corresponds to the compound {1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclohexyl}acetonitrile; and Comparative 5 corresponds to the compound N'-cyano-4-(cyanomethyl)-4-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]piperidine-1-carboximidamide.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the above description. Each reference cited in the present application is incorporated herein by reference in its entirety.

C-91/2661/2013

We claim:

1. {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-c]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile, or pharmaceutically acceptable salt thereof.
2. {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile, phosphoric acid salt.
3. A composition comprising a compound of claim 1 or a salt of claim 2, and at least one pharmaceutically acceptable carrier.
4. The composition of claim 3 which is suitable for topical administration.
5. The composition of claim 3 which is suitable for oral administration.

Dated this 1st day of September, 2010

AMRISH TIWARI
Of K & S Partners
Attorney for the Applicant

15 MAR 2013

ANNEXURE-15 Colly 397

FORM 27

THE PATENT ACT, 1970
(39 of 1970)
&
THE PATENTS RULES, 2003

STATEMENT REGARDING THE WORKING OF THE PATENTED INVENTION ON COMMERCIAL SCALE IN INDIA

[See section 146 (2) and rule 131(1)]

IN THE MATTER OF PATENT NO:**270765**

I/We

Patentee Name:	INCYTE HOLDINGS CORPORATION
Patentee Address:	1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States of America
Grantee Name:	INCYTE CORPORATION
Grantee Address:	Experimental Station Building 336 Route 141 & Henry Clay Road City of Wilmington State of Delaware United States of America.

THE PATENTEE(S) OR LICENSEE(S) UNDER PATENT NO: 270765 HEREBY FURNISH THE FOLLOWING STATEMENT REGARDING THE WORKING OF THE PATENTED INVENTION REFERRED TO ABOVE ON A COMMERCIAL SCALE IN INDIA FOR THE YEAR **2017**

REASON FOR MAKING THE ABOVE REQUEST ARE AS FOLLOWS-

(i)THE PATENTED INVENTION:

(1)REASON FOR NOT WORKING AND STEPS BEING TAKEN FOR WORKING OF THE INVENTION:**Claimed invention is in development (clinical or pre-clinical) and cannot be sold until regulatory approval is obtained.**

I/WE DECLARE THAT THE FACTS AND MATTERS STARTED HEREIN ARE TRUE TO THE BEST OF MY/OUR KNOWLEDGE, INFORMATION AND BELIEF

SIGNATURE
(.....)

To,
The Controller of Patents,
The Patent Office
AT **MUMBAI**

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FORM 27
THE PATENT ACT, 1970
(39 OF 1970)
&
THE PATENTS RULES, 2006
STATEMENT REGARDING THE WORKING
OF THE PATENTED INVENTION ON A COMMERCIAL SCALE IN INDIA
(See Section 146(2) and rule 131(1)

In the matter of Patent No 270765 of 10/03/2009

We, INCYTE HOLDINGS CORPORATION., of 1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States of America.; the patentee or licensee under Patent No. 270765 hereby furnish the following statement regarding the working of the patented invention referred to above on a commercial scale in India for the year 2018:

The patented invention: "AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS"

(i) **(√) Worked.** ( ) Not worked (tick mark the relevant box)

(ii) ~~If not worked reasons for not working and steps being taken for working of the invention:~~

(iii) If worked: quantum and value (in Rupees), of the patented product:

Product Description	**Rcvd Qty**	**Invoice Value**
OLUMIANT TAB 2 MG	1,627	5,255,698
OLUMIANT TAB 4 MG	5,763	18,616,219
OLUMIANT TAB 4 MG samples	995	3,214,149

Manufactured in India: **NO**
Imported from other countries (Give country wise details): **Spain**

(iv) The licenses and sub-licenses granted during the year: **NONE**

(v) State whether public requirement has been met partly/**adequately**/to the fullest extent at reasonable price:
While we (Eli Lilly) cannot know for sure, Eli Lilly believes that the public requirement is being adequately met at a market appropriate price.

The facts and matters stated above are true to the best of our knowledge, information and belief.

Dated this 11 day of February 2019



ANUPAM TRIVEDI
OF K&S PARTNERS
ATTORNEY FOR THE APPLICANT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE
AT MUMBAI

FORM 27
THE PATENT ACT, 1970
(39 OF 1970)
&
THE PATENTS RULES, 2006
STATEMENT REGARDING THE WORKING
OF THE PATENTED INVENTION ON A COMMERCIAL SCALE IN INDIA
(See Section 146(2) and rule 131(1)

In the matter of Patent No 270765 of 10/03/2009

We, INCYTE HOLDINGS CORPORATION., of 1801 Augustine Cut-Off, Wilmington, Delaware 19803, United States of America.; the patentee or licensee under Patent No. 270765 hereby furnish the following statement regarding the working of the patented invention referred to above on a commercial scale in India for the year 2019:

The patented invention: "AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS"

(i) **(√) Worked.** ( ) Not worked (tick mark the relevant box)

(ii) ~~If not worked reasons for not working and steps being taken for working of the invention:~~

(iii) If worked: quantum and value (in Rupees), of the patented product:

Product Description	**Rcvd Qty**	**Invoice Value**
OLUMIANT TAB 2 MG	263	849,569
OLUMIANT TAB 4 MG	7997	25,832,709
Olumiant physician samples	810	2,616,543

Manufactured in India: **NO**
Imported from other countries (Give country wise details): **Spain**

(iv) The licenses and sub-licenses granted during the year: **Registration Certificate and Import License granted by DCGI for Olumiant on 05-Sep-2018**

(v) State whether public requirement has been met partly/adequately/to the fullest extent at reasonable price: **To the best of patentee's knowledge, public requirement has been met adequately to the fullest extent at a reasonable price.**

The facts and matters stated above are true to the best of our knowledge, information and belief.

Dated this 13 day of March 2020



ANUPAM TRIVEDI
OF K&S PARTNERS
ATTORNEY FOR THE APPLICANT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE
AT MUMBAI

FORM 27
THE PATENT ACT, 1970
(39 OF 1970)
&
THE PATENTS RULES, 2006
STATEMENT REGARDING THE WORKING
OF THE PATENTED INVENTION ON A COMMERCIAL SCALE IN INDIA
(See Section 146(2) and rule 131(1)

In the matter of Patent No **270765 of 10/03/2009**

We, **ELI LILLY AND COMPANY, a corporation of the State of Indiana, United States of America, of Lilly Corporate Center, City of Indianapolis, State of Indiana 46285, United States of America**, the licensee under Patent No. 270765 hereby furnish the following statement regarding the working of the patented invention referred to above on a commercial scale in India for the year 2019:

The patented invention: ***"AZETIDINE AND CYCLOBUTANE DERIVATIVES AS JAK INHIBITORS"***

(i) **(√) Worked.** ( ) Not worked (tick mark the relevant box)

(ii) ~~If not worked reasons for not working and steps being taken for working of the invention:~~

(iii) If worked: quantum and value (in Rupees), of the patented product:

Product Description	**Rcvd Qty**	**Invoice Value**
OLUMIANT TAB 2 MG	263	849,569
OLUMIANT TAB 4 MG	7997	25,832,709
Olumiant physician samples	810	2,616,543

Manufactured in India: **NO**
Imported from other countries (Give country wise details): **Spain**

(iv) The licenses and sub-licenses granted during the year: We have already been granted exclusive license to develop and commercialize the patented technology.

(v) State whether public requirement has been met partly/adequately/to the fullest extent at reasonable price: **To the best of our knowledge, public requirement has been met adequately to the fullest extent at a reasonable price.**

The facts and matters stated above are true to the best of our knowledge, information and belief.

Dated this 1st day of January 2021

Digitally signed and filed through e-filing

ANUPAM TRIVEDI
OF K & S PARTNERS
ATTORNEY FOR EXCLUSSIVE LICENSEE
IN/PA-1003

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE
MUMBAI

Form 27
THE PATENTS ACT, 1970
(39 of 1970)
AND
THE PATENTS RULES, 2003

STATEMENT REGARDING THE WORKING OF PATENTED INVENTION(S) ON A COMMERCIAL SCALE IN INDIA
[*See* section 146(2) and rule 131(1)]

I/We, the Patentee(s)/Licensee
Name : Eli Lilly and Company (Licensee),
Address : United States of America,
State : Not Applicable,
Country : U.S.A.
Nationality : Not Applicable
,in respect of patent number(s) **270765**
furnish this statement,
(Explanation: One form may be filed in respect of multiple patents, provided all of them are related patents, wherein the approximate revenue / value accrued from a particular patented invention cannot be derived separately from the approximate revenue/value accrued from related patents, and all such patents are granted to the same patentee(s)).
in respect of the financial year **2020-2021**

Please state whether each patent in respect of which this form is being filed is worked or not worked

Worked Patent(s)

		Approximate revenue / value accrued in India to the patentee(s) licensee furnishing the statement from patent number(s) where the working is through:	
Patent Number(s)	Brief in respect of above	Manufacturing in India (in INR)	Importing into India (in INR)
270765	Baricitinib has been approved for the treatment of Rheumatoid arthritis. Recently, on 3rd May 2021, the Licensee (Lilly) was granted a restricted emergency use for baricitinib (2 mg and 4 mg) in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) by the Drug Regulatory Authorities. Lilly is working with local Indian pharmaceutical companies to execute royalty-free voluntary licensing agreements to accelerate the manufacturing and distribution of the medicine in India during the pandemic and ensure continuous and sufficient supply of baricitinib. In the meantime, Lilly has decided to donate baricitinib to the Indian Government through Direct Relief to make the same readily available for free. As an initial donation Lilly is making immediately available 400,000 baricitinib tablets to the Indian government for eligible hospitalized COVID-19 patients in India.	0	69460000

Not Worked Patent(s)

Not Applicable

The facts and matters stated above are true to the best of my/ our knowledge, information and belief.
Dated this 5 day of May 2021

Signature(s) .....

To

The Controller of Patents,

The Patent Office,

at MUMBAI

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X-11026/07/2020-PRO
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Public Relation Office)

ANNEXURE-16

FDA Bhawan, Kotla Road
New Delhi-110002
Date: 19/3/2020

NOTICE

Novel Corona-virus Disease (COVID-19) has spread over 118 countries with now more than 191,127 cases and 7807 people have lost their lives as on 18.03.2020. World Health Organization (WHO) has declared it as pandemic. At present there is no current evidence from randomized clinical trials to recommend any specific treatment for suspected or confirmed patients with COVID-19.

In order to encourage research & development of drug or vaccine for prevention or treatment of COVID-19, any application submitted to CDSCO will be processed on high priority. CDSCO will also provide guidance on regulatory pathway on such matter.

The details are as under -

1. Any firm having a Drug/Vaccine under development for COVID-19 can directly approach DCG(I) through Public Relations Office for seeking guidance for regulatory pathway.
2. Any firm or research institute having protocol for repurposing of existing drugs/vaccines for treatment of COVID-19 will also be given priority for review and approval.
3. Applications for Clinical Trial permission and applications to import or manufacture Drug/Vaccine for sale and distribution would be processed on priority though expedited review/accelerated approval.
4. Any firm having Drug/Vaccine already approved for COVID-19 in any other country can directly approach DCG(I) through Public Relations Office regarding expedited review/accelerated approval for marketing in India.
5. Data requirement for animal toxicity study, clinical study, stability study etc. may be abbreviated, deferred, or waived on case to case basis depending upon the type of vaccine, nature of drug, plant from which the drug is extracted & its experience in case of Phyto-pharmaceuticals.
6. Applications to manufacture or import Drug/Vaccine for test, analysis and further use BA/BE or Clinical Trial may be processed within 7 days.
7. In case of emergency, Import license (Form 10) would be granted without Registration Certificate (Form 41) subject to approval of Central Government.

For any additional information kindly contact Public Relations Office through toll free number **1800 11 1454** & write to **startupinnov@cdsco.nic.in** .

(Dr. V. G. Somani)
Drugs Controller General (India)

To,

All Stakeholders through CDSCO web site

Copy for Information,

PS to JS(R), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi

$~8.

* **IN THE HIGH COURT OF DELHI AT NEW DELHI**

\+ W.P.(C) 3031/2020

RAKESH MALHOTRA ..... Petitioner

Through: Petitioner in person.

versus

GOVERNMENT OF NATIONAL CAPITAL TERRITORY OF INDIA AND ORS ..... Respondents

Through: Mr. Rahul Mehra, Sr. Advocate with Mr. Satyakam, ASC, and Mr. Chaitanya Gosain and, Advocate for GNCTD.
Mr. Chetan Sharma, ASG with Ms. Monika Arora, CGSC and Mr. Shriram Tiwary, Advocate for R-3.

CORAM:
HON'BLE MR. JUSTICE VIPIN SANGHI
HON'BLE MS. JUSTICE REKHA PALLI

O R D E R

% 20.04.2021

1. At the outset, it is pointed out that the appearance of Mr. Rahul Mehra, learned senior counsel representing the GNCTD and Mr. Satyakam, ASC has not been correctly recorded in our last order dated 19.04.2021.

2. The correct position may be recorded. Mr. Satyakam, ASC states that he is instructing. Mr. Rahul Mehra, learned senior counsel on behalf of the GNCTD.

3. We have heard the learned Additional Solicitor General, Mr. Chetan

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Signing Date:20.04.2021 23:05

Sharma, petitioner-in-person, Mr. Rakesh Malhotra, Mr. Rahul Mehra, Learned Senior Counsel appears alongwith Mr. Satyakam on behalf of respondent Nos. 1 & 2 as well as two senior officers of the Central Government, namely, Ms. Roli Khare, Director and Mr. Nipun Vinayak, Joint Secretary, Ministry of Health and Family Welfare at substantial length.

4. In terms of our order passed yesterday, the Central Government has filed an affidavit. Mr. Mehra states that though all efforts were made to file the affidavit on behalf of the GNCTD, the same could not be completed and, therefore, the same has not been filed today. Let the affidavit be filed by the GNCTD by 1:00 PM on 22.04.2021. The same shall be circulated to all the others present in the proceedings.

5. We have perused the affidavit filed on behalf of the Central Government, filed by Mr. Rajender Kumar, Under Secretary, Ministry of Health and Family Welfare. The affidavit has, firstly, dealt with the aspect of availability of COVID beds, as made available by the Central Government in the NCT of Delhi. It discloses that in a meeting held on 09.04.2021, it was decided that 500 ICU bedded DRDO COVID Care Hospital be established in Delhi Cantt. It is stated that 250 ICU beds have been operationalised by DRDO and another 250 beds shall be operationalised by 22.04.2021. It has been further decided to provide 25 medical officers and 75 paramedics to this COVID care centre from Central Armed Paramilitary Forces.

6. The Central Government has also called upon the States and Union Territories to provide their requirements for Ventilators in the States, so as to consider the supply of Ventilators as per the availability at the earliest. It

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ROHELLA
Signing Date:20.04.2021 23:05

is further stated that as per the demand of the GNCTD, 763 ventilators have been supplied by the Government of India. In addition to that, Safdarjung Hospital has been provided with 105 ventilators, Ram Manohar Lohia Hospital with 5 ventilators, LHMC with 5 ventilators, Ayush Hospital with 2 ventilators, ESIC Hospital with 10 ventilators and the DRDO facility has been provided with 500 ventilators.

7. The availability of beds for COVID patients, as on 19.04.2021 in the named Central Government run hospitals has also been provided in paragraph 8 of the affidavit. The same add up to 1432 beds. These are apart from 250 beds that the DRDO would make available, 250 beds in LHMC and 36 in Safdarjung Hospital, which are also being planned. She points out that in other hospitals and facilities – other than thos detailed in the affidavit, 2105 beds have been made available by the Central Government in the NCT of Delhi, and with the addition of these beds, the current COVID beds allocated stand at about 4091 bed. The complete break up of these COVID beds, should be indicated in the affidavit to be filed by the Central Government on 22.04.2021 by 01:00 p.m. The same should contain details of ICU/ Non ICU beds, and beds with/ without oxygen, and with/ without ventilator.

8. Mr. Mehra has submitted that last year, when the pandemic was raging, the Central Government had made 4,112 beds available for COVID patients in its hospitals and facilities at Delhi. He states that the number of COVID positive patients are four times presently than the peak figures of last year. He submits that the Central Government should allocate more beds in its hospitals and facilities for COVID patients.

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ROHELLA
Signing Date:20.04.2021 23:05

9. Ms.Roli Khare, Director, Ministry of Health and Family Welfare has stated that the Central Government is endeavoring to make more beds available. She states that presently the hospitals of the Central Government are occupied by non-covid patients in need of critical care, such as patients who require dialysis, or suffering from cancer and other serious disease. Considering the fact that the number of COVID patients, who are now needing hospitals if for greater than the numbers which were turning up last year – even during the peak of the pandemic, the Central Government should urgently look to allocate more beds among their hospitals for COVID patients. We direct the Central Government to look into the aspect of bed allocation for COVID patients keeping in view the prevailing circumstances, and report in this regard on the next date of hearing i.e. 22.04.2021.

10. The other aspect on which we have heard submissions, is the aspect of availability of medical Oxygen in the NCT of Delhi. On this front, the situation is rather alarming. We have been informed during the course of hearing that the availability of Oxygen – as we pass this order, has dropped dramatically in Hospitals. The situation is such, that the Oxygen pressure has been reduced, to keep it going longer, with the result that serious patients, who are in need of Oxygen have suffered drastic fall in their Oxygen levels, which is turning out to be one of the major causes of fatality of COVID patients.

11. Dr.Nipun Vinayak, Joint Secretary, Ministry of Health and Family Welfare has explained to us that the Department for Promotion of Industries and Internal Trade(DPIIT) is looking into the aspect of diversion of Oxygen from industrial use for medical use in view of the urgent need of Oxygen. He submits that allocations of Oxygen have been made on the basis of the

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demands made by the States, and on the basis of the formula evolved by the experts about the requirement of Oxygen for patients suffering from COVID. He states that the allocation for Delhi is 378 MT per day.

12. On the other hand, Mr.Mehra submits that there is grave dearth of medical Oxygen in Delhi's hospitals, and the requirement according to him is 700 MT of medical Oxygen per day. He submits that there is non-compliance of the order passed by us yesterday, whereby we required M/s INOX to honor its contract with the GNCTD and Delhi hospital and to supply 140 MT of Oxygen to Delhi. He states that the reason for non-compliance is stated to be the possible law and order situation that may be created, in case the M/s INOX were to transport the Oxygen from Uttar Pradesh to Delhi, where the manufacturing unit of INOX is situated.

13. Mr. Vinayak has also informed us of the industries, which are permitted to continue with the use of Oxygen. He submits that apart from those industries, all others have been directed not to use Oxygen, so that the same could be made available for medical use in the country. Amongst the permitted industries, we find that the Steel and Petro-Chemical industries are also included.

14. Looking to the serious and emergent situation, we call upon the Central Government to seriously consider issuing appropriate orders in respect of the Steel and Petro-Chemical industries, so that a balance can be maintained between the needs of the people at large – who are suffering from COVID and are serious, and the needs of the industries. After all, if more and more people are going to suffer seriously from COVID – which in turn may result in extended lockdown and closures, the purpose of full production of Steel and Petroleum products would also be of no avail, as

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their consumption is bound to fall in that scenario. We, therefore, expect the Central Government to urgently hold a meeting with all stakeholders including from the Steel and Petro-Chemical industries, so that sufficient portion of the Oxygen produced by these industries could be diverted for medical needs for the period required to tide over the prevailing medical emergency.

15. Mr.Vinayak has also pointed out that the Central Government had sanctioned funds in December, 2020 to set up Pressure Swing Adsorption(PSA) plants for production of oxygen throughout the country. For the NCT of Delhi, eight such plants were sanctioned. He states that only one has become operational till date, and two of the hospitals, namely, Satyawadi Raja Harish Chandra Hospital and Vardhaman Mahavir Medical College & Safdarjung Hospital have not yet provided the site clearance where the PSA plant could be installed. Two of the hospitals have now provided the site clearance and the equipment would be installed by 30.04.2021. We direct the respondents to ensure that the remaining hospitals – who have not acted in response to the said scheme of the Central Government, act immediately. Compliance be reported on the next date.

16. Looking to the number of COVID positive patients all over the country, and the pattern which is emerging with regard to the spread of the viral infection and the severity with which it is impacting people in different States and regions, we direct the Central Government to review the allocation of Oxygen on a dynamic basis i.e. on a day to day basis, so that its utilization is achieved in the most efficient manner.

17. Another aspect highlighted by Mr.Vinayak is with regard to the efficient usage of Oxygen. He points out that the State of Kerala has led by

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example in this regard, and the use of Oxygen by Kerala is most efficient, which should be followed by all.

18. As we pass this order, we are informed that the Oxygen supplies in various Covid hospitals in Delhi, including Sir Ganga Ram Hospital, and Max Hospital are about to get exhausted in the next about 4-8 hours. The decision taken by the Central Government to divert supplies from industrial use for medical use, for some obscure reason, has been sought to be implemented only from 22.04.2021.

19. We do not find any justification for the same. The need for oxygen is now. Any delay in this regard would lead to loss of precious lives. We, therefore, direct the Central Government to implement the said decision forthwith, and make available oxygen to hospitals which are running out of their supplies, lest there is grave loss of life suffered by patients being treated thereat.

20. Since M/s INOX has not complied with our last order dated 19.04.2021, we direct issuance of Notice of Contempt to M/s INOX returnable on 22.04.2021. Notice be served through email. We direct the Managing Director/ Owner of M/s INOX to personally remain present during the hearing on the next date of hearing. The State of UP, through the Chief Secretary should also remain present during the hearing. Notice shall also be issued to him.

21. On the aspect of ramping up of the testing facilities for Covid-19 through the RT-PCR test, there are certain aspects which need to be addressed by the Central Government, and its instrumentalities. We are informed that the equipment for setting up RT-PCR test labs are imported, and medical equipment/ machines for which import orders have been placed,

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are being dealt with routinely at Customs Ports. It is essential that all such medical machines/ equipments, medicines, etc. which are imported should be handled and cleared at top priority by the Customs. We direct the Central Government to issue necessary directions in this regard forthwith.

22. For the purpose of setting up of Covid testing facilities, the entrepreneurs/ doctors have to obtain clearance from the Indian Council for Medical Research (ICMR). It has been brought to our notice that the procedure for such clearances is also highly time consuming. We do not wish to, in any way, impinge on the authority of ICMR, and we do not expect the ICMR to relax its standards in the matter of granting its permissions and clearances. However, looking to the present day situation, we direct the ICMR to give top priority for such clearances so that the RT-PCR Labs could be set up or expanded without any delay.

23. Another aspect that has been brought to our notice, which is also resulting in delay in preparation of RT-PCR Test Reports, is the Software deviced for uploading of the Test results on the website. The patients who undergo the RT-PCR test,s are required to provide their Aadhar Cards. Despite that being the position, the testing agencies are required to fill up detailed forms online, which take up to 15 minutes per form. We, therefore, direct the Central Government, and the ICMR, to review the form in which the information is required to be uploaded by the testing agencies, so as to reduce their burden and wastage of time, as this appears to be acting as a bottleneck in the matter of preparation of reports.

24. We have also noticed reports in newspapers about the critical medicines required for the treatment of serious Covid-19 patients falling in short supply, and also being sold at a premium in the black market. It

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appears that the requisite drugs are being hoarded by some unscrupulous persons/ dealers or retailers. We direct the Central Government, and its agencies, particularly the Drug Controller of India, to issue necessary directions in this regard to all the licensees, and the Government should undertake checking on a regular basis to unearth all such cases of hoarding which is leading to scarcity of drugs in the marked for the needy patients. Strict penal action should be taken against those indulging in such practices.

25. The affidavit filed by the Central Government discloses that – so far as Remedesivir Drug is concerned, the Central Government has supplied 10.40 lakh vials to all the States and Union Territories during the last 9 days (between 11th and 19th April), out of which 40,132 vials have been supplied to Delhi. Meanwhile, DGCI has granted immediate permission to license holders for manufacture of the Remedesivir at 20 additional sites, adding production capacity of 35.3 vials/ month. It is stated that this would ramp up the production capacity for manufacturing this drug to around 74.10 lakh vials/ month.

26. The Central Government should dynamically review the distribution of Remedesivir in the States and Union Territories on a daily basis, on the basis of the need, assessed on the basis of the serious active Covid patients, who need to be administered the said Drug. This is essential to maximise the efficient use of the said Drug.

27. There are a number of other drugs which are being used for treatment Covid-19 patients, such as *Tocilizumab, Favipiravir, Ivermectin, Dexamathasone, Methylprednisolone, Dalteparin, Enoxaparin, HCQ and Baricitinib*. As per news reports, there are shortages of some, if not all, of the aforesaid drugs. Looking to the emergent situation, we direct the Central

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Government to immediately reach out to the manufacturers/ patent holders/ licensees so as to forthwith ramp up the production capacities of the above, and all such other medications, as are essential for treatment of Covid positive patients. We may take note of the fact that the Patents Act provides for Compulsory Licenses under Section 84, and Special Provision for Compulsory Licenses or Notifications by the Central Government, under Section 92. Section 100 provides the power of the Central Government to use inventions for purposes of the Government.

28. Looking to the present day situation, there can be no doubt that a case is made out for exercise of its power by the Central Government/ Controller under the aforesaid provisions of law. At the same time, the interests of the Patent holders/ licensees should be kept in mind, since it on account of their investments, inventions and hard work that such like medicines are made available to the public at large. The best course would be encourage the existing manufacturers to ramp up their production on a war footing. They should also be encouraged to grant voluntary licenses to other entities to manufacture the requisite drugs. However, if such efforts do not fructify soon enough, the Government/ Controller should not hesitate to invoke their jurisdiction and powers under the aforesaid provisions of the Patents Act, since the lives of thousands of people are being lost each day in the country due to COVID. The lives of the people take priority over everything else. Even if such like powers are exercised, the patent holders/ manufacturers can be adequately compensated by fixation of fair license fee. The Central Government should swing into action in terms of this order in this regard without any delay, and report progress on the next date of hearing.

29. Another aspect that we may take note of is that as per one of the

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reports, as many as about 44 lakhs vaccines have been wasted out of the 10 crores vaccines allocated to different States. This is because of the restriction with regard to the age, or category of people who are entitled to take the vaccine. According to the present dispensation, people who are above 45 years of age are entitled to take the vaccine. The Government has recently announced that from 01.05.2021, all above the age of 18 years would be entitled to take the vaccine. In our view, wastage of even a single dose of vaccine, when the same is proving to be life–saving, would be a criminal waste. We are informed that each vial of the vaccine has 10 doses. Once the vial is opened, it has to be either fully consumed, or the remainder goes waste. It should be possible for the Government(s) to devise ways and means so as to register volunteers who may be below the age group of 45 years, and above the age of 18 years – who could be called upon to take the residual doses of vaccine, in case, there are doses left unutilised after, say, 05.00 P.M on each day. That would ensure that all the doses are fully utilised, and not wasted. We may observe that this flexibility is available in other countries such as United States of America. For this purpose, the Government should modify their mobile COVIN application appropriately, urgently. We direct the Government to look into this aspect forthwith and report status on the next date.

30. List on 22.04.2021.

VIPIN SANGHI, J

REKHA PALLI, J

APRIL 20, 2021
N.Khanna/ K.D.

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Reportable

IN THE SUPREME COURT OF INDIA
CIVIL ORIGINAL JURISDICTION

Suo Motu Writ Petition (Civil) No.3 of 2021

IN RE: DISTRIBUTION OF ESSENTIAL SUPPLIES AND SERVICES DURING PANDEMIC.

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Chetan Kumar
Date: 2021.05.02
20:42:45 IST
Reason:

O R D E R

This order has been divided into the following sections to facilitate analysis:

A Introduction

B Outline of the Disaster Management Act

C Medical Infrastructure

C.1 Submissions in UOI's Affidavits

C.2 National Policy for Admission in Hospitals

D Oxygen allocation and availability

E Vaccines

E.1 Vaccine capacity and disbursal

E.2 Vaccine pricing

F Potentiality of Compulsory Licensing for vaccines and essential drugs

G Supply of Essential Drugs

G.1 Submissions in the Central Government's Affidavits

G.2 Recommendations

G.3 Black Marketing

H Recommendations for augmenting healthcare workforce

I Epilogue

J Conclusion

A Introduction

1 The genesis of this *suo motu* writ petition is in an order dated 22 April 2021. This Court took note of the unprecedented humanitarian crisis in the country, following the outbreak of the COVID-19 pandemic. Notices were issued to the Union of India[1], the Governments of the States and Union Territories[2], and to several petitioners who were before the High Courts. The Court observed:

> "the Union Government, the State Governments/Union Territories and the parties, who appeared to have approached the High Courts to show cause why uniform orders be not passed by this Court in relation to
> a) Supply of oxygen;
> b) Supply of essential drugs;
> c) Method and manner of vaccination; and
> d) Declaration of lockdown"

The Court directed the Central Government to :

> "1. Report on the existence or otherwise and requirement of setting up of a coordinating body that would consider allocation of the above resources in a consultative manner (with the involvement of concerned States and Union Territories).
> 2. Consider declaration of essential medicines and medical equipment including the above articles as essential commodities in relation to COVID.
> 3. In respect of coordination of logistical support for inter-State and intra-State transportation and distribution of the above resources."

2 The Court also had appointed an *Amicus Curiae* to assist it. However, the *Amicus Curiae* was, on his request, relieved of his position on 23 April 2021. Hearings in the matter were then conducted on 27 April 2021, where the Court appointed two new *Amici:* Mr Jaideep Gupta and Ms Meenakshi Arora, learned Senior Counsel. They will be assisted by Mr Kunal Chatterjee and Mr Mohit Ram,

[1] "**UOI**", referred interchangeably as "**Central Government**"
[2] Collectively referred as "**State Government**"

learned counsel and Advocate-on-Record. The Court began the hearing by noting that the jurisdiction it assumed under Article 32 did not automatically lead to the erosion of a High Court's jurisdiction under Article 226. Rather, the Court stressed on the importance of the jurisdiction under Article 226, and how High Courts may be better equipped to deal with issues within their own States. However, this Court assumed jurisdiction over issues in relation to COVID-19 which traverse beyond state boundaries and affect the nation in its entirety.

3 The Court noted that it was in receipt of an affidavit dated 23 April 2021 filed by the UOI. However, the Court directed the UOI to file an additional affidavit and the respective governments of the States/Union Territories to file fresh affidavits on four issues. The relevant extract of the order reads thus:

> "(i) Supply of oxygen – The Court should be apprised by the Union of India on
> (a) The projected demand for oxygen in the country at the present point of time and in the foreseeable future;
> (b) The steps taken and proposed to augment the availability of oxygen, meeting both the current and projected requirements;
> (c) The monitoring mechanism for ensuring the supply of oxygen, particularly to critically affected States and Union Territories as well as the other areas;
> (d) The basis on which allocation of oxygen is being made from the central pool; and
> (e) The methodology adopted for ensuring that the requirements of the States are communicated to the Central Government on a daily basis so as to ensure that the availability of oxygen is commensurate with the need of each State or, as the case may be, Union Territory.
>
> (ii) Enhancement of critical medical infrastructure, including the availability of beds, Covid treatment centres with duly equipped medical personnel on the basis of the projected requirement of healthcare professionals and anticipated requirements. The Union government will consider framing a policy specifying the standards and norms to be observed for admitting patients to hospitals and covid centres and the modalities for admission;

(iii) The steps taken to ensure due availability of essential drugs, including Remdesivir and Favipiravir among other prescribed drugs and the modalities which have been set up for controlling prices of essential drugs, for preventing hoarding and for ensuring proper communication of the requirements at the level of each District by the District health authorities or Collectors to the Health Departments of the States and thereafter by the states to the Union Ministry of Health and Family Welfare so that the projected requirements are duly met and effectively monitored on a daily basis.

(iv) Vaccination
(a) Presently two vaccinations have been made available in the country, namely, Covishield and Covaxin;
(b) As of date, the vaccination programme has extended to all citizens of the age of 45 years and above;
(c) From 1 May 2021, the vaccination programme is to be opened up also to persons between the age groups of 18 to 45, in addition to the existing age group categories. The Union of India shall clarify (i) the projected requirement of vaccines as a result of the enhancement of coverage; (ii) the modalities proposed for ensuring that the deficit in the availability of vaccines is met; (iii) steps proposed for enhancement of vaccine availability by sourcing stocks from within and outside the country; (iv) modalities for administering the vaccines to meet the requirements of those in the older age group (forty five and above) who have already received the first dose; (v) modalities fixed for administering the vaccine to meet the additional demand of the 18-45 population; (vi) how the supplies of vaccines will be allocated between various states if each state is to negotiate with vaccine producers; and (vii) steps taken and proposed for ensuring the procurement of other vaccines apart from Covishield and Covaxin and the time frame for implementation; and
(d) The basis and rationale which has been adopted by the Union government in regard to the pricing of vaccines. The government shall explain the rationale for differential pricing in regard to vaccines sourced by the Union government on one hand and the states on the other hand when both sources lead to the distribution of vaccines to citizens."

4 This Court then received an additional affidavit dated 29 April 2021 from the UOI, and fresh affidavits by the various States/UTs addressing the four issues mentioned in its order dated 27 April 2021. In the hearing conducted on 30 April 2021, this Court heard submissions by Mr Tushar Mehta, learned Solicitor

General of India, who was appearing on behalf of the Central Government. Several other counsels have made brief interjections, including Mr Vikas Singh, Senior Counsel and President of the Supreme Court Bar Association. This Court also heard a presentation on oxygen supply in India by Ms Sumita Dawra, Additional Secretary, Department of Promotion of Industry and International Trade, Ministry of Commerce and Industry. As such, unless specified otherwise, the directions and observations in the present order are limited to the UOI.

5 During the course of the hearing, this Court directed that the individual States/UTs shall be given an opportunity to discuss their affidavits at a later hearing. Further, the Court also directed the learned *Amici* to prepare a tabular compilation in relation to all the Interlocutory Applications which have been filed in this petition. On the basis of the issues raised, they shall also be considered in a later hearing. Before delving into a substantive discussion, we would like to clarify that the jurisdiction exercised in this matter is merely to facilitate a dialogue of relevant stakeholders, the UOI, the States and this Court, in light of the pressing humanitarian crisis, and not with a view to usurp the role of the executive and the legislature. This bounded-deliberative approach[3] is exercised so that the UOI and States can justify the rationale behind their policy approach which must be bound by the human rights framework which presently implicates the right to life under Article 21 and right to equality under Article 14 of the Constitution.

[3] Sandra Fredman, "Adjudication as Accountability: A Deliberative Approach" in Nicholas Bamforth and Peter Leyland (eds), *Accountability in the Contemporary Constitution* (Oxford University Press, 2013)

B Outline of the Disaster Management Act

6 The Disaster Management Act, 2005[4] came into effect on 26 December 2005. The DMA provides for the effective management of disasters and matters connected or incidental to such disasters. COVID-19 falls under the definition of a disaster under Section 2(d)[5] of the DMA and the provisions of the DMA were invoked for the first time to deal with the present pandemic. Under Section 6(2)(i) of the DMA, the National Disaster Management Authority[6] issued an order dated 24 March 2020 directing the Ministries, UOI, State/UTs and their authorities to take effective measures to prevent the spread of COVID-19 in the country. Thereafter, the Home Secretary, Ministry of Home Affairs as the Chairperson of the National Executive Committee, which assists the NDMA in its functions, in an order dated 24 March 2020 issued guidelines for the initial 21 days' lockdown on account of COVID-19.

7 Section 2(e) defines disaster management as a continuous and integrated process of planning, organizing, coordinating and implementing measures in relation to the disaster. Section 2(e) provides:

> "2…
> (e)"disaster management" means a continuous and integrated process of planning, organizing, coordinating and implementing measures' which are necessary or expedient for--
> (i) prevention of danger or threat of any disaster;
> (ii) mitigation or reduction of risk of any disaster or its' severity or consequences;
> (iii) capacity-building;

[4] "**DMA**"
[5] ""2…(d) "disaster" means a catastrophe, mishap, calamity or grave occurrence in any area, arising from natural or man-made causes, or by accident or negligence which results in substantial loss of life or human suffering or damage to, and destruction of, property, or damage to, or degradation of, environment, and is of such a nature or magnitude as to be beyond the coping capacity of the community of the affected area;"
[6] "**NDMA**"

(iv) preparedness to deal with any disaster;
(v) prompt response to any threatening disaster situation or disaster;
(vi) assessing the severity or magnitude of effects of any disaster;
(vii) evacuation, rescue and relief;
(viii) rehabilitation and reconstruction;.."

Section 2(n) of DMA defines a "National Plan" as the plan for disaster management for the whole country prepared under Section 11 of DMA. Section 3 of the DMA constitutes the NDMA with the Prime Minister as the Chairperson, *ex officio*. Section 6 lists down the powers and functions of the NDMA. Under Section 6(2)(b), NDMA has the power to approve the National Plan. Section 11 of the DMA provides the procedure for drawing up and implementation of the National Plan in the following terms:

"11. National Plan
(1) There shall be drawn up a plan for disaster management for the whole of the country to be called the National Plan.
(2) The National Plan shall be prepared by the National Executive Committee having regard to the National Policy and in consultation with the State Governments and expert bodies or organisations in the field of disaster management to be approved by the National Authority.
(3) The National Plan shall include--
(a) measures to be taken for the prevention of disasters, or the mitigation of their effects;
(b) measures to be taken for the integration of mitigation measures in the development plans;
(c) measures to be taken for preparedness and capacity building to effectively respond to any threatening disaster situations or disaster;
(d) roles and responsibilities of different Ministries or Departments of the Government of India in respect of measures specified in clauses (a), (b) and (c).
(4) The National Plan shall be reviewed and updated annually.
(5) Appropriate provisions shall be made by the Central Government for financing the measures to be carried out under the National Plan.
(6) Copies of the National Plan referred to in sub-sections (2) and (4) shall be made available to the Ministries or Departments of the Government of India and such Ministries

> or Departments shall draw up their own plans in accordance with the National Plan."

8 A National Plan includes, *inter alia*, measures for disaster prevention, mitigation, preparedness and roles and responsibilities of different Ministries in terms of Section 11(3) of DMA. A National Plan for the entire country was prepared in the year 2016 and was revised and notified in November, 2019. The National Plan, 2019 provides a framework to the Government agencies to deal with different aspects of disaster management. Section 11(4) of the DMA provides that the National Plan is to be revised and updated annually making it a 'dynamic document'. The executive summary of the National Plan succinctly captures its purpose and contours in the below extract:

> "...The National Disaster Management Plan (NDMP) provides a framework and direction to the government agencies for all phases of disaster management cycle. The NDMP is a "dynamic document" in the sense that it will be periodically improved keeping up with the emerging global best practices and knowledge base in disaster management. It is in accordance with the provisions of the DM Act, 2005, the guidance given in the National Policy on Disaster Management (NPDM) 2009, and the established national practices..."

9 Section 12 of the DMA empowers the NDMA to recommend guidelines for the minimum standard of relief to be provided to persons affected by disaster. NDMA can create guidelines stipulating minimum standards of relief for providing ex gratia assistance on account of loss of life and restoration of means of livelihood in terms of Section 12(iii) of DMA. In light of the human suffering and loss of livelihood that has accompanied this pandemic, NDMA may consider laying down minimum standards of relief in this regard. We clarify that this is not

a direction of this Court, however a suggestion that can be looked into by the NDMA. Under Section 12(iv) of the DMA, the NDMA has been given wide powers to provide guidelines for any such relief that may be necessary.

10 In addition to the above provisions, Section 35 of the DMA empowers the Central Government to take measures which it deems to be necessary or expedient for the purpose of disaster management. Section 35(2)(a) provides for coordination of actions between the Central Government and State Governments and their respective authorities in relation to disaster management. Section 35(2)(e) obliges the Central Government to assist and cooperate with the State Governments as requested by them or otherwise deemed appropriate by it.

11 Section 36 of DMA provides for the responsibilities that have to be undertaken by the Ministries or Departments of the Central Government. While Section 36(h) empowers the Central Government to take any actions that it may consider necessary for disaster management, Section 36(d) specifically enables it to review its policies with a view to incorporate provisions necessary for prevention of disaster, mitigation or preparedness. Under Section 36(f), it is the responsibility of every Ministry or Department of Central Government to provide assistance to the State Governments for (i) drawing up mitigation, preparedness and response plans, capacity-building, data collection and identification and training of personnel in relation to disaster management; (iii) carrying out rescue and relief operations in the affected area; (iii) assessing the damage from any disaster; and (iv) carrying out rehabilitation and reconstruction. Section 35(g) provides that the Central Government is responsible for making available its resources to the National Executive Committee or a State Executive Committee

for the purposes of, *inter alia*, transporting personnel and relief goods to and from the affected area.

12 The provisions of Sections 35 and 36 of the DMA that have been discussed above have been enacted in the spirit of cooperative federalism in order to ensure that Central Government can assist and enable the State Governments to effectively tackle the disaster in question.

13 The learned Solicitor General has submitted that the Central Government is operating under the broad framework of the National Plan and the plan is already in force. The plan specifically deals with "Biological and Public Health Emergencies". Further, different States have their own Disaster Management Plans in place. It has been submitted that the National Plan does not and cannot contain step by step instructions or specific directions for the day to day management of the pandemic by the Government agencies. Such aspects are kept open for executive decision, in view of the dynamic nature of the disaster in question. Further, since COVID-19 is a novel virus, the knowledge in relation to such a virus is contemporaneous in nature and is subject to constant development. A three Judge bench of this Court in its judgement in **Centre for Public Interest Litigation** vs **Union of India**[7] had noted that there was no need to develop a fresh National Plan under Section 11 for COVID-19 since a National Plan was already in place, which was being supplemented by various orders and measures taken by competent authorities under DMA. Justice Ashok Bhushan, speaking for this Court, observed that:

[7] 2020 SCC OnLine SC 652

> "40. The Disaster Management Act, 2005 contain ample powers and measures, which could be taken by the National Disaster Management Authority, National Executive Committee and Central Government to prepare further plans, guidelines and Standard Operating Procedure (SOPs), which in respect to COVID-19 had been done from time to time. Containment Plan for Novel Coronavirus, 2019 had been issued by Ministry of Health and Family Welfare, Government of India. There were no lack of guidelines, SOPs and Plan to contain COVID-19, by Nodal Ministry had been brought on record issued by Ministry of Health and Family Welfare, Government of India, i.e., Updated Containment Plan for Large Outbreaks Novel Coronavirus Disease, 2019 (COVID-19)."

14 Therefore, the National Plan, 2019 can be supplemented by the issuance of additional guidelines to tackle any aspect of disaster management including the issue of admission to hospitals and access to essential drugs and vaccines in respect of COVID-19.

C Medical Infrastructure

C.1 Submissions in UOI's Affidavits

15 In relation to the broad issue of medical infrastructure, the Central Government begins its affidavit dated 23 April 2021 and additional affidavit dated 29 April 2021 by describing its 'three-tier setup' of Covid Care Centers[8], Dedicated COVID Health Centers[9] and Dedicated COVID Hospitals[10] which was recommended to the States for tackling the COVID-19 pandemic, for which the UOI also provided funds under an emergency response package from the National Health Mission and State Disaster Response Fund.

[8] "**CCC**"
[9] "**DCHC**"
[10] "**DCH**"

16 The present status of these is: (i) 2,084 DCH (of which 89 are under the Central Government and the rest 1,995 with State Governments); (ii) 4,043 DCHC; and (iii) 12,673 CCC. Cumulatively, they have 18,52,265 beds in total, out of which 4,68,974 beds are in DCH. It was also noted that Central Government hospitals have also been converted into DCH.

17 Further, tertiary care hospitals under ESIC, Defence, Railways, paramilitary forces, Steel Ministry, *et al*, are also being leveraged for case management. Even as many as 3816 railways coaches spread over 16 railway zones have been converted into CCC. Finally, the DRDO has also set up large field hospitals with capacities ranging from 1,000 to 10,000 isolation beds.

18 It was noted that through coordination between Central Government and State Governments, isolation beds (with/without oxygen) were increased to around 15.7 lakhs, as compared to 10,180 before the first lockdown; similarly, ICU beds were increased to more than 85,000, as compared to 2,168 before the first lockdown. Similar upgrades were provided to necessary equipment such as Ventilators, N95 masks and PPEs.

19 The affidavit provides the following details of the efforts taken by UOI to create projections for each State, and how it was communicated to them:

(i) It has developed an IT module for projections of expected cases based on ongoing caseload, so as to alert States and districts to be prepared in advance. The projections by the Central Government were regularly shared in writing with the States, along with reports containing emergency

plans. This tool was also made available to States, to map their own projections at the State level;

(ii) Details of the meetings conducted by the Prime Minister, the Minister of Health and Family Welfare, the Cabinet Secretary, the Secretary (H) and the DGHS were provided; and

(iii) Details of letters (which seem to have been sent on a monthly basis) sent by the Central Government to the State Governments indicate that they informed the State Governments of the projected cases for the coming month, along with the number of Oxygen Supported Beds, ICU Beds and of Ventilators that will be required to manage the projected cases. Thereby, the State Governments which were found lacking in their numbers were directed to ramp up their facilities.

20 In relation to the preparedness for the second wave of the COVID-19 pandemic, the affidavits state that:

(i) After the first wave, the Central Government has been consistently writing to the State Governments from 4 December 2020 with numbers of projected cases, along with the directions requiring them to arrange the necessary infrastructure which will be needed;

(ii) State Governments were requested by the UOI to formulate a comprehensive plan in relation to:

(a) Bed capacities, ICU beds, further identification of additional hospitals, preparation of field hospital facilities, ensuring sufficient oxygen supported beds and oxygen supplies;

(b) Deployment of requisite HR training and mentoring of doctors and nurses for management of patients, strengthen ambulance services and centralized call center-based services for allocation of beds;

(c) Suitable initiatives for (among other things) achieving and maintaining adequate level of testing, surveillance and risk communication for promoting wearing of masks, physical distancing, hand hygiene;

(d) Sufficient referral linkages for districts with deficit infrastructure through deployment of additional ambulances, wherever necessary; and

(iii) On 20 April 2021, the Ministry of Health and Family Welfare[11] wrote to the State Governments with their projections and reminded them also of the funding avenues being made available to all States under NHM funding, State Disaster Response Fund, and other initiatives.

21 The affidavits also note that the Central Government had developed a live portal with all the States and districts where they were asked to feed in their data of cases and details such as people under home isolation, on isolation beds (with or without oxygen) and on ICU beds. Further, the State Governments were also directed to feed in details of the COVID dedicated health care infrastructure created by them, besides the details of containment zones so specified by them. However, the Central Government has alleged that States and districts did not upload their data regularly enough. Additionally, there was also a 'Facility App' which could be used by Covid Health facilities to monitor their patients as well as the availability of logistics with their health facility. However, the Central

[11] "**MoHFW**"

Government alleges that States, districts and facilities did not use this Facility App.

C.2 National Policy for Admission in Hospitals

22 It has been submitted by the Central Government that health being a state subject, the medical infrastructure is largely created and maintained by the respective State Governments. Since we are yet to hear from the State Governments, we shall not be issuing any directions or making comprehensive observations in relation to this issue.

23 However, based on the affidavits submitted by the Central Government and the hearings which followed, we have come to understand that there is no national policy on how admissions must take place in the various tiers of hospitals (CCC, DCHC and DCH). Gaining admission into a hospital with a bed is one of the biggest challenges being faced by most individuals during this second wave of the COVID-19 pandemic. Left to their own devices, citizens have had to suffer immeasurable hardship. Different states and local authorities follow their own protocols. Differing standards for admission in different hospitals across the nation leads to chaos and uncertainty. The situation cannot brook any delay. Accordingly, we direct the Central Government to frame a policy in this regard, in exercise of its statutory powers under the DMA, which will be followed nationally. The presence of such a policy shall ensure that no one in need is turned away from a hospital, due to no fault of their own. Such a policy should, *inter alia*, address the following issues in relation to admission:

(i) Requirement of a positive test for COVID-19 virus, which may become difficult for many individuals since testing facilities are overwhelmed, test results are taking inordinately long time and the new strain of the COVID-19 virus is sometimes not even picked up by a regular RT-PCR test;

(ii) Some patients are being refused service based on arbitrary factors. For example, the hospitals in Ahmedabad were initially refusing to take in patients who did not arrive in the government-run '108' ambulances. While this rule has now been removed, after objections were noted by the Gujarat High Court during hearings in a *suo motu* public interest litigation[12], we note that such rules cannot be allowed to crop up in other places;

(iii) Some reports have also been brought to our attention that hospitals are refusing to admit individuals who cannot produce a valid ID card which shows that they belong to the city where the hospital is located. Given how overstretched our hospitals are during the second wave of the COVID-19 pandemic, it is entirely plausible that individuals may travel to other cities in desperation, since beds may not be available in their city. The rural health infrastructure is seriously deficient. Hence, no hospital should be allowed to deny them entry solely based on this reason or any other issues with identity proofs;

(iv) A related issue is when individuals often get their family member admitted in a hospital in one city, but have to travel to another city to look for oxygen or essential drugs and are denied their use because they are to be bought

[12] **Suo Motu** vs **State of Gujarat**, R/Writ Petition (PIL) No 53 Of 2021

for an individual admitted in a different city. As was true for the above such rule, this is also unacceptable and should not be allowed;

(v) Admissions to hospital must be based on need. The Central Government, in consultation with the respective State Governments, must formulate guidelines on the stage at which hospitalization is required so as to ensure that scarce hospital beds are not occupied by persons who do not need hospitalization. This aspect should be based on the advice of medical experts and can be suitably altered given the needs of each State (or regions within the State) and in the course of the experiences gained during the pandemic; and

(vi) Directions are hereby issued to all States, Union Territories, and all public agencies, to ensure that the above orders are implemented forthwith. The Central, State and Union Territory governments shall issue necessary orders and circulars, incorporating the above directions, within three days, which shall be in force till replaced by an appropriate uniform policy, devised by the central government, statutorily.

D Oxygen allocation and availability

24 The Central Government has argued the following:

(i) By its order dated 11 September 2020, the Ministry of Home Affairs[13], in exercise of its powers under Section 10(2)(h) of the DMA had constituted an Empowered Group-II as an inter-ministerial body to ensure availability of essential medical equipment and oxygen management;

(ii) Medical oxygen is critical to treatment of COVID affected patients. The entire available capacity of oxygen is used for supply for industrial and medical use, which is in the form of Liquid Medical Oxygen[14]. The major suppliers for both industrial and medical oxygen are steel plants in the public and private sectors, and private entities;

(iii) Oxygen is not produced evenly in India. While some States may be oxygen producing States such as Maharashtra, Rajasthan and Jharkhand; other States/UTs such as Delhi, Goa and Madhya Pradesh, do not have production capacity and rely on supply of oxygen from oxygen producing States;

(iv) For an estimation of the required oxygen supply, an Empowered Group I was constituted which categorized patients into three categories:

- Class I comprising of 80% of the cases which are mild and do not require oxygen;

[13] "**MHA**"
[14] "**LMO**"

- Class II comprising of 17% cases which are moderate and can be managed on non-ICU beds and 50% of these may require oxygen @10L/min; and
- Class III comprising of 3% of cases which are severe ICU cases requiring approximately 24L/min oxygen.

(v) On the basis of the categorization provided by Empowered Group I, oxygen requirement of different States on the basis of active cases is being calculated which is around 8462 MT. Based on the trend of active cases, the "doubling rate of cases" is calculated for each State, which implies, the number of days in which COVID cases are likely to double. The number of active cases are projected on the basis of the doubling rate and oxygen requirement is calculated. These projections get changed daily on the basis of real time change;

(vi) In order to ensure supply of oxygen to all States, a mapping exercise of the sources of supplies with the demand of medical oxygen to the critically affected States was undertaken jointly by the Department of Promotion of Industry and Internal Trade, MoHFW, Ministry of Steel, Petroleum and Explosives Safety Organisation, oxygen manufacturers etc. During the course of the mapping exercise, States were requested to indicate their projections for requirement of medical oxygen based on expected active case load. These projections were to be given as on 20 April, 25 April, and 30 April 2021. The following was the forecast provided by the major States:

S. No.	State	Forecast for requirement for medical oxygen (MT) as on		
		Apr-20	Apr-25	Apr-30
1	Maharashtra	1500	1750	2000
2	Uttar Pradesh	400	650	800
3	Chhattisgarh	215	295	382
4	Karnataka	300	155	111
5	Kerala	89	99	104
6	Delhi	300	349	445
7	Tamil Nadu	200	320	465
8	Madhya Pradesh	445	565	700
9	Rajasthan	125	124	124
10	Gujarat	1000	1050	1200
11	Haryana	180	180	180
12	Punjab	126	82	82
TOTAL		**4880**	**5619**	**6593**

(vii) Based on these projections, an indicative mapping framework was drawn up and approved by an order dated 15 April 2021, which provided the name of the supply point, the State to which supply was allocated and the quantity to be supplied. Subsequently, due to continuous changes in the number of cases and the need for medical oxygen, a revised projection was issued by States for 20 April 2021, which provided:

S. No.	State	Forecast for requirement for medical oxygen (MT) for 20th April		
		Initial	Revised	Remarks
1	Maharashtra	1500	1500	-
2	Uttar Pradesh	400	800	100% increase
3	Chhattisgarh	215	215	-
4	Karnataka	300	300	-

S. No.	State	Forecast for requirement for medical oxygen (MT) for 20th April		
		Initial	Revised	Remarks
5	Kerala	89	89	-
6	Delhi	300	700	133% increase
7	Tamil Nadu	200	200	-
8	Madhya Pradesh	445	445	-
9	Rajasthan	125	147	18% increase
10	Gujarat	1000	1000	-
11	Haryana	180	180	-
12	Punjab	126	126	-
13	Telangana	-	350	-
14	Andhra Pradesh	-	400	-
15	Uttarakhand	-	75	-
TOTAL		**4880**	**5619**	

(viii) Following this, a revised supply plan for medical oxygen to 15 States for meeting their demand was issued by an order dated 18 April 2021. Certain States, such as Delhi, Rajasthan, Punjab, Uttar Pradesh, Uttarakhand and Madhya Pradesh, faced challenges despite this allocation. Issues such as logistical bottlenecks in transportation, incidents of local authorities in disrupting supplies to other states were reported. Due to this, allocation orders were further amended by orders dated 21 April 2021, 22 April 2021, 24 April 2021, 25 April 2021 and 26 April 2021. The MHA also issued orders dated 22 April 2021 and 25 April 2021 under the DMA to direct States/UTs to ensure uninterrupted movement of medical oxygen;

(ix) The major principles on the basis of which the amendments were made were to: (a) ensure that projected requirement of LMO is allocated as far as possible; (b) allocate sources located within the State or closest to the State while balancing requirements from States which have no/low internal

manufacturing capacity; (c) ensure feasible transportation; (d) ensure minimum disruptions in existing supply chains;

(x) As an instance, the allocation summary for 28 April 2021 has been placed on record:

Sl No	State	Production Capacity on 28/04/2021 (MT)	Need of State (MT)	Existing Allocation (MT)	Oxygen lifted by the respective States on 26/04/2021 (MT)
1	Maharashtra	1209.18	1784	1784	1389.19
2	Goa	No Bulk Manufacturing Plant	11	11	
3	Gujarat	847.00	1000	975	904.20
4	Dadra & Nagar Haveli	No Bulk Manufacturing Plant	20	20	
5	Karnataka	625.00	770	802	441.19
6	Madhya Pradesh	No Bulk Manufacturing Plant	649	649	613.82
7	Delhi	No Bulk Manufacturing Plant	470	490	361.90
8	Haryana	246.86	180	232	228.64
9	Uttar Pradesh	244.00	857	857	640.68
10	Punjab	No Bulk Manufacturing Plant	137	177	180.38
11	Chandigarh		20	40	
12	Tamil Nadu	366.00	280	220	396.48

(xi) After the Central Government procures and allocates the quantity of medical oxygen to each State, it is the State Government's responsibility to arrange transportation to pick up their allotted quantity from the supply point;

(xii) Given the fact that the mapping exercise has to be continuously updated according to the need of the situation across States, the Central Government also put in an interactive mechanism called the "Virtual Central Control Room" consisting of senior officers of Additional/Joint Secretary rank to monitor and find solutions to any problems that may arise on a real time basis. We have been apprised that the daily allocation of the

supply of oxygen is sanctioned and uploaded on this virtual room, in which the Chief Secretaries of all States/UTs are members;

(xiii) In addition to the management of supply and demand of medical oxygen, the Central Government has also taken the following steps to ensure augmentation of supply in the country:

(a) **Licenses to industrial gas manufacturers:** By an order dated 7 April 2020, the Drug Controller General of India[15] allowed licenses to be issued to industrial gas manufacturers for manufacturing medical oxygen within 24 hours of receipt of the application by DCGI;

(b) Enhanced production of LMO in steel plants and by private manufacturers: Steps have been taken to reduce production of other liquid products which are required for manufacturing steel (such as argon and nitrogen) and enhance the capacity of liquid oxygen. This has resulted in immediate enhancement of 293 MT. Additionally, the steel sector has made available the liquid oxygen in its storage tanks (approx. 16,000 MT as on 21 April 2021). Supplies have increased from 1000 MT in the first week of April 2021 to 2600 MT on 21 April 2021. Moreover, private manufacturers have also enhanced production of medical oxygen;

(c) Restrictions on use of industrial oxygen: By an order dated 18 April 2021, the MoHFW restricted industrial use of oxygen. Supply of oxygen for all industrial use was completely prohibited on 21 April 2021, except for certain industries such as ampoules and vials; pharmaceuticals;

[15] "**DCGI**"

petroleum refineries; nuclear energy facilities; and oxygen cylinder manufacturers. These have added 1000 MT of additional oxygen;

(d) **Augmentation in availability of tankers:** India has 1224 oxygen tankers (16732 MT capacity) and efforts are being made to increase this capacity to 2000 tankers through conversion of nitrogen and argon tankers and import of 138 cryogenic tankers;

(e) **Commissioning of PSA plants:** Pressure Swing Absorption[16] is a technology to generate oxygen at a local level. PSA plants established in hospitals enable self-sufficiency in generation of oxygen. MoHFW is in the process of commissioning 162 PSA Plants (154 MT capacity). The following statistics have been furnished :

Number of plants installed:	38
Number of plants to be installed by 30 April 2021	21
Number of plants to be installed by 31 May 2021	105
Number of plants to be installed by 30 June 2021[17]	51
Number of PSA Plants for district headquarters (under planning)	500

(f) **Import of medical oxygen:** A global tender was floated to import 50,000 MT of medical oxygen to be supplied in 90 days and quotations have been received. As an interim measure, quotations from bidders were called within 24 hours as to the quantities they could offer, prices etc. Orders have been placed with 2 foreign suppliers, i.e., SSB Cryogenic Equipment Ltd. for 200 MT and Gulf Industrial Gases Abu

[16] "**PSA**"

[17] As per the affidavit dated 23 April 2021, the UOI has stated that "a further 105 plants will be installed by 31.05.2021 and thereafter increasing to 156 plants by 30.06.2021."

Dhabi for 1800 MT. Another order is also being placed with M/s Ultra-Pure Gases India for import of 500-1500 MT;

(g) **Augmentation of availability of cylinders:** 1,02,400 oxygen cylinders were procured in April and May 2020 and distributed to States. Orders for additional 1,27,000 cylinders were placed on 21 April 2021. The Central Government proposes to address the additional demand through regulated portable oxygen system technology;

(h) **Setting up of jumbo container based COVID hospitals using gaseous oxygen**: Apart from LMO, the gaseous oxygen production capacity in the steel sector is 43,000 MT per day against which 26,000 MT per day is being produced. Two private entities, AMNS and JSW are setting up "Jumbo" COVID centres with 1000 bed oxygen facilities in Hazira, Vijayanagar and Dolvi using gaseous oxygen; and

(i) **Transportation by Air & Rail:** Railways are being used for long distance transport of tankers through 'roll on roll off' service and an "Oxygen Express" - a double engine train which gets a green corridor - is being run from supply point to destination. As an instance, the first rake with 7 empty tankers reached Mumbai from Vizag to transport 105 MT from RINL Vizag to Kalamboli. In addition to this, defence aircraft for carrying empty tankers to supply point are being deployed. However, it is technically not possible to bring in oxygen filed tankers in an aircraft.

25 During the course of the hearing, the Solicitor General has also sought to lay down the facts and figures pertaining to production and supply of oxygen, daily supply to States and challenges faced in supply chain logistics before the

Court by means of a power point presentation. We note the submission of the Solicitor General that the figures given in the power point presentation are revised on a daily basis and that the presentation is not to be treated as a submission made on oath by the Solicitor General, which may give rise to a cause of action for litigation in future either before this Court or the High Courts. Ms Sumita Dawra, Additional Secretary, Department of Promotion of Industry and Internal Trade, Ministry of Commerce and Industry, who is one of the senior administrative officers in charge of oxygen procurement and supply coordination, has given an overview of these issues and made a presentation before us. We would like to record our appreciation for the contribution made by Ms Dawra and her team, who despite being infected by the COVID-19 virus, has continued to work and manage the supply of medical oxygen that the country so desperately needs today. It is through the earnest contribution of officers such as Ms Dawra, who are working round the clock, that the country is able to deal with the storm created by one of the worst humanitarian crises we have seen.

26 Based on the above facts and figures, the Solicitor General has stated that there is no dearth of oxygen supply in the country as on date and steps are being taken continuously to augment the supply of oxygen. Having said that, the Solicitor General has also admitted that there has been a shortage of supply to certain States and has attributed this shortage to various factors including the failure of State Governments to lift the allocated quantity of oxygen from the supply point; transportation bottlenecks caused by inter-State movement of tankers; and technical failure of certain plants leading to reassessment of allocation on a real time basis.

27 Submissions have also been made on the issue of supply of oxygen by Mr Rahul Mehra, learned Senior Counsel appearing for the Government of National Capital Territory of Delhi[18]. Mr Rahul Mehra submits that the GNCTD is facing an acute shortage of the supply of oxygen as it had been allocated a substantially lower quantity of oxygen as against its projected demand. Mr Mehra pointed out that initially as on 15 April 2021, the projected demand of GNCTD for 20 April 2021 was 300 MT/day, for 25 April 2021 it was 349 MT/day, and for 30 April 2021 it was 445 MT/day. However, due to a surge in cases, the projected demand was revised by GNCTD on 18 April 2021 to 700MT/day and this was immediately communicated to the Central Government. Despite the increase in projected demand, the supply of oxygen to GNCTD has continued in terms of the allocation order dated 25 April 2021, in which 490 MT/day were allocated. As against this as well, the manufacturers have only been able to supply 445 MT/day. Mr Mehra has clarified that as on the date of the hearing their demand was 700MT/day, however their projected demand for the coming days is stated to be 976 MT/day as the GNCTD has planned an increase in medical infrastructure, including beds with oxygen cylinders and beds for patients in intensive care unit.

28 Opposing his submission, the Solicitor General and Ms Dawra stated that no revised projections have been received from GNCTD till date. The Solicitor General has also sought to highlight that the government of GNCTD has failed to offtake the allocated quantity of oxygen from the supply point.

29 Having heard the submissions of both counsels on the issues pertaining to supply of oxygen to GNCTD, we note that the Central Government (on page 63)

[18] "**GNCTD**"

in its affidavit dated 23 April 2021 has admitted that the projected demand for GNCTD as of 20 April 2021 had increased by 133% from 300 MT/day to 700 MT/day. According to the figures of allocation given in the affidavit dated 23 April 2021 and the presentation given by Ms Dawra, the existing allocation of GNCTD remains at 490 MT/day. This situation must be remedied forthwith. The situation on the ground in Delhi is heart rending. Recriminations between the Central Government (which contends that GNCTD has not lifted its allocated quantity) and GNCTD (which contends that despite its projected demand the quantity allocated has not been enhanced) can furnish no solace to citizens whose lives depend on a thin thread of oxygen being available. On the intervention of the Court during the hearing, the Solicitor General states that he has instructions to the effect that GNCTD's demand of medical oxygen will be met and that the national capital will not suffer due to lack of oxygen. We issue a peremptory direction in those terms. In the battle of shifting responsibility of supplying/off-taking of oxygen, lives of citizens cannot be put in jeopardy. The protection of the lives of citizens is paramount in times of a national crisis and the responsibility falls on both the Central Government and the GNCTD to cooperate with each other to ensure that all possible measures are taken to resolve the situation. Learned Senior Counsel for GNCTD has assured the court after taking instructions at the 'highest' level that the issue will be resolved completely in a spirit of co-operation. During the course of the hearing, the Solicitor General has assured that henceforth he will ensure that the deficit of oxygen is rectified and supply is made to the GNCTD according to their projected demand (which may be revised in the future) on a day by day basis. We accept his submission and

direct compliance within 2 days from the date of the hearing, that is, on or before midnight of 3 May 2021.

30 With regard to the issue of the supply and availability of medical oxygen for the entire country, we have noted that efforts are being made to augment the availability of oxygen. While the Central and State Governments are in the process of managing the supply of oxygen, at the same time, it is critical that a buffer emergency stock of oxygen is created so that in the event that the supply chain is disrupted to any one or more hospitals in an area for any reason, the buffer or emergency stocks can be used to avoid loss of human lives. These emergency stocks must be so distributed so as to be easily accessible without delay in every local area. We have also seen the situation that has developed in the last 24 hours in Delhi where patients, including among them medical professionals, died because of the disruption of supplies and the time lag in the arrival of tankers. This deficit shall be rectified immediately by the Central Government by creating buffer stocks and collaborating with the States through the virtual control room on a 24 by 7 basis. In view of the deaths which are being caused daily by the disruption of supplies, this direction is more crucial than ever. We therefore, direct the Central Government in collaboration with the States to prepare a buffer stock of oxygen to be used for emergency purposes to ensure supply lines continue to function even in unforeseen circumstances. The location of the emergency stocks shall be decentralised so as to be immediately available if the normal supply chain is disrupted to any hospital for any reason. The emergency stocks shall be created within the next four days. The replenishment of the emergency stocks will also be monitored on a real time basis through the

virtual control room in active consultation with each state/UT. This is in addition to the day to day allocations.

31 In addition to the above, we direct the Central Government to consider the following suggestions, which may assist in increasing the availability of oxygen and ensure transparency of demand-supply management, and provide a clarification to this Court:

(i) We understand that the Virtual Central Control Room of the Central Government displays the allocation of supply of oxygen by the Central Government to each State/UT. By extension of this, a mechanism for displaying real time updates of supply of oxygen from each State to hospitals in each district, along with the remaining stock of oxygen with the hospitals may be maintained and shared with the citizens to ensure transparency. This will also ensure that citizens can easily identify the hospitals where medical aid can be availed;

(ii) The government shall clarify the steps being taken on planning on the use of oxygen concentrators to reduce the demand of LMO, such that LMO is needed only for critical patients. A comprehensive plan on augmenting the production/import of these oxygen concentrators may be considered;

(iii) The expected supply of oxygen/containers to be received from outside India should be suitably augmented to cater to anticipated increases in the demand and shortfall of domestic availability. Pending the early finalization of the global tender a decision may be taken on the need to continue imports to bridge the gap in availability; and

(iv) A review shall be made of any restrictions on inter-State travel of trucks or tankers carrying oxygen/other medical aid equipment (such as GST related issues, documentation) which might cause a hindrance in their movement.

The Central Government may consider implementing a system to track and map the supply tankers which would allow better management of resources and allow diversion of resources from one State to the other in case of emergencies.

E Vaccines

32 The previous order of this Court dated 27 April 2021 directed the Central Government to clarify, *inter alia*: (i) the projected availability of vaccines and proposed steps to boost supply and distribution; and (ii) the vaccine pricing and distribution *among* states. Upon perusing the affidavits filed by the Central Government and after having the benefit of oral arguments of the Solicitor General, we have arrived at the following understanding on the two broad issues outlined above. We would once again re-iterate that we do not attempt to delve into the role of the executive in designing policy choices. We are merely seeking to enter into a dialogue with the relevant stakeholders in order to ensure probity and transparency of the measures underway. We are cognizant that it is ultimately up to the executive to frame and implement policies that it deems appropriate, with the topmost regard to public interest.

E.1 Vaccine capacity and disbursal

33 The Central Government has apprised us of its constitution of a National Expert Group on Vaccine Administration for COVID-19[19] on 7 August 2020 and operationalization of the immunization programme from December 2020. It was further stated that as of 26 April 2021, over 13.5 crore vaccine doses (approx. 9% of the Indian population) have been administered to Frontline Workers, Healthcare Workers and persons who are 45 years of age and higher in the 3 Phases of immunization. It was submitted that these vaccines have been

[19] "**NEGVAC**"

centrally procured and administered free of cost to the abovementioned groups who were identified based on specific vulnerabilities and a higher mortality rate on account of the COVID-19 infection.

34 On 20 April 2021, the Central Government rolled out a revised strategy of COVID-19 vaccination for all persons over 18 years of age, with effect from 1 May 2021. This new age group consists of approximately 59 crore people, which would require 122 crore vaccine doses under the current two-dose vaccine regime of Covishield and Covaxin which have been authorized for emergency use in India. This revised strategy enables vaccine procurement by State Governments and private hospitals, purportedly for accelerating the immunization programme which is critical to curb the pandemic. In response to the query of this Court on the necessity of the revised strategy, the Central Government furnished the following justification:

> "During the ongoing consultation with the states, demands/concerns were raised by the various State Governments to expand the scope of vaccination drive to include the beneficiaries beyond the priority groups identified by NEGVAC as approved by Central Government. As a matter of co-operative federalism, it was felt necessary to allow play in the joints and to de-centralize vaccine procurement and to enable the States to expand vaccination drives to other groups between the age of 18-44 years. However, **since the priority group as identified by Union of India (which had more vulnerability) was not fully vaccinated, it was considered imperative to carry out two drives separately i.e. in a decentralized manner to achieve higher efficiency and reach. Thus the States were given a participatory role to undertake the procurement of vaccine and for vaccination of any other 'groups identified drive' for the 18-44 age group. This would also keep the existing drive of critical groups unobstructed as the 50 percent of the vaccines procured through the GoI channel would continue to support and provide free of cost vaccine to the most vulnerable age groups of 45 years plus in the country health care workers and frontline worker**

> **identified by the Union of India who were entitled to get vaccinated under Phase II."**
>
> **(emphasis supplied)**

35 In response to the queries of the Court on how the supplies of vaccines will be allocated between various states if each State Government is to negotiate with vaccine producers, the Central Government has furnished the following justification in order to iron out the inequities between States:

> "**For the remaining 50% non-government of India channel, the states and the private hospitals are free to procure vaccine for 18-44 years population, however, to have an equitable distribution of vaccine across the country, states have been allocated the available vaccine quantity in proportion to the population between 18-44 years of age of the respective state so as to ensure equitable distribution of vaccine as there is a possibility of some states having better bargaining power due to geographical advantage etc.**"
>
> **(emphasis supplied)**

36 During the course of the hearing, this Court has expressed its reservations *prima facie* on the validity of the revised policy under which the states and private hospitals are to procure 50% of the vaccines in order to immunize persons in the 18-44 years age group. For one thing, even this age group would consist of persons who suffer from vulnerabilities. Once the vaccination programme has been opened up for persons other than the 45 plus age group, it would not be logical to impose the obligation to source vaccinations for the 18-44 age group on the State Governments. This will, *inter alia*, leave each State Government to negotiate supply schedules, delivery points and other logistical arrangements with the manufacturers. At present, there are only two manufacturers for the authorized vaccines (with one other vaccine - Sputnik V, in the process of

manufacture). The available stock of vaccines is not adequate to deal with the requirements of both the categories. The Central Government must take the responsibility of providing guidance to every State on the quantities to be supplied to each State, the vaccine(s) being allocated, the period of delivery, and the number of persons who can be covered for vaccination, among other details. Leaving the State Governments to negotiate directly with manufacturers will produce chaos and uncertainty. The object of vaccinating the 18-44 age group cannot be achieved in the absence of stocks being available.

37 Besides the above issues, the Central Government is directed to clarify the following issues in order to ensure the protection of the fundamental rights to equality and to life and personal liberty for all persons who will be eligible to take the vaccine from 1 May 2021:

(i) Whether the Central and State Governments have introduced any initiatives for ensuring the immunization of persons who do not have access to digital resources as otherwise the mandatory requirement of registration over the Co-WIN digital portal for persons in the age group of 18-44 years will deprive a large class of citizens of vaccination;

(ii) Since the Central Government commits to vaccinating persons over 45 years, free of cost, in view of their vulnerability, whether walk-in facilities for vaccination will continue for these persons after 1 May 2021;

(iii) Whether the Central or State Governments propose to undertake targeted vaccination drives for persons who are providing on-ground assistance during the second wave of the pandemic - such as crematorium workers,

who were not considered as Frontline or Healthcare workers for Phase 1 of the vaccination drive;

(iv) Whether, and if so what, steps being undertaken by INYAS, the nation-wide mass awareness campaign for COVID-19 vaccination, for ensuring outreach in rural areas and socio-economically underprivileged sections of society including the possibility of using mobile vans, vehicles and railways to vaccinate such people as well as those living in remote areas, near their doorsteps so as to minimize their travel and potential infection with COVID-2019. Efforts must also be made that a lack of an identity proof does not create a hindrance in the process of immunization of all individuals, specifically, the underprivileged;

(v) Whether the Central government will revisit its policy by procuring 100% of the doses which can then be equitably disbursed to the State Governments; and

(vi) Since the vaccine administration is now to be a shared responsibility of the Union and the States, the Central Government and the State Governments shall provide- (a) a breakup of the current and projected availability of vaccine stocks for the next 6 months; and (b) a timeline for achieving immunization of the newly eligible 59 crore persons who are aged between 18-44 years.

These issues are of vital importance, since vaccination appears to be one of the most important strategies to combat further spread of the pandemic, and would also provide a measure of security and assure the people about their health and well-being.

E.2 Vaccine pricing

38 Since the advent of the revised rollout strategy with effect from 1 May 2021, only persons aged 45 years and above are guaranteed a free vaccine. The reason of higher efficiency and speed has been furnished as a justification for enabling State Governments and private hospitals to directly procure vaccines. We have come to understand that a few State Governments have committed to free immunization under the revised strategy. On specific enquiry on the rationale in regard to the differential pricing for procurement by the Central Government and the State Governments, the Central Government has furnished the following justification:

> "**It is submitted that liberty to decide prices on arm's length basis by and between the State Government and hospitals is based on the concept of creating an incentivized demand for the private vaccine manufacturers in order to instill a competitive market resulting in increased production of vaccines and market driven affordable prices for the same**. Simultaneously, the free vaccination by the Central Government for above referred priority age groups would continue and it is always open for each State Government either to offer free vaccination or subsidise it for the additional identified earmarked priority group identified by the State Governments [age 18-44 years].
>
> 63. The new strategy was devised after multiple Inter-Ministerial teams were deputed by Govt. of India to various manufacturing sites to understand their requirement and to provide pro-active and customized support to significantly augment vaccine production capacities [which is the prime priority of the Central Government at this juncture], in the form of advance payments, facilitating more sites for production etc. **This approach, on the one hand, incentivizes vaccine manufacturers to rapidly scale up their production and on the other hand, it would also attract new vaccine manufacturers. It would make pricing, procurement and administration of vaccines more flexible and competitive and would further ensure augmented vaccine production as well as wider availability of vaccines in the countr**y."
>
> (**emphasis supplied**)

39 *Prima facie*, there are several aspects of the vaccine pricing policy adopted by the Central government which require that policy be revisited. All vaccines, whether in the quantity of 50% purchased by the Central Government or the remaining 50%, are to be used for vaccinating citizens. The end use is the same. The Central Government proposes to purchase half of the total quantity falling within its fifty per cent quota while for the rest, the manufacturers would declare in advance the price to be fixed, allowing the State Governments to negotiate their terms. As of date, the manufacturers have suggested two different prices, a lower price which is applicable to the Central Government and a higher price which is applicable to the quantities purchased by the State Governments. It is likely that compelling the State Governments to negotiate with manufacturers on the ground of promoting competition and making it attractive for new vaccine manufactures will result in a serious detriment to those in the age group of 18 to 44 years, who will be vaccinated by the State Governments. The social strata of this age group also comprises persons who are *Bahujans* or belong to other under privileged and marginalized groups, like many in the other population age groups. They may not have the ability to pay. Whether or not essential vaccines will be made available to them will depend upon the decision of each State Government, based on its own finances, on whether or not the vaccine should be made available free or should be subsidized and if so, to what extent. This will create disparity across the nation. The vaccinations being provided to citizens constitute a valuable public good. Discrimination cannot be made between different classes of citizens who are similarly circumstanced on the ground that while the Central government will carry the burden of providing free vaccines for the 45 years and

above population, the State Governments will discharge the responsibility of the 18 to 44 age group on such commercial terms as they may negotiate. *Prima facie*, the rational method of proceeding in a manner consistent with the right to life (which includes the right to health) under Article 21 would be for the Central Government to procure all vaccines and to negotiate the price with vaccine manufacturers. Once quantities are allocated by it to each State Government, the latter would lift the allocated quantities and carry out the distribution. In other words, while procurement would be centralized, distribution of the vaccines across India within the States/UTs would be decentralized. While we are not passing a conclusive determination on the constitutionality of the current policy, the manner in which the current policy has been framed would *prima facie* result in a detriment to the right to public health which is an integral element of Article 21 of the Constitution. Therefore, we believe that the Central Government should consider revisiting its current vaccine policy to ensure that it withstands the scrutiny of Articles 14 and Article 21 of the Constitution.

40 In light of the justification offered for non-interference in the prices that are set by the manufacturers, irrespective of their variance from the prices for procurement of the Central Government, we would like to seek the following clarifications:

(i) Whether any other alternatives were considered by the Central Government for ramping up the immunization drive in India, particularly in light of its initial strategy of a centralized free immunization drive;

(ii) The methodology which the Central Government was envisaging to procure adequate vaccine doses for the population prior to the revised strategy which was announced amidst the second wave of COVID-19; and

(iii) Whether any studies and figures were relied upon in order to arrive at the conclusion that decentralized procurement would spur competitive markets to incentivize production and eventually drive down the prices of the vaccines. Whether these studies are of relevance in a pandemic when vaccines are a scarce and essential commodity which is being produced by a limited number of manufacturers for a limited number of vaccines.

41 The Central Government has submitted that the Finance Ministry has sanctioned a credit of Rs 3000 crores for Covishield manufacturer - Serum Institute of India[20] and Rs 1500 crores to Covaxin manufacturer - Bharat Biotech. Additionally, another Rs 65 crores is stated to have been provided to Bharat Biotech's production center at Bangalore. In bolstering its argument for augmentation of vaccine production, the Central Government has provided the Court with further information on advance funding (of unspecified amounts) that is being provided to R&D and manufacturing facilities. In light of this investment, the Central Government should consider revisiting its policy bearing in mind what has been stated above, the following issues and other relevant information:

[20] "**SII**"

(i) Whether, and if so, the Finance Ministry or any other funding organization of the Government of India have made any grants/sanctions to Bharat Biotech and the SII in the past, like the current infusion of Rs 1500 crores and Rs 3000 crores, respectively. If so, breakup and corelation with the total cost of development and production of the two vaccines;

(ii) Whether the current procurement prices for the Central Government account for infusion of funds for production, infrastructure and other aid provided by it. If so, the basis on which the same benefit is denied to procurement by State Governments which equally service the needs of citizens; and

(iii) The full extent of direct and indirect grant/aid provided for research, development and manufacture of all existing vaccines and future vaccines that it proposes to authorize. For instance, the Central Government has submitted in its affidavit that the Department of Biotechnology has facilitated the trials for Sputnik V.

F Potentiality of Compulsory Licensing for vaccines and essential drugs

42 Several drugs that are at the core of the COVID treatment protocol are under patents in India including Remdesivir, Tociluzumab and Favipiravir. On 2 October 2020, a communication was issued by the UOI, along with South Africa, to the Council for Trade-Related Aspects of Intellectual Property which stated that there were several reports about intellectual property rights hindering timely

provisioning of affordable medical products to patients[21]. The communication also reported that some members of the World Trade Organization had carried out urgent amendments to their national patent laws to expedite the process of issuing compulsory/government use licenses.

43 In India, the patent regime is governed by the Patents Act, 1970[22], Section 92 of which envisages the grant of a compulsory license, *inter alia*, in circumstances of national emergency and extreme urgency. Once a declaration of national emergency is made, and the relevant patents notified, any person interested in manufacturing the drug can make an application to the Controller General of Patents who can then issue a compulsory license. The patentee would be paid a reasonable royalty as fixed by the Controller General of Patents. Further, under Section 100 of the Patents Act, the Central Government can authorize certain companies to use any patents for the "purpose of the government". Indian companies can begin manufacturing the drugs while negotiating the royalties with the patentees. If the Central Government or its authorized company is not able to reach an agreement with the patentee, the High Court has to fix the reasonable royalty that is to be paid to the patentee. Another alternative is for the Central Government to acquire the patents under Section 102 from the patentees. If the Central Government and the patentee is not able to reach a consensus on the price of the patents, it is up to the High Court to fix the royalty. Additionally, under Section 66 of the Patents Act, the Central Government is also entitled to revoke a patent in the public interest.

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[21] Council for Trade-Related Aspects of Intellectual Property Rights, Waiver From Certain Provisions Of The Trips Agreement For The Prevention, Containment And Treatment Of Covid-19, Communication From India And South Africa, IP/C/W/669, 2nd October, 2020, *available at* https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:/IP/C/W669.pdf&Open=True

[22] "**Patents Act**"

44 The utilization of these flexibilities has also been detailed in the Trade Related Aspects of Intellectual Property Rights Agreement[23]. Even as TRIPS obliges countries to ensure a minimum level of patent protection, it creates a permissive regime for the carving out of exceptions and limitations that further public health objectives[24]. This is evident from a conjoint reading of Articles 7, 8, 30 and 31 of TRIPS. Article 7 outlines the objectives of the TRIPS as being to ensure the effective enforcement of intellectual property in a way that, *inter alia*, is 'conducive to social and economic welfare'. Article 8 gives member countries the freedom to take measures that protect public health and nutrition. Article 8(2) allows for the taking of TRIPS-compatible measures aimed at preventing the abuse of intellectual property rights. Articles 30 and 31 deal with exceptions to the rights of patent owners, by allowing grant of compulsory licenses. It leaves countries with significant breathing space to determine how the compulsory licensing or government-use levers can be triggered. While such determinations must be made on the individual merits of each case[25], the aforesaid caveat does not apply when the compulsory license grant is for national emergency, extreme urgency or public non-commercial use[26].

45 According to the 2001 Doha Declaration, TRIPS should be interpreted in a manner supportive of the right of members to protect public health and to promote access to medicines[27]. It recognizes the right of WTO members to use the full extent of the TRIPS flexibilities to secure this objective. Para 5(b) of the Doha

[23] "**TRIPS**"
[24] Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines Promoting Innovation and Access to Health Technologies, (United Nations Secretary-General, 2016), p. 16.
[25] TRIPS Agreement, Article 31(a).
[26] TRIPS Agreement, Article 31(b).
[27] World Trade Organization, 'Ministerial Declaration of 14 November 2001' (November 2001) WT/MIN(01)/DEC/1, 41 ILM 746, para 4.

Declaration provides the freedom to each member to grant compulsory licenses and to determine the grounds on which the licenses are granted. Para 5(c) leaves it up to each nation to determine what constitutes a national emergency or extreme urgency. In the context of the COVID-19 pandemic, we note that several countries such as Canada and Germany have relaxed the legal regimes governing the grant of compulsory licenses[28].

46 Whether and if so, the extent to which these provisions should be utilized is a policy decision for the Central Government. We have flagged the issue for its consideration. We have only outlined the legal framework within which the Central Government can possibly consider compulsory licensing and government acquisition of patents. The Central Government is free to choose any other course of action that it deems fit to tackle the issue of vaccine requirements in an equitable and expedient manner, which may involve negotiations with domestic and foreign producers of vaccines. We clarify that it is up to the Central

[28] 'COVID-19 IP Policy Tracker' (WIPO, 16 July 2020), *available at* https://www.wipo.int/covid19-policy-tracker/#/covid19-policy-tracker/access.

Government to choose the best possible measures it can undertake during the current crisis keeping in mind that public interest is of paramount importance.

G Supply of Essential Drugs

G.1 Submissions in the Central Government's Affidavits

47 In relation to the broad issue of "Supply of Essentials", in its affidavit dated 23 April 2021 and additional affidavit 29 April 2021, with respect to Remdesivir, the UOI urged that:

(i) Remdesivir is a patented drug which is being manufactured in India under licensing agreements between the patent holder, M/s Gilead, a US based company and seven Indian companies. Under such agreements, these Indian companies are allowed to manufacture Remdesivir for distribution;

(ii) In its affidavit dated 23 April 2021, it was submitted on behalf of the Central Government that the current production is about 74 lakhs vials per month and once the additional manufacturing sites of the seven manufacturers become operational by May 2021, the production capacity will increase to 90 lakhs vials per month. In its additional affidavit dated 29 April 2021, the Central Government has submitted that as on 23 April 2021, the production capacity has increased to 1.03 crore vials per month;

(iii) The Central Government allocated 11 lakhs vials of Remdesivir to nineteen States with a high case load between 21 to 30 April through a letter issued on 21 April 2021. This allocation was revised and expanded to all States and UTs through a letter issued on 24 April 2021;

(iv) The Central Government has directed the States to appoint nodal officers to ensure unrestricted and timely movement of Remdesivir. A control room has been set up in this regard by the National Pharmaceutical Pricing Authority[29] which is monitoring supplies as allocated. A helpline has been set up by NPPA and manufacturers have been directed to address the hindrances in the movement of the drug. A WhatsApp group with nodal officers has also been created to enable coordination and officials of MHA, NPPA and CDSCO are also part of the group;

(v) Remdesivir, its Active Pharma Ingredients[30] and formulations have been placed under export ban since 11 April 2021;

(vi) The Ministry of Finance has issued a notification on 20 April 2021 exempting customs duty on the Remdesivir injection, and API of Remdesivir and Betacyclodexterin, which are used in the manufacture of the injection. All the SEZ/EOU manufacturing units of M/s Mylan and M/s Honous Lab, who are manufacturing Remdesivir on behalf of some of the seven manufacturers have also been directed to start manufacturing Remdesivir for domestic supply;

(vii) CDSCO has directed all State Drug Controllers on 10 April 2021 to conduct a special investigation drive to prevent hoarding and black-marketing of Remdesivir in the country. DCGI and State Drug Controllers have been taking stringent action against such activities and enforcement action has been taken in thirty-four cases across the country;

[29] "**NPPA**"
[30] "**API**"

(viii) MHA has issued an advisory on 22 April 2021 to States and Union Territories to facilitate smooth movement of supplies. A "Covid Drug Management Cell" consisting of the Department's Senior Officers and others has been constituted on 26 April 2021 to oversee and identify common concerns raised by States in relation to Remdesivir;

(ix) NPPA has revised the maximum retail price of a 100 mg/vial of Remdesivir to Rs 3500; and

(x) The Central Government is also looking at the possibility of importing Remdesivir.

48 The UOI made the following submissions on the availability of Tociluzumab injections:

(i) Tociluzumab is manufactured by a Swiss Company, M/s Roche, which does not have any manufacturing facility in India or any agreements with domestic pharma companies to manufacture the drug. It is imported in the country by Cipla. India is completely dependent on imports;

(ii) It is listed as an investigational therapy drug (off-label) under the National Clinical Management Protocol for COVID-19 for severe cases. There are domestically produced alternatives which are equivalent to or better than Tociluzumab such as itulizumab, dexamethasone and methyl prednisolone. However, an incorrect public perception has been created that only Tociluzumab can treat the inflammatory burst condition in COVID-19 patients since it is an imported drug. This has led to the acute shortage in the availability of the drug and has created public panic; and

(iii) The supply of Tociluzumab is being monitored by NPPA and CDSCO.

49 The UOI has made the following submissions on the availability of other drugs:

(i) The National Clinical Management Protocol for COVID-19 does not include Favipirarvir (popularly known as Fabiflu) due to insufficient peer reviewed evidence to substantiate its use in mild to moderate cases of COVID-19. However, it is being prescribed by certain doctors. The clinical management protocol is a dynamic document which is reviewed periodically and is subject to further evaluation based on medical research and evidence that comes up in future; and

(ii) On 24 April 2021, Department of Pharmaceuticals[31], NPPA and DCGI had reviewed the production and supply of other drugs such as Favipiravir, Enoxaparin, Ivermectin, Methylprednisolone, Paracetamol and Hydroxy-chloroquine. A meeting was conducted on 25 April 2021 by NPPA and DCGI with manufacturers to review stock position, availability and production plans.

G.2 Recommendations

50 In respect of the essential drugs, this Court has been informed that the Central Government is taking steps to augment the production of Remdesivir. It has been brought to our notice that seven Indian companies are manufacturing this drug under a licensing agreement with a US based company, M/s Gilead. The current production capacity as on 23 April 2021 is noted to be at 1.03 crores vials per month. The Central Government should provide us with the details of the actual rate of production and a breakup of demand for the drug from different

[31] "**DoP**"

States. Further, while it has been submitted on behalf of the Central Government that it is allocating the stocks based on a rational criterion of equitable distribution keeping in mind the existing constraints on the availability of the drug, this Court should be provided with details of the methodology used for such allocation.

51 We have been informed by the Central Government in its affidavit that NPPA has revised the maximum retail price of Remdesivir to Rs 3500. However, it has come to our notice that several other drugs which are being prescribed by doctors for treating COVID-19 patients like Favipiravir, Tociluzumab, Enoxaparin, Ivermectin, Methylprednisolone, Paracetamol and Hydroxy-chloroquine are being priced at exorbitant rates creating issues of access and affordability. While this is not a direction of this Court, the Central Government can consider invoking its statutory powers under paragraphs 19 and 20 of the Drugs Price Control Order, 2013. Under paragraph 19[32] of the Drugs Price Control Order, 2013 the Government in extraordinary circumstances, if it considers necessary in public interest, can fix a ceiling price or retail price of the drug for a certain period. COVID-19 is a crisis of an unprecedented nature and qualifies as an extraordinary circumstance. It will be in public interest to ensure that the price of essential drugs is fixed in such a manner that it is available even to the most marginalized sections of the society. The Government can even monitor the prices of the drugs under paragraph 20[33] of the Drugs Price Control Order, 2013

[32] "19: Fixation of the Ceiling Price Under Certain Circumstances: Notwithstanding anything contained in this order, the Government may, in case of extraordinary circumstances, if it considers necessary to do so in public interest, fix the ceiling price or retail price of any drug, as it may deem fit and where the ceiling price or retail price of the drug is already fixed and notified, the Government may allow an increase or decrease in the ceiling price or the retail price, as the case may be, irrespective of annual wholesale price index of that year."

[33] "20: Monitoring the Prices of Non-Scheduled Formulations: (1) the Government shall monitor the maximum retail prices (MRP) of all the drugs, including the non-scheduled formulations and ensure that no manufacturer increases the maximum retail price of a drug more than ten percent of maximum retail price during preceding twelve months and where the increase is beyond ten percent of maximum retail price, it shall reduce the same to

and ensure that no manufacturer increases the prices of the drugs by more than 10% of the maximum retail price during the preceding 12 months and where the increase is beyond 10% of the maximum retail price, it can oblige the manufacturer to reduce it to the level of 10% for the next 12 months.

52 The Central Government has submitted that it plans to import Remdesivir. It can also consider importing other essential drugs to meet the immediate demand of the drug while the production is ramped up. We hasten to clarify that this does not constitute a direction of this Court and ultimately this decision falls under the domain of the executive.

53 We note that there are certain medicines which are being prescribed by doctors which are not mentioned in the National Clinical Management Protocol for COVID-19 like Favipiravir. However, since these medicines are being prescribed by doctors, people are facing significant inconvenience in obtaining them due to their shortage in certain parts of the country. The Central Government should consider whether the production of such medicines should be augmented to meet the demand or instructions should be given to the doctors to not recommend such medicines unless they have been included in the national protocol.

54 It has been submitted on behalf of the Central Government that on 24 April 2021, DoP, NPPA and DGCI reviewed the production and supply of drugs such as Favipiravir, Enoxaparin, Ivermectin, Methylprednisolone, Paracetamol and Hydroxy-chloroquine. The supply of Remdesivir and Tociluzumab is already under the consideration of the Central Government. A meeting was also held on

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the level of ten percent of maximum retail price for next twelve months. (2) The manufacturer shall be liable to deposit the overcharged amount along with interest thereon from the date of the increase in price in addition to the penalty."

25 April 2021 by DoP, NPPA and DGCI with the manufacturers to review stock position, availability and production plans. The Central Government should provide details of estimated demand of essential drugs mentioned above, production capacity, existing stocks, details of allocation and supply of such drugs.

55 As discussed in **Section F**, the Central Government can also consider using its powers under Sections 92, 100 or 102 of the Patents Act to increase production of essential drugs to ensure that it is commensurate to the demand. The Central Government's affidavit testifies to existence of capacity of public sector organizations and institutes, which can assist in augmenting production of various drugs and formulations. The utilization of these capabilities to augment production, once licensing is resorted to, will be in the interests of the general public. This Court is further of the opinion that *prima facie* the present circumstance warrant the government's examination of its the extraordinary powers, meant to be used in extreme situations, such as the current pandemic, for fixing drug prices, be it vaccines, or patented formulations, having regard to the provisions of the Drugs and Cosmetics Act, 1940 and other provisions[34]. We are cognizant that invocation of the above provisions, if any, is ultimately a policy decision of the Central Government and may encompass negotiations with the concerned stakeholders. We hope that the Central Government will adopt a route that best serves the public interest.

[34] Paragraph 3 and 19 of the Drugs Price Control Order, 2013

G.3 Black Marketing

56 This Court would like to take judicial notice of the fact that several critical drugs, used to treat COVID-19, such as Remdesivir and Tocilizumab, are being sold at significantly inflated prices or in fake form. This is a condemnable attempt to exploit people's misery and profit from their helplessness.

57 In order to clamp down on this practice, the Central Government can consider constituting a special team to identify and prosecute those who: (a) sell medical grade oxygen/COVID-19 medicines at exorbitant prices; and (b) sell fake substances and recover the concerned substances. A protocol for ambulances must also be evolved to avoid citizens being exploited by extracting unconscionable charges. The Central Government can consider creating a platform for easy reporting and redressal of such cases.

H Recommendations for augmenting healthcare workforce

58 It is common knowledge that a large number of medical, nursing and pharmacy students, who graduated in 2020 and would be in the process of graduating in 2021, would be available to augment the workforce in the health sector. The Central Government should, we feel, look into this aspect, and ensure the optimal manner of utilization of their services, regard being had, of course, to their safety and well-being.

59 The Central Government should also consider using health care workforce available with the armed forces and para military forces for the purpose of vaccination.

I Epilogue

60 The World Health Organisation[35], while discussing the rapid spread of COVID-19 has not only labelled it an epidemic but also an "infodemic", due to the overabundance of information on the internet, which was riddled with misinformation and disinformation[36]. This highlights the key role internet and technology currently has in all our lives, as the COVID-19 pandemic rages on. Indeed, the WHO recently also conducted a study to understand how individuals between the ages of 18-40 years dealt with the ongoing pandemic using social media[37].

61 It is only appropriate then that when many cities in India are suffering through the second wave of the COVID-19 pandemic, many have turned to the internet, using applications/websites to find critical support. On these platforms, online communities led by members of the civil society and other individuals, have assisted the needy in multiple ways – often by helping them procure oxygen, essential drugs or find a hospital bed through their own networks or by amplifying original requests, and even by offering moral and emotional support. However, it is with deep distress that we note that individuals seeking help on such platforms have been targeted, by alleging that the information posted by them is false and has only been posted in social media to create panic, defame the administration or damage the "national image". We do not hesitate in saying that such targeting

[35] "**WHO**"

[36] "Managing the COVID-19 infodemic: Promoting healthy behaviours and mitigating the harm from misinformation and disinformation - Joint statement by WHO, UN, UNICEF, UNDP, UNESCO, UNAIDS, ITU, UN Global Pulse, and IFRC" (*WHO*, 23 September 2020) available at <https://www.who.int/news/item/23-09-2020-managing-the-covid-19-infodemic-promoting-healthy-behaviours-and-mitigating-the-harm-from-misinformation-and-disinformation>

[37] "Social media & COVID-19: A global study of digital crisis interaction among Gen Z and Millennials" (*WHO*, 23 September 2020) available at <https://www.who.int/news-room/feature-stories/detail/social-media-covid-19-a-global-study-of-digital-crisis-interaction-among-gen-z-and-millennials>

shall not be condoned, and the Central Government and State Governments should ensure that they immediately cease any direct or indirect threats of prosecution and arrest to citizens who air grievances or those that are attempting to help fellow citizens receive medical aid. If this does keep happening even after the current order, this Court shall be constrained to use the powers available to it under it contempt jurisdiction. We also direct that all Directors General of Police shall ensure compliance down the ranks of the police forces within their jurisdictions.

62 In these trying times, those desperately seeking help for their loved ones on these platforms should not have their misery compounded through the actions of the State and its instrumentalities. Further, there are two more crucial reasons why such a clampdown on information sharing must be absolutely stopped immediately.

63 The first reason is because sharing information widely is in itself an important tool in combating public tragedies, like the current COVID-19 pandemic. In **K.S. Puttaswamy (Privacy-9J.)** vs **Union of India**[38], one of us (DY Chandrachud, J) speaking for four Judges of a nine-Judge bench of this Court noted academic literature documenting the widespread availability of information and the resultant acknowledgement of the problem is what prevented the drought in Maharashtra in 1973 from becoming as bad as the Bengal Famine of 1943, where the British tried to deny the problem even existed. It was noted thus:

> "267. Civil and political rights and socio-economic rights do not exist in a state of antagonism. The conditions necessary for realising or fulfilling socio-economic rights do not postulate

[38] (2017) 10 SCC 1

the subversion of political freedom. The reason for this is simple. Socio-economic entitlements must yield true benefits to those for whom they are intended. This can be achieved by eliminating rent-seeking behaviour and by preventing the capture of social welfare benefits by persons who are not entitled to them. Capture of social welfare benefits can be obviated only when political systems are transparent and when there is a free flow of information. Opacity enures to the benefit of those who monopolise scarce economic resources. **On the other hand, conditions where civil and political freedoms flourish ensure that governmental policies are subjected to critique and assessment. It is this scrutiny which subserves the purpose of ensuring that socio-economic benefits actually permeate to the underprivileged for whom they are meant. Conditions of freedom and a vibrant assertion of civil and political rights promote a constant review of the justness of socio-economic programmes and of their effectiveness in addressing deprivation and want. Scrutiny of public affairs is founded upon the existence of freedom. Hence civil and political rights and socio-economic rights are complementary and not mutually exclusive.**

268. Some of these themes have been addressed in the writings of the Nobel laureate, Amartya Sen. Sen compares the response of many non-democratic regimes in critical situations such as famine with the responses of democratic societies in similar situations. [Amartya Sen, Development as Freedom (Oxford University Press, 2000) at pp. 178-79.]…

269. In the Indian context, Sen points out that the Bengal famine of 1943 “was made viable not only by the lack of democracy in colonial India but also by severe restrictions on reporting and criticism imposed on the Indian press, and the voluntary practice of “silence” on the famine that the British-owned media chose to follow” [Amartya Sen, The Idea of Justice (Penguin Books, 2009) at p. 339.] . Political liberties and democratic rights are hence regarded as “constituent components” of development. [Id, at p. 347] In contrast during the drought which took place in Maharashtra in 1973, food production failed drastically and the per capita food output was half of that in sub-Saharan Africa. Yet there was no famine in Maharashtra where five million people were employed in rapidly organised public projects while there were substantial famines in sub-Saharan Africa. This establishes what he terms as “the protective role of democracy”. Sen has analysed the issue succinctly:

“The causal connection between democracy and the non-occurrence of famines is not hard to seek. Famines kill millions of people in different countries in the world, but they

> don't kill the rulers. The kings and the presidents, the bureaucrats and the bosses, the military leaders and the commanders never are famine victims. And if there are no elections, no opposition parties, no scope for uncensored public criticism, then those in authority don't have to suffer the political consequences of their failure to prevent famines. Democracy, on the other hand, would spread the penalty of famines to the ruling groups and political leaders as well. This gives them the political incentive to try to prevent any threatening famine, and since famines are in fact easy to prevent (the economic argument clicks into the political one at this stage), the approaching famines are firmly prevented." [Amartya Sen, Development as Freedom (Oxford University Press, 2000) at p. 180.]..""
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> **(emphasis supplied)**

As such, preventing clampdowns on sharing of information on online platforms is not just in the interest of individuals sharing the information, but the larger democratic structures of our nation. Without the ready availability of such information, it is entirely possible that the COVID-19 pandemic may turn into a tragedy worse than what it already is.

64 The second reason is because sharing information widely will help in the creation of a "collective public memory" of this pandemic. The presence of collective public memory, which refers "*to an extant and taken-for-granted group memory*"[39], is important for the creation of knowledge of the problems plaguing us today, so they may be passed on across time[40]. This is important since we do not have to travel back too much in our past to realise that the pandemic caused by the "Spanish" flu of 1918, which is said to have infected every third person in the world and killed between 50-100 million individuals (compared to the 17 million

[39] Theodore O. Prosise, 'The collective memory of the atomic bombings misrecognized as objective history: The case of the public opposition to the national air and space museum's atom bomb exhibit', (1998) 62 Western Journal of Communication 3:316-347, pg 318

[40] Bryan Hubbard and Marouf A. Hasian, 'Atomic Memories of the 'Enola Gay': Strategies of Remembrance at the National Air and Space Museum' (1998) 1 Rhetoric and Public Affairs 3:363-385, pg 364

who died in World War I), has been almost entirely erased from our collective public memory[41]. Therefore, the widespread sharing of information by individuals living through the COVID-19 pandemic becomes crucial. Furthermore, the role of Courts in creating and preserving this collective public memory cannot be understated. Professors Austin Sarat and Thomas R. Kearns, in their book *History, Memory, and the Law*, describe the function that is played by Courts in the following terms[42]:

> "Law in the modern era is, we believe, one of the most important of our society's technologies for preserving memory. Just as the use of precedent to legitimate legal decisions fixes law in a particular relation to the past, memory may be attached, or attach itself, to law and be preserved in and through law. Where this is the case, it serves as one way of orienting ourselves to the future. **As Drucilla Cornell puts it: "Legal interpretation demands that we remember the future." In that phrase, Cornell reminds us that there are, in fact, two audiences for every legal act, the audience of the present and the audience of the future. Law materializes memory in documents, transcripts, written opinions; it re-enacts the past, both intentionally and unconsciously, and it is one place where the present speaks to the future through acts of commemoration.**
>
> **Because the litigated case creates a record, courts can become archives in which that record serves as the materialization of memory. Due process guarantees an opportunity to be heard by, and an opportunity to speak to, the future. It is the guarantee that legal institutions can be turned into museums of unnecessary, unjust, undeserved pain and death. The legal hearing provides lawyers and litigants an opportunity to write and record history by creating narratives of present injustices, and to insist on memory in the face of denial.** By recording such history and constructing such narratives lawyers and litigants call on an imagined future to choose Justice over the "jurispathic" tendencies of the moment."
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> **(emphasis supplied)**

[41] Jonathan Freedland, 'History suggests we may forget the pandemic sooner than we think' (*The Guardian*, 29 January 2021) available at <https://www.theguardian.com/commentisfree/2021/jan/29/history-forget-pandemic-spanish-flu-covid>

[42] Austin Sarat and Thomas R. Kearns, *History, Memory, and the Law* (University of Michigan Press, 2009) pgs 12-13

Hence, in the present proceedings, we hope to not only initiate a dialogue so as to better tackle the current COVID-19 pandemic but also to preserve its memory in our public records, so that future generations may evaluate our efforts and learn from them.

65 We speak not only as members of this Court, but also as grateful citizens of the country, and commend the outstanding work of our all healthcare professionals (doctors, nurses, healthcare workers, laboratory technicians, ward staff, ambulance drivers, crematorium workers etc.) during this crisis. They have truly gone beyond their call of duty and toiled day in and day out, relentlessly without rest amidst great challenges. It is absolutely necessary to take urgent steps for their well-being to ensure that our appreciation for their tremendous efforts is not reduced to rhetoric. This is especially important since another factor which affects how collective public memory of any event is created is by the rhetoric surrounding it[43]. As such, our public memory of this public event has to transcend its conception as a "war" against the virus of COVID-19 itself, but rather to remember that it is "*the complex epidemiological circumstances that promote these outbreaks and the under-resourced health systems that are tasked with disease containment*"[44]. While the healthcare professionals have been at the forefront of tackling this crisis, we have to recognize their contribution as medical healthcare professionals who have undertaken "*to protect public health using*

[43] Nicole Maurantonio, "The Politics of Memory" in Kate Kenski and Kathleen Hall Jamieson (eds), *The Oxford Handbook of Political Communication* (Oxford University Press, 2014)
[44] Luke Shors, 'Waging Another Public Health "War?"' (*Think Global Health*, 26 February 2020) available at <https://www.thinkglobalhealth.org/article/waging-another-public-health-war>

proven scientific evidence and best practices and to serve to community at large"[45], and not just as "CORONA WARRIORS".

66 We also do not hesitate to note that the treatment meted out to these public healthcare professional during this COVID-19 pandemic has sometimes been less than ideal. The following are some of the issues we wish to highlight:

(i) Recently, there were reports that the Pradhan Mantri Garib Kalyan Package Insurance Scheme, an insurance scheme of Rs 50 lakhs which had been extended to about 22 lakh healthcare professionals, was set to expire on 24 March 2021 and would not be renewed. While we are happy to note that UOI's affidavit of 23 April 2021 states that this Scheme has been extended for one year starting April 2021, we have also been informed that till date only 287 claims have been settled under it, which includes claims from the families of 168 doctors who died after contracting COVID-19 while treating patients. We direct the Central Government to inform this Court as to how many claims are pending under the Scheme, and the timeline within which the Central Government expects to settle them;

(ii) Healthcare personnel are at an obvious heightened risk of contracting the COVID-19 virus. However, we are aware of reports that indicate that infected healthcare personnel are left to fend for themselves without adequate availability of beds, oxygen or essential drugs. Further, some of them have also often been asked to report back to duty within 10 days of first testing positive for COVID-19 (provided they are asymptomatic), even

[45] Elena N. Naumova, 'The traps of calling the public health response to COVID-19 "*an unexpected war against an invisible enemy*"' (2020) Journal of Public Health Policy (2020) 41:233-237, pg 233

though a longer recuperation period is often recommended. While we are dealing with a terrible second wave of the COVID-19 pandemic, there must be an effective policy to ensure that the nation truly acknowledges their effort and creates incentives for them. We hope it will be remedied soon by the Central and State Governments through the introduction of appropriate guidelines and measures;

(iii) It is unclear what measures are currently being taken to ensure that healthcare personnel can continue to serve others while not risking the health of their family members. We hope that the respective State Governments, with necessary assistance from the Central Government, can ensure this takes place; and

(iv) The Central Government should, we feel examine and ensure that in addition to the schemes it has framed, other facilities such as availability of food, resting facilities during intervals between work, transportation facilities, non-deduction of salary or leave account, if afflicted by COVID 2019 or related infection, overtime allowance, in both public and private hospitals, and a separate helpline for doctors, and healthcare professionals, in cases of COVID 2019 related emergencies, is provided. All these, we feel, would show these professionals that we do not show our appreciation in mere words, but also care for them.

67 The issues mentioned above are only symptomatic of the other broader issues that are being faced by healthcare professionals, who are instrumental in combating the pandemic. Hence, we hope their welfare is considered seriously by the Central and State Governments. Further, we would wish to use this order to

place on record our sincerest appreciation for all the public healthcare professionals - not just limited to the doctors, but also nurses, hospital staff, ambulance drivers, sanitation workers and crematorium workers. It is through their dedicated efforts that the effect of COVID-19 pandemic is being currently tackled in India.

68 In light of the continuing surge of infections in the second wave of the pandemic, we direct the Central Government and State Governments to put on record the efforts taken to curb the spread of the virus and the measures that they plan on taking in the near future. At the same time, we would seriously urge the Central and State Governments to consider imposing a ban on mass gatherings and super spreader events. They may also consider imposing a lockdown to curb the virus in the second wave in the interest of public welfare. Having said that, we are cognizant of the socio-economic impact of a lockdown, specifically, on the marginalized communities. Thus, in case the measure of a lockdown is imposed, arrangements must be made beforehand to cater to the needs of these communities.

J Conclusion

69 The present order has primarily considered the submissions (written and oral) of the UOI. These submissions have been reproduced here as a matter of public record and to contextualize the clarifications that are being sought by our Court in order to serve its dialogic role. We reiterate, for abundant caution, that the data and submissions reproduced above are not its endorsement or acceptance. In terms of the above discussion, we hereby pass the following directions:

(i) The UOI shall ensure, in terms of the assurance of the Solicitor General, that the deficit in the supply of oxygen to the GNCTD is rectified within 2 days from the date of the hearing, that is, on or before the midnight of 3 May 2021;

(ii) The Central Government shall, in collaboration with the States, prepare a buffer stock of oxygen for emergency purposes and decentralize the location of the emergency stocks. The emergency stocks shall be created within the next four days and is to be replenished on a day to day basis, in addition to the existing allocation of oxygen supply to the States;

(iii) The Central Government and State Governments shall notify all Chief Secretaries/Directors General of Police/Commissioners of Police that any clampdown on information on social media or harassment caused to individuals seeking/delivering help on any platform will attract a coercive exercise of jurisdiction by this Court. The Registrar (Judicial) is also directed to place a copy of this order before all District Magistrates in the country;

(iv) The Central Government shall, within two weeks, formulate a national policy on admissions to hospitals which shall be followed by all State Governments. Till the formulation of such a policy by the Central Government, no patient shall be denied hospitalization or essential drugs in any State/UT for lack of local residential proof of that State/UT or even in the absence of identity proof;

(v) The Central Government shall revisit its initiatives and protocols, including on the availability of oxygen, availability and pricing of vaccines, availability

of essential drugs at affordable prices and respond on all the other issues highlighted in this order before the next date of the hearing, that is, 10 May 2021. Copies of all affidavits to be served upon the *Amici* in advance; and

(vi) Several other suggestions have been made before this Court in IAs and writ petitions filed by diverse parties. In order to streamline the further course of hearing, we have requested the *Amici* to collate and compile these suggestions which would be taken up later. The present order has focused on certain critical issues in view of the urgency of the situation.

…….....J.
[Dr Dhananjaya Y Chandrachud]

…….....J.
[L Nageswara Rao]

…….....J.
[S Ravindra Bhat]

New Delhi;
April 30, 2021

ANNEXURE-19
Novel Coronavirus Disease (COVID-19)
Situation Update Report – 68

World Health Organization India

May 19, 2021

HIGHLIGHTS

- Gap between two doses of Covishield vaccine extended from 6-8 weeks to 12-16 weeks based on recommendation of COVID-19 Working Group (Link)
- DCGI approves phase II/III clinical trial of COVAXIN in 2-18 ag group (Link)
- Government initiating steps to ramp up availability of Amphotericin B to fight Mucormycosis (Link)
- Anti COVID drug, 2-DG launched by Defense Minister & Health Minister (Link)
- National AEFI Committee submits report to MoHFW stating that bleeding and clotting events following COVID vaccination are miniscule in India (Link)
- Helpline for elderly ELDERLINE (14567) becomes operational in several states to address the sub-group's problems during the pandemic (Link)
- Convalescent plasm removed from COVID-19 clinical management protocol (Link)
- Prime Minister interacts with State and District officials regarding COVID-19 situation and urges them to share best practices for utilization in different parts of the country (Link)

WHO Situation Update

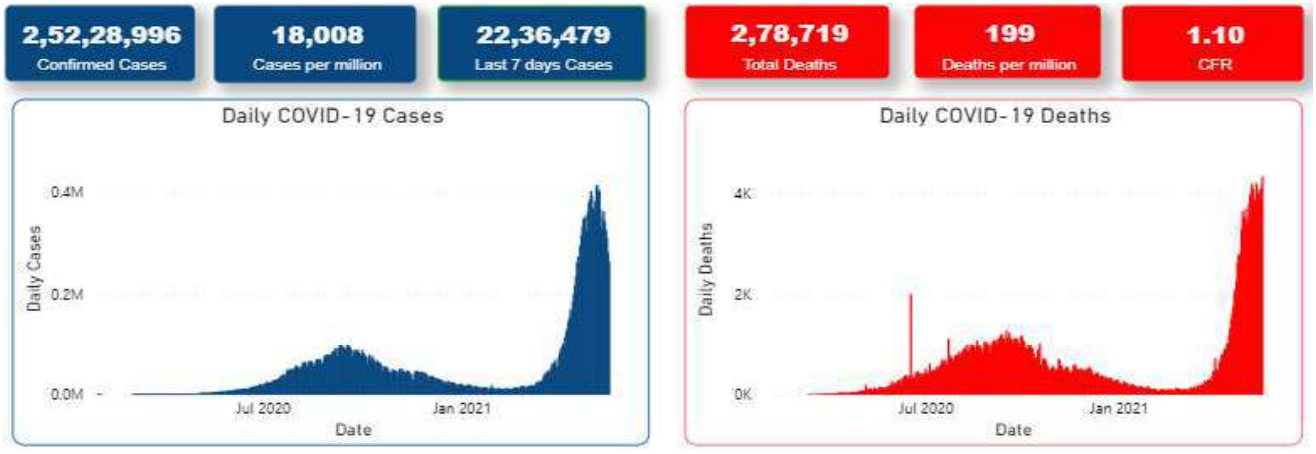
India
2,52,28,996 Confirmed Cases
2,78,719 Total Deaths

South East Asia Region
28,671,811 Confirmed Cases
349,375 Total Deaths

World
163,312,429 Confirmed Cases
3,386,825 Deaths

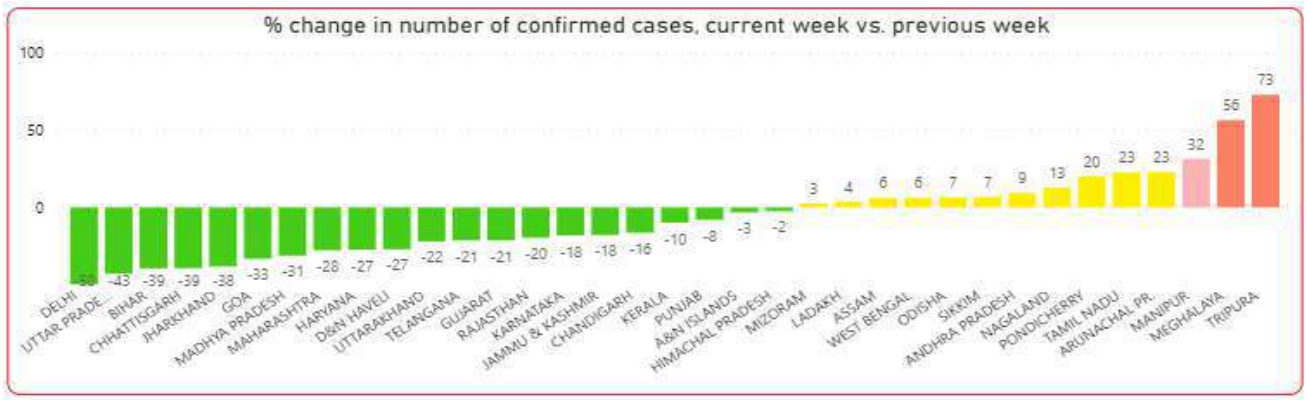
INDIA SITUATION

- India reported continuous decline in daily cases after reporting the highest number of cases (4,14,188) on 7 May 2021;



COVID-19: STATUS ACROSS STATES

- In the past week, as compared to previous week, 21states/UTs have shown a decrease in cases. Higher increase, among larger states was reported from Tamil Nadu (23%), Andhra Pradesh (9%) and Odisha (7%).



- In **Chhattisgarh**, Chief Minister has issued directives for constitution of a Pediatrics State Task Force in preparation for the third wave, for which experts have warned
- In **Karnataka**, Chief Secretary has issued guidelines for medical oxygen management, in line with which 24X7 state oxygen units will be supported by helplines at the state and district levels
- In **Gujarat**, guidelines have been issued regarding Mucormycosis which includes information on clinical features and management, prevention, vulnerable population, etc.
- In **Odisha**, State level committee has been constituted in response to the reported rise in incidence of Mucormycosis amongst COVID-19 patients

WHO GLOBAL UPDATE

- WHO advice to hospitals on how to ease pandemic pressure in Western Pacific region, details here
- Together with the United Nations Refugee Agency (UNHCR), other United Nations agencies and nongovernmental organizations, WHO/Europe has been working with Member States to ensure that refugees and migrants are included in national COVID-19 vaccine deployment plans as part of a commitment to universal health coverage and leaving no one behind, details here
- Egypt & Iraq receives second shipments of COVID-19 vaccines through the COVAX Facility, details here (1) (2)

WHO COUNTRY UPDATE

Coordination

- WCO continues to provide technical support to MoHFW, NCDC, ICMR and NDMA at the national level and through task force/control rooms at the state and district level in **Andhra Pradesh, Karnataka, Kerala, Tamil Nadu, Telangana, and Puducherry**
- 4000 oxygen concentrators have been sent to different States/ UTs according to the distribution plan WCO made in consultation with MOHFW
- WCO has carried out COVID-19 situational analysis for states that are witnessing high levels of surge in cases. Profile for Andhra Pradesh, Haryana, Manipur and Uttarakhand shared with respective state authorities.
- WHO field representatives participated in meetings regarding COVID-19 surge, response, and vaccination chaired by Chief Ministers, Health Ministers, Chief and/or Health Secretaries, MDs – NHM, etc in **Assam, Arunachal Pradesh, Chhattisgarh, Madhya Pradesh, Kerala, Manipur, Meghalaya, Mizoram, Puducherry, and Tamil Nadu**

COVID-19 vaccination

- WCO is supporting monitoring of vaccination sessions across the country and continues to provide surge support for training, microplanning and monitoring
- Supporting **Odisha** with development of global e-tender for procurement of COVID vaccine
- Assessing vaccination status of hospitalized COVID-19 patients in **Madhya Pradesh** to evaluate vaccine effectiveness as per state request
- Supporting **Rajasthan** in framing SOPs for vaccination of government employees

Contact Tracing, Containment and Surveillance

- Country office continues to provide technical support for COVID-19 containment activities in **Uttar Pradesh** and **Andhra Pradesh**; and supporting house to house survey for ILI/SARI in UP and Rajasthan
- Advocating for strengthening ILI/SARI passive surveillance in **Odisha** in response to the surge in cases

Information and Planning

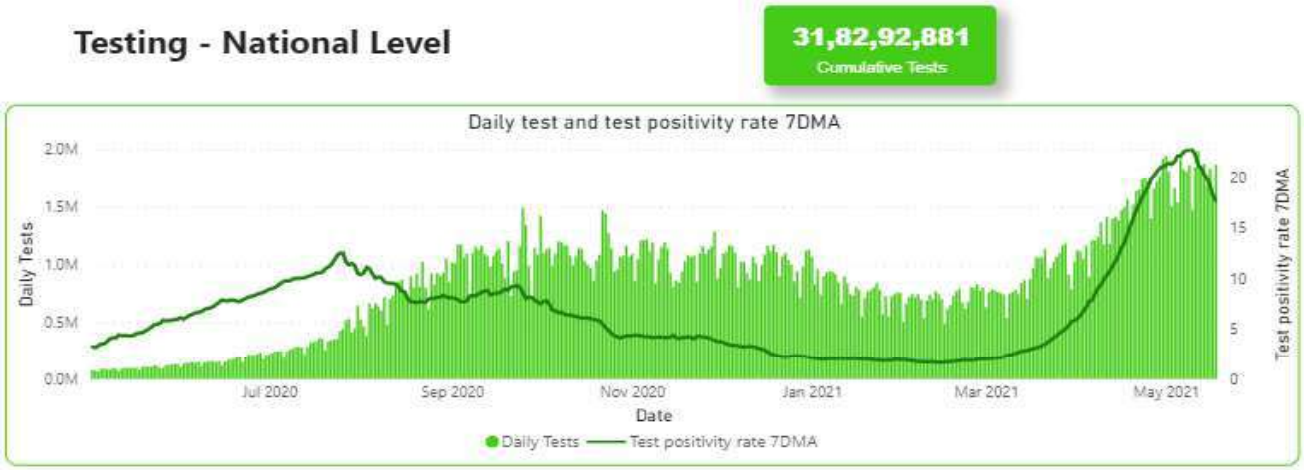
- Supporting **Madhya Pradesh** in development of guidance for management of pediatric cases of COVID-19 and cases of mucormycosis

- Supporting development of SOPs for COVID-19 management in tea gardens in **Assam**; and assisting training of District and Block Programme Management Unit officers on Public Health Social measures
- Assessed preparedness of Dedicated COVID Hospitals in select districts of **Gujarat** for impact of cyclone Tauktae
- Supporting planning for establishment of mobile kiosks in rural areas of **Madhya Pradesh**; and advocating for prioritization of teachers for vaccination

Essential Services

- Supporting **Chhattisgarh** and **Jammu & Kashmir** for roll out of Pneumococcal Vaccine (PCV)
- Contributing in sensitization efforts for surveillance of AFP/ MR/ DPT in **Puducherry**
- Supporting **Puducherry and Telangana** in strengthening and streamlining AEFI surveillance
- Continuing to provide support for orientation of state health officials regarding fever and rash surveillance in **Maharashtra**

As of 18 May 2021, India has tested more than 318 M samples. Tests include both, RTPCR and Rapid Antigen. India's current test positivity rate (7DMA) is 17.6%.



India continued to drive Covid-19 vaccinations among various age group with preconditions, details here.

Cumulative Coverage Report of Covid-19 vaccination (as on 18 May 2021, 07:00 AM)

	Beneficiaries vaccinated		
India	1st Dose	2nd Dose	Total Doses
	14,24,28,227	4,20,24,922	18,44,53,149
	12,67,201 in last 24 Hours	2,43,217 in last 24 hours	15,10,418 in last 24 Hours

IMPORTANT GUIDELINES THIS WEEK

- COVID-19 Vaccine Introduction and deployment Costing tool (CVIC tool)- Ver.2 [LINK]
- Preventing and mitigating COVID-19 at work [LINK]
- SOP on COVID-19 Containment & Management in Peri-urban, Rural & Tribal areas (*by MoHFW*) [LINK]

FOR MORE INFORMATION CONTACT

In case of any queries on COVID-19, call +91-11-23978046 or 1075 (Toll-free). State Helpline here.
WHO Country Office for India I Telephone number: +91-11- 66564800 I Email: wrindia@who.int

ANNEXURE-20

EMAIL COMMUNICATION FOR VOLUNTARY LICENSE WITH INCYTE HOLDINGS CORPORATION AND ELI LILLY & COMPANY

From: Manisha Sargar <manisha@bajajhealth.com>
Sent: 14 May 2021 18:57
To: IPO <ipo@knspartners.com>; Postmaster <postmaster@knspartners.com>; caltrider@lilly.com; b-roll@lilly.com
Cc: bajaj@bajajhealth.com; pakshal@bajajhealth.com; dereck.lobo@bajajhealth.com
Subject: Baricitinib API and Formulation Co-manufacturing and marketing for Covid-19 treatment in India in this current pandemic situation

Dear Sir/Madam,

To:-
1.INCYTE HOLDINGS CORPORATION through Attorney on their email: ipo@knspartners.com, , gurgaon@knspartners.com
2. ELI LILLY AND COMPANY: CC marked to Mr. Steven P. Caltrider , Vice President and General Patent Counsel

Hope you are doing well and safe in this pandemic.

Subject :- Regarding Baricitinib API and Formulation Co-manufacturing and marketing for Covid-19 treatment in India in this current pandemic situation.

I am Ms. Manisha Sargar from Regulatory Department of Bajaj Healthcare Ltd, India. We are in the manufacturing and distribution of API's (more than 40 APIs) and formulation (more than 150 Finished products) business located in Maharashtra and Gujarat, India. Our head office is in Mumbai.

This email has reference due to current pandemic situation in India, Baricitinib API and Formulation used for COVID-19 treatment in combination with Remdesivir as an emergency drug. We appreciate your esteem organisation for development of Baricitinib treatment in COVID -19.

We have manufacturing facilities of API and Formulation for production of Baricitinib API and Baricitinib tablet 1mg , 2mg and 4mg. Also we will apply for the necessary permission and license from CDSCO for the manufacturing and distribution of this Baricitinib API and formulation.

We would like to apply for non-exclusive, voluntary license for the patent **IN270765** and any other relevant patent to your company.

Below is the brief introduction of our Manufacturing facilities of API and Formulation units:-

Founded in 1993, Bajaj Healthcare Ltd is engaged in manufacturing large range of Active pharmaceutical ingredients, intermediates, nutraceuticals and finished formulations. With Headquarters in Mumbai, Bajaj Healthcare Ltd has several manufacturing facilities located in Maharashtra and Gujarat.
So far, we operate one Formulation unit and 18 state-of-the-art manufacturing units where Intermediates, APIs and nutraceuticals are produced. Our API unit situated in Savli Vadodara is

an **EU GMP certified**, **Korean FDA** approved and **WHO-GMP** certified facility. We are the leading manufacturers of Formulation in solid dosage forms **(Tablets, Capsules & Sachets)**.

Our formulation unit is located at Manjusar - Gujarat which is designed to meet the regulatory market requirements.

It is **WHO-GMP & ISO 9001:2015 Certified** & along with the approval of **MOH- Sri Lanka, Malawi and Lesotho.**

We have strong R&D backup team they are aggressively working on new molecules.

We are also manufacturing new complex speciality molecules such as: -

- Fosfomycin Tromethamine USP
- Fosfomycin Trometamol BP/EP
- Ticagrelor IH/IP
- Diosmin BP/EP/USP/IH
- Ascorbic Acid IP/BP/EP/USP
- Chlorhexidine Gluconate Solution IP/BP/EP/USP

We therefore would like to seek your kind support and request you to guide us on further course of action for manufacturing and sales of Baricitinib tablets in Indian market under non -exclusive, voluntary license.

As this matter is urgent and looking current pandemic situation in India and necessity of Baricitinib tablets market, we request you to consider this as matter of extremely urgency.

We would highly appreciate your prompt response.

Thanks and Best Regards,

Manisha Sargar
Regulatory Affair - Manager
BAJAJ HEALTHCARE LIMITED
6th Floor, Bhoomi Velocity Infotech Park,
Above ICICI Bank,
Road No. 23, Wagle Industrial Estate,
Thane (w) Pincode : 400 604
Tel: + 91-22-66177400/ 66177465
www.bajajhealth.com

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From: Amrish Tiwari <amrish@knspartners.com>
Sent: 16 May 2021 12:17
To: manisha@bajajhealth.com; bajaj@bajajhealth.com; pakshal@bajajhealth.com; dereck.lobo@bajajhealth.com
Cc: Sanjeev Kumar Tiwari <sanjeev.tiwari@knspartners.com>
Subject: RE: Baricitinib API and Formulation Co-manufacturing and marketing for Covid-19 treatment in India in this current pandemic situation

Dear Ms. Manisha,

We thank you for your interest in seeking a voluntary license for Lilly's drug baricitinib for COVID-19 in India.

Please refer to the attached reply under instructions from Eli Lilly.

Best, Amrish

Amrish Tiwari (Mr.)
Partner

K&S partners
Intellectual Property Attorneys

K&S Partners | Intellectual Property Attorneys
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F: +91 124 4708 760/780
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W: www.knspartners.com
LinkedIn : https://www.linkedin.com/in/amrishtiwari/
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K&S partners

Intellectual Property Attorneys

May 16, 2021

Ms. Manisha Sargar
Regulatory Affair - Manager
BAJAJ HEALTHCARE LIMITED
6th Floor, Bhoomi Velocity Infotech Park,
Above ICICI Bank, Road No. 23,
Wagle Industrial Estate, Thane (w) Pincode : 400 604

Dear Ms. Sargar,

We write under instructions from our client Eli Lilly having corporate office at Lilly Corporate Center, Indianapolis, IN 46285, U.S.A., as under:

We thank you for your interest in seeking a voluntary license for Lilly's drug baricitinib for COVID-19 in India. Moreover, we appreciate your request in order to make sure that baricitinib is made available and accessible to many patients and as early as possible in India.

As you may have heard, Lilly is offering continuous donations of baricitinib to the Indian government in big quantities to treat the eligible Covid-19 patients. Moreover, we have already announced the signature of 6 royalty-free voluntary licensing agreement to ensure baricitinib is available in the country for the Covid-19 patients in sufficient quantities and good quality. Couple of additional agreements are in the final phase of negotiations and may be announced soon. In the last few weeks, we have been inundated with many pharma companies who are also interested in the above purpose. We prioritized the negotiations with those companies who have reached out first and committed to ensure the licensed product will be available in the market as soon as possible. As you can understand, it will be challenging for Lilly to sign Voluntary Licensing Agreements with all companies who have requested for the same. Thus, we decided to stop at this stage responding to additional Voluntary licensing requests and will only make sure we conclude those that are already about to be executed.

We, therefore, thank you for your interest in partnering with Lilly for the benefit of the Covid-19 patients in India and assure you of our full commitment to ensure the accessibility of our medicine to all patients in need. If the situation changes in the near future and in case the events would justify the issuance of additional licenses, we will reach out to you appropriately.

Thanking you

Yours truly,

Amrish Tiwari
Partner
K&S Partners

Dear Sir/ Madam,

To: -
1.INCYTE HOLDINGS CORPORATION through Attorney on their email: ipo@knspartners.com, , gurgaon@knspartners.com
2. ELI LILLY AND COMPANY: marked to Mr. Steven P. Caltrider , Vice President and General Patent Counsel

Dear Mr. Amrish,

We are thankful to you for your prompt response.

Enclosed herewith letter for re-consideration of our request for license to manufacture and supply Baricitinib API and tablets in Indian market.

Your valuable feedback will be highly appreciated.

Thanks and Best Regards,

Manisha Sargar
Regulatory Affair - Manager
BAJAJ HEALTHCARE LIMITED
6th Floor, Bhoomi Velocity Infotech Park,
Above ICICI Bank,
Road No. 23, Wagle Industrial Estate,
Thane (w) Pincode : 400 604
Tel: + 91-22-66177400/ 66177465
www.bajajhealth.com

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BAJAJ

May 18, 2021

To,
Mr. Amrish Tiwari
Partner, K&S partners
Chimes 61, Sector 44, Gurugram, Haryana – 122003,
National capital region

Mailing address: 515-B, Platinum Tower, 5th floor,
Sohna Road, Sector 47, Gurgaon – 122002,
National capital region, India
Email: Gurgaon@knspartners.com

Subject: Regarding re-consideration of our request for license to manufacture and supply Baricitinib API and tablets in Indian market

Dear Mr. Tiwari,

We understand that you are working for and under the instructions of your client Eli Lilly having a corporate office at Lilly Corporate Center, Indianapolis, IN 46285, U.S.A.

In reference to our email dated 14.05.2021 and your reply thereto dated 16.05.2021 we wish to state further as:

First of all, we are thankful to you for your prompt response. We appreciate the efforts being taken by Eli Lilly for making available the Baricitinib tablets in India.

We also appreciate the licensing options that the patentee/rights holder are exploring for the same purpose. Considering the serious COVId-19 situation in the country and the large number of patients requiring the Remdesivir-Baricitinib co-treatment, we requested the non-exclusive license under the patent IN270765 and for other related patents for manufacture and supply of Baricitinib tablets in India. You have mentioned in your email dated 16.05.2021 that Eli Lilly has issued 6 royalty free licenses and a couple of licensing agreements are under negotiations. However, looking at the urgency, pandemic situation and requirement from all over India we again request the patentee/right holder(s) to grant us the license for the purposes mentioned above.

We seek a voluntary license for manufacturing and sales of Baricitinib API and tablets of strengths 1mg, 2mg and 4mg in Indian market. As already mentioned, we have world class facilities, capability and resources to manufacture and distribute Baricitinib API and formulation as well. We adhere to all guidelines and follow cGMP and cGLP practices in manufacturing and testing of pharmaceutical products. One of our API unit situated in Savli, Vadodara is an EU GMP certified, Korean FDA approved and WHO-GMP certified facility.

BAJAJ

Further, in addition to our formulation unit we have 18 state-of-the-art manufacturing units where Intermediates, APIs and nutraceuticals are produced. We strictly maintain the quality checks in all our operations and maintain best quality for all the pharmaceutical products we manufacture.

If given a license to manufacture and supply Baricitinib API and tablets, we shall try to keep the price affordable to the Indian patient population. We also mention here that we are ready to pay the mutually agreeable royalty to the patentee/rights holder as the case may be. This arrangement will be beneficial for all the stakeholders including the patients as we will be able to fill/mitigate to the large extent the requirement-supply gap at the cost affordable to patients and will also be able to give you the royalty payments.

At this time of COVID-19 pandemic necessity and extreme urgency for Baricitinib tablets we urge the patentee/rights holder to reconsider our request and grant us the license on mutually agreeable terms including royalty at the earliest.

Further to this we would request you to arrange a teleconference call meeting with the patentee/rights holder (Incyte Holdings Corporation, Eli Lilly as the case may be) with our marketing team for better clarity from our end and the further discussions in this matter. Since this is a matter of extreme urgency, request you to confirm their availability on any suitable day in the next three days with the suitable time for the said teleconference.

Thanking you,

With best regards,

From and on behalf of Bajaj Healthcare Ltd., India

18/05/2021

BAJAJ HEALTHCARE LTD. MUMBAI

Manisha Sargar
Regulatory Affair - Manager

From: Amrish Tiwari <amrish@knspartners.com>
Sent: Wednesday, May 19, 2021 5:32 PM
To: Manisha Sargar <manisha@bajajhealth.com>
Cc: Sanjeev Kumar Tiwari <sanjeev.tiwari@knspartners.com>; bajaj@bajajhealth.com; pakshal@bajajhealth.com; dereck.lobo@bajajhealth.com
Subject: RE: Baricitinib API and Formulation Co-manufacturing and marketing for Covid-19 treatment in India in this current pandemic situation

Dear Ms. Manisha,

Thanks for your below email and responding to our reply. We are again thankful for your interest in seeking a voluntary license for Lilly's drug baricitinib for COVID-19 in India.

As indicated earlier, it is really challenging for Lilly to sign Voluntary Licensing Agreements with all the Indian companies who have requested for the same. Lilly has now executed 7 Voluntary licenses. At this stage, Lilly has decided to stop considering any additional Voluntary licensing requests. Lilly, at this stage, would like to ensure that licenses executed are concluded.

If the situation changes in the near future and in case the events would justify the issuance of additional licenses, we will reach out to you appropriately.

We appreciate your kind understanding in this matter. Thank-you.

Best, Amrish

Amrish Tiwari (Mr.)
Partner

K&S partners
Intellectual Property Attorneys

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W: www.knspartners.com
LinkedIn : https://www.linkedin.com/in/amrishtiwari/
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FORM CT-11

(See rules 53, 54, 55, 56, 57 and 58)

PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR EXAMINATION, TEST AND ANALYSIS

Licence Number CT11/AZ/21/000568

The Central Licencing Authority hereby grant permission M/s Bajaj Healthcare Ltd Block No. 588, Savli Karachia Road, At & Post - Gothada-391776 Taluka Savli, Dist Vadodara, Gujarat, India Savli (India) - 391776 Telephone No.: 91 22 66177400, 433, 444 FAX: 91 22 66177458 E-Mail : bajaj@bajajhealth.com to manufacture the new drug or investigational new drug for examination, test and analysis.

S.No.	Name of the new drug or investigational new drug	Class of Drug	Strength	Quantity to be manufactured.
1	Baricitinib	Antiviral Drugs	-	10 Kgs

2. This licence is subject to the conditions specified in the Chapter VIII of New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.
3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance
4. Details of manufacturer and manufacturing site under this licence.

S.No.	Site Name & Address	Site Type	Drug Type
1	Bajaj Healthcare Ltd. (Registered Office) 602-606, Bhoomi velocity Infotech park, Road no. 23, Wagle Industrial Estate, Thane west, Maharashtra - 400604 (India) CONTACT: 02266177400 FAX: 02266177458	Manufacturer Address	API
2	Bajaj Healthcare Ltd. Unit-II Block No. 588, Savli Karachia Road, At & Post - Gothada-391776, Savli, Vadodara, Gujarat - 391776 (India) CONTACT: 912667220100 FAX: 912667220100	Manufacturing Site Address	API

Date: 20-May-21

Place: Ahmedabad

Central Licencing Authority

Stamp

वीरेन्द्र सिंह/VIRENDRA SINGH
सहायक औषधि नियंत्रक (भारत)
Assistant Drugs Controller (India)
सी.डी.एस.सी.ओ. पोर्ट ऑफिस, एयर इंडिया कार्गो,
CDSCO, Port Office, Air Airport,
अहमदाबाद/Ahmedabad-380016.

Conditions

1. After obtaining permission in CT-11 or CT-14 or CT-15 as the case may be, the person, who intends to manufacture the new drug or investigational new drugs for CT or BA/BE study or for examination, test and analysis of new drugs or Investigational new drugs, shall make an application for grant of license to manufacture the new drug or investigational new drugs by the respective State Licensing Authority (SLA) in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

2. This licence for manufacture of Drugs is for Examination, Test and Analysis only and Not for CT/BA-BE studies.

3. The licencee shall adhere to the relevant provisions of the Drugs and Cosmetics Act, 1940 and The New Drugs and Clinical Trail Rules, 2019.

4. In case of Narcotis/Psychotropic Drugs, you are also directed to approach The Narcotic Commissioner of India,

19th The Mall Morar, Gwalior-6 so far as the provisions of the NDPS Act and the Rules are concerned in the matter.

FORM CT-11

(See rules 53, 54, 55, 56, 57 and 58)

PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR EXAMINATION, TEST AND ANALYSIS

Licence Number CT11/AZ/21/000569

The Central Licencing Authority hereby grant permission M/s Bajaj Healthcare Ltd Block No. 588, Savli Karachia Road, At & Post - Gothada-391776 Taluka Savli, Dist Vadodara, Gujarat, India Savli (India) - 391776 Telephone No.: 91 22 66177400, 433, 444 FAX: 91 22 66177458 E-Mail : bajaj@bajajhealth.com to manufacture the new drug or investigational new drug for examination, test and analysis.

S.No.	Name of the new drug or investigational new drug	Class of Drug	Strength	Quantity to be manufactured.
1	Baricitinib Tablets 1mg	Immunosuppressant	1 milligram (mg)	32000 Tablets
2	Baricitinib Tablets 2mg	Immunosuppressant	2 milligram (mg)	32000 Tablets
3	Baricitinib Tablets 4mg	Immunosuppressant	4 milligram (mg)	32000 Tablets

2. This licence is subject to the conditions specified in the Chapter VIII of New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.
3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance
4. Details of manufacturer and manufacturing site under this licence.

S.No.	Site Name & Address	Site Type	Drug Type
1	Bajaj Healthcare Ltd. (Registered Office) 602-606, Bhoomi velocity Infotech park, Road no. 23, Wagle Industrial Estate, Thane west, Maharashtra - 400604 (India) CONTACT: 02266177400 FAX: 02266177458	Manufacturer Address	API
2	Bajaj Healthcare Ltd. Unit-II Block No. 588, Savli Karachia Road, At & Post - Gothada-391776, Savli, Vadodara, Gujarat - 391776 (India) CONTACT: 912667220100 FAX: 912667220100	Manufacturing Site Address	API
3	Bajaj Healthcare Ltd. (Registered Office) 602-606, Bhoomi velocity Infotech park, Road no. 23, Wagle Industrial Estate, Thane west, Maharashtra - 400604 (India) CONTACT: 02266177400 FAX: 02266177458	Manufacturer Address	Formulation
4	Bajaj Healthcare Ltd. (Formulation Division) R.S. No. 1818, Manjusar-savli road, At & post Manjusar, Tal. - Savli, Dist. Vadodara, Gujarat - 391775 (India) CONTACT: 912667264587 FAX: 912667264399	Manufacturing Site Address	Formulation

Date: 20-May-21

Central Licencing Authority

Stamp

वीरेन्द्र सिंह/VIRENDRA SINGH
सहायक औषधि नियंत्रक (भारत)
Assistant Drugs Controller (India)
सी.डी.एस.सी.ओ. पोर्ट कार्यालय, पुराना एयर पोर्ट,
CDSCO, Port Office, Old Airport,
अहमदाबाद/Ahmedabad-380016.

Place: Ahmedabad

Conditions

1. After obtaining permission in CT-11 or CT-14 or CT-15 as the case may be, the person, who intends to manufacture the new drug or investigational new drugs for CT or BA/BE study or for examination, test and analysis of new drugs or investigational new drugs, shall make an application for grant of license to manufacture the new drug or investigational new drugs by the respective State Licensing Authority (SLA) In accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

2. This licence for manufacture of Drugs is for Examination, Test and Analysis only and Not for CT/BA-BE studies.

3. The licencee shall adhere to the relevant provisions of the Drugs and Cosmetics Act, 1940 and The New Drugs and Clinical Trail Rules, 2019.

4. In case of Narcotis/Psychotropic Drugs, you are also directed to approach The Narcotic Commissioner of India, 19th The Mall Morar, Gwalior-6 so far as the provisions of the NDPS Act and the Rules are concerned in the matter.