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Task Force on Repurposing of Drugs (TFORD) for COVID19

S&T Core Group on COVID19 constituted by PSA to GoI

Molecule Brief: Baricitinib

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About this document: *This document summarizes information available on drug candidates for COVID19. One Molecule Brief document covers one candidate at a time.*	
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1. Summary Information on Baricitinib

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Baricitinib
Brand Name	Olumiant
Category/ Type	Immunomodulator
Drug Bank ID/Link	DB11817 https://www.drugbank.ca/drugs/DB11817
Mode of Action	Baricitinib selectively and reversibly inhibits JAK1 and JAK2 to modulate their signaling pathways, thereby reducing the phosphorylation and activation of STATs which disrupts the activation of downstream signaling molecules and proinflammatory mediators. https://www.drugbank.ca/drugs/DB11817
Therapeutic Target	Tyrosine-protein kinase JAK1, Tyrosine-protein kinase JAK2, Protein-tyrosine kinase 2-beta, Tyrosine-protein kinase JAK3 https://www.drugbank.ca/drugs/DB11817
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Rheumatoid arthritis
Approved Dose	OLUMIANT - 2 mg once daily and 4 mg once daily.
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	1-8 mg https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6122435/
Adverse events/Side effects reported at the current approved dose	Adverse reactions (greater than or equal to 1%) include: upper respiratory tract infections, nausea, herpes simplex, and herpes zoster
Reported Drug-	OLUMIANT is not recommended in patients taking strong Organic Anion

Drug Interactions	Transporter 3 (OAT3) inhibitors (e.g., probenecid) *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf https://www.tga.gov.au/sites/default/files/auspar-baricitinib-190321.pdf
Current TRL level of the Drug	TRL-9
Has the drug been repurposed for any other indication before?	No. But has been tested in the following conditions: • Severe Atopic Dermatitis (NCT03559270) • Severe Alopecia Areata (NCT03570749) • Systemic Lupus Erythematosus (NCT03616912, NCT03616964) • Chronic Anterior Antinuclear Antibody-Positive Uveitis (NCT04088409)
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Formulation manufacturer- Eli Lilly and Company India Pvt Ltd https://www.pharmacompass.com/listed-active-pharmaceutical-ingredients/baricitinib
International Manufacturer(s)	Formulation manufacturer- Eli Lilly and company
Price of the Drug in India	Rs. 17900/strip of 7 tablets https://www.ncbi.nlm.nih.gov/books/NBK549721/
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	Cytokine Release Syndrome (CRS)/Cytokine storm is a systemic inflammatory response characterized by a sharp increase in the level of a large number of pro-inflammatory cytokines. Evidence indicate that cytokine storm is observed in COVID-19 patients (as in SARS and MERS patients) and is responsible for the occurrence of ARDS multiorgan failure, and eventually death. Many cytokines implicated in COVID-19-associated CRS signal via the JAK-STAT pathway including IL-2, IL-6, IL-7, IL-10, G-CSF, GM-CSF, and IFN-γ. https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930216-2 https://www.sciencedirect.com/science/article/pii/S1359610120300927 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7144601/pdf/main.pdf https://pubmed.ncbi.nlm.nih.gov/31986264/ https://pubmed.ncbi.nlm.nih.gov/32360286/ https://www.karger.com/Article/FullText/508247
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	A molecular modeling study using machine learning shows Baricitinib binds with high affinity to AP2-associated protein kinase 1 (AAK1), a regulator of clathrin mediated SARS-CoV-2 endocytosis. Authors conclude that disruption of AAK1 could interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. Authors also mention that known plasma concentration of Baricitinib on therapeutic dosing (either as 2 mg or 4 mg once daily) is sufficient to inhibit AAK1 (based on binding and cell based assay potencies). https://www.thelancet.com/article/S1473-3099(20)30132-8/fulltext#seccestitle10 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7137985/
Status of Clinical Trials	9 Ongoing Trials
Trial Details	See table below

Trial ID/Link	Type of Trial	No. of patients	Drug Combination/Dose/ Stage of Disease	Primary and Secondary Measures	Has data from the trial been published?
NCT0432	Interventional	200	Baricitinib +	Primary:	No

0277	Open-label, Pilot Study		Lpoinavir/Ritonavir Dose: Baricitinib 4 mg/day/orally for 2 weeks Stage:Mild to moderate COVID-19 confirmed patients	The percentage of patients requiring transfer to ICU as compared with the rate of transfers observed in controls. [Time Frame: 2 weeks] Secondary: The percentage of patients achieving the remission; CRP, IL-6 and TNFα values at baseline and during the treatment course; the number of AEs. [Time Frame: 2 weeks]	
NCT04321993	Non-Randomized, Open label	1000	Baricitinib (2 other arms have HCQ and Lpoinavir/Ritonavir) not in combination Dose: 2 mg po daily for 10 days Stage: Moderate disease	Primary: Clinical status of subject at day 15 (on a 7 point ordinal scale). [Time Frame: Up to 15 days] Secondary: Status on an ordinal scale assessed daily while hospitalized and on days 15 and 29 and 180. [Time Frame: Up to 180 days] Length of time to clinical improvement. [Time Frame: Up to 29 days]	No
NCT04358614	Interventional Open-label, Pilot Study	12	Baricitinib + (Lopinavir/Ritonavir) Dose: Baricitinib 4 mg Oral Tablet for 2 weeks Stage: COVID-19 patients with moderate pneumonia	Primary: To assess the safety of baricitinib combined with antiviral (lopinavir-ritonavir) in terms of serious or non-serious adverse events incidence rate. [Time Frame: 2 weeks] Secondary: To evaluate the impact of baricitinib in terms of clinical, laboratory, respiratory parameters. [Time Frame: 2 weeks] CU admission rate [Time Frame: 2 weeks] Discharge rate. [Time Frame: 2 weeks]	Yes (See Data from Clinical Trials Section)
NCT04340232	Single arm, open label, single site study	80	Baricitinib. Dose: 2mg, once daily, 14 days Stage: Data not available	Primary: Cumulative incidence of Grade 3 and 4 adverse events (AEs) [Time Frame: Day 0 (screening) through Day 29] Cumulative incidence of serious adverse events (SAEs) [Time Frame: Day 0 (screening) through Day 29] Changes in white blood cell count (CBC) through Day 15 [Time Frame: Day 1 to Day 15 Secondary: Change in the 8-point ordinal scale [Time Frame: Day 1 to Day 29] Change in National Early Warning Score (NEWS) [Time Frame: Day 1 through Day 29 or hospital discharge, whichever is first]	No
NCT04346147	Interventional, Prospective,	165	HCQ + Baricitinib Other Arms –	Primary: Time to clinical improvement [	No

	Phase II, Randomized, Open-label, Parallel Group Study		HCQ + Imatinib HCQ+ Lopinavir/Ritonavir Dose: HCQ - 200mg 1 tablet every 12 hours Baricitinib - 4 mg 1 tablet 24 hours Stage: Patients With Pneumonia by COVID-19	Time Frame: baseline to day 14] Secondary: Safety of treatments [Time Frame: through study completion, an average of 1 month] Tolerability of treatments [Time Frame: during treatment and up to 30 days after the last treatment dose]	
NCT04345289	Interventional, Adaptive multi-arm trial	1500	Baricitinib Other Arms - Convalescent Plasma, Sarilumab, HCQ Dose: Baricitinib 4 mg, oral administration for 7 days Stage: Adults With COVID-19 Pneumonia	Primary: All-cause mortality or need of invasive mechanical ventilation [Time Frame: 28 days] Secondary: Frequency of adverse events [Time Frame: 90 days] Frequency of severe adverse events [Time Frame: 90 days] Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status [Time Frame: 90 days Ventilator-free days [Time Frame: 28 days]	No
NCT04373044	Interventional, Phase II Randomized Double-Blind Trial	144	Baricitinib + HCQ Other Arms – HCQ only Dose: Baricitinib and HCQ PO daily Stage: Patients With Moderate and Severe COVID-19	Primary: Proportion of patients requiring invasive mechanical ventilation or dying [Time Frame: Up to 14 days] Secondary: Identification of clinical features (vitals signs - body temperature) [Time Frame: Up to 28 days] Identification of clinical features (vital signs - respiratory rate, heart rate, BP, WBC etc.) [Time Frame: Up to 28 days]	No
NCT04362943	Observational, retrospective	576	Baricitinib Other Arms – Anakinra Dose: Data not available Stage: Hospitalized Older Adults (>70 yrs)	Primary: Mortality [Time Frame: 1 month] Secondary: X-ray changes [Time Frame: 1 month] Disability changes [Time Frame: 1 month] Ambulation changes [Time Frame: 1 month] lymphocyte count changes [Time Frame: 1 month] C-Reactive Protein changes [Time Frame: 1 month] Ferritin changes [Time Frame: 1 month]	No
NCT04365764	Observational, multicenter	400	Data for use of Baricitinib (and other drugs hydroxychloroquine, azithromycin, remdesivir, baricitinib, tocilizumab, sarilumab,	Primary: Composite of death and mechanical ventilation [Time Frame: 14-days follow-up] Secondary: Death [Time Frame: 14-days follow-up]	No

			lopinavir/ritonavir and oseltamivir)	Mechanical ventilation [Time Frame: 14-days follow-up] Composite of death and mechanical ventilation [Time Frame: 28-days follow-up] World Health Organization score [Time Frame: 14-days follow-up]	

Key Data from Clinical Trials	NCT04358614: Baricitinib at 4 mg/day/orally was given to 12 patients with moderate COVID-19 pneumonia. Key results: • Fever, SpO2, PaO2/FiO2, CRP, and MEWS significantly improved in the Baricitinib-treated group compared with controls (p: 0.000; 0.000; 0.017; 0.023; 0.016, respectively). • ICU transfer was requested in 33% (4/12) of controls and in none of the Baricitinib-treated patients (p=0.093). • Discharge at week 2 occurred in 58% (7/12) of the Baricitinib-treated patients vs 8% (1/12) of controls (p=0.027). At discharge, 57% (4/7) had negative viral nasal/oral swabs. • No adverse events were recorded after 2 weeks in Baricitinib treated patients. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177073/
TRL Level for COVID19	TRL > 7 (Phase III/IV Trials)
`Other Key References	https://pubchem.ncbi.nlm.nih.gov/compound/Baricitinib https://link.springer.com/article/10.1007/s40265-018-0908-4

IP Status

Status/ Molecule	Baricitinib
Pending applications	201717021246 Title: Process for the preparation of Baricitinib and an intermediate thereof Assignee: Sun Pharmaceutical Industries Limited Priority date: 05/12/2014 Publication date: 09/06/2014 Status: FER issued on 26/09/2019 201741022642 Title: Polymorphic forms of Baricitinib Assignee: Mylan Laboratories Ltd Priority date: 28/06/2017 Publication date: 03/01/2019 Status: Deadline to file request for examination is 28/06/2021 WO2019114258 (PCT application designating India) Title: Method for preparing Baricitinib Assignee: Jiangsu Zhongbang Pharmaceutical Co., Ltd Priority date: 13/12/2017 Publication date: 20/06/2019 Status: Deadline to enter into Indian national phase will expire on 13/07/2020 WO2019121290 (PCT application designating India) Title: Co-crystal of an orally available janus kinase inhibitor Assignee: Sandoz AG Priority date: 20/12/2017 Publication date: 27/06/2019 Status: Deadline to enter into Indian national phase will expire on 20/07/2020 WO2019137325 (PCT application designating India) Title: Novel crystalline form of Baricitinib phosphate and preparation method thereof Assignee: Sunshine Lake Pharma Co., Ltd Priority date: 09/01/2018 Publication date: 18/07/2019 Status: Deadline to enter into Indian national phase will expire on 13/08/2020

	WO2020072870 (PCT application designating India) Title: Co-crystal forms of Baricitinib Assignee: Johnson Matthey Public Limited Company Priority date: 05/10/2018 Publication date: 09/04/2020 Status: Deadline to enter into Indian national phase will expire on 05/05/2021 WO2020081346 (PCT application designating India) Title: Treatment of primary biliary cholangitis and primary sclerosing cholangitis with Baricitinib Assignee: Eli Lilly And Company Priority date: 17/10/2018 Publication date: 23/04/2020 Status: Deadline to enter into Indian national phase will expire on 17/05/2021
Approved and Active applications	270765 Title: Azetidine and cyclobutane derivatives as JAK inhibitors Assignee: Incyte Corporation (Licensee Eli Lilly & Company) Priority Date: 11/03/2008 Grant date: 22/01/2016 Expected expiry date: 10/03/2029
Expired or Lapsed application or examination request not filed	1102/DELNP/2015 Title: Deuterated Baricitinib Assignee: Concert Pharmaceuticals Inc Priority Date: 17/08/2012 Publication date: 26/06/2015 Status: Application has been abandoned 201617035401 Title: Amorphous form of Baricitinib Assignee: Sun Pharmaceutical Industries Limited Priority date: 28/03/2014 Publication date: 14/04/2017 Status: No status on Indian patent site 201617038592 Title: Crystalline form of Baricitinib Assignee: Sun Pharmaceutical Industries Limited Priority date: 01/05/2014 Publication date: 24/02/2017 Status: Application appears to have been abandoned 201717028647 Title: Process for the preparation of Baricitinib and an intermediate thereof Assignee: Sun Pharmaceutical Industries Limited Priority date: 02/02/2015 Publication date: 10/11/2017 Status: No status on Indian patent site WO2010039939 (PCT application designating India) Title: Janus Kinase Inhibitors For Treatment Of Dry Eye And Other Eye Related Diseases Assignee: Incyte corporation Priority date: 02/10/2008 Publication date: 08/04/2010 Status: Deadline to enter into Indian national phase has expired on 02/05/2011 WO2016141891 (PCT application designating India) Title: Crystal form of JAK inhibitor and preparation method thereof Assignee: Crystal Pharmatech Co, Ltd Priority date: 11/03/2015 Publication date: 15/09/2016 Status: Deadline to enter into Indian national phase has expired on 11/10/2017 WO2016205487 (PCT application designating India) Title: Processes and intermediates for the preparation of {1-(ethylsulfonyl)-3-[4-(7h-pyrrolo[2,3-d]pyrimidin-4-yl)-1h-pyrazol-1-yl]azetidin-3-yl}acetonitrile Assignee: Eli Lilly and Company Priority date: 19/06/2015 Publication date: 22/012/2016 Status: Deadline to enter into Indian national phase has expired on 19/01/2018 WO2017082760 (PCT application designating India) Title: {3-[4-(7h-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrazol-1-yl]-1-ethylsulphonyl-azetidin-3-yl}-acetonitrile dichloroacetate as a janus kinase inhibitor Assignee: R-Pharm Joint Stock Company

	Priority date: 13/11/2015 Publication date: 18/05/2017 Status: Deadline to enter into Indian national phase has expired on 13/06/2018 WO2017109524 (PCT application designating India) Title: Method and intermediate for the production of Baricitinib Assignee: Egis Gyógyszergyár Zrt Priority date: 23/12/2015 Publication date: 29/06/2017 Status: Deadline to enter into Indian national phase has expired on 23/07/2018 WO2017125772 (PCT application designating India) Title: Baricitinib salts Assignee: Egis Gyógyszergyár Zrt Priority date: 21/01/2016 Publication date: 27/07/2017 Status: Deadline to enter into Indian national phase has expired on 21/08/2018 WO2018099680 (PCT application designating India) Title: Citrate salts of a janus kinase (JAK) inhibitor Assignee: Sandoz AG Priority date: 29/11/2016 Publication date: 07/06/2018 Status: Deadline to enter into Indian national phase has expired on 29/06/2019 WO2018113801 (PCT application designating India) Title: Crystalline forms of 2-[1-ethylsulfonyl-3-[4-(7h-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile with phosphoric acid and a method of their preparation Assignee: Zentiva, K.S. Priority date: 21/12/2016 Publication date: 28/06/2018 Status: Deadline to enter into Indian national phase has expired on 21/07/2019 WO2018233437 (PCT application designating India) Title: Crystal form of Baricitinib and preparation method thereof Assignee: Crystal Pharmaceutical (Suzhou) Co., Ltd Priority date: 22/06/2017 Publication date: 27/12/2018 Status: Deadline to enter into Indian national phase has expired on 22/01/2020

2. Background information

About TFORD-COVID19
The Principal Scientific Advisor to the GoI, Dr K VijayRaghavan, has constituted a S&T Core Group on COVID19. Under the aegis of the S&T Core Group on COVID19, a Task Force has been constituted focused on Repurposing of Drugs for COVID19 (in short "TFORD-COVID19"). The Task Force is being coordinated by Dr V Premnath, Head, NCL Innovations at CSIR-NCL and Director, Venture Center and Dr Anurag Agarwal, Director, CSIR-IGIB. The Nerve Center for the Coordination is located be at Venture Center, Pune (located in the campus of CSIR-NCL).

Credits
Editor: Dr Priya Nagaraj; Contributors: Dr Priya Nagaraj, Dr Vidula Walimbe, Dr Smita Kale, Dr Kirtee Wani, Dr Tejas Shah, Dr Mugdha Lele, Mr Navnath Kadam, Dr Manisha Premnath, Dr Premnath V; Information also contributed by Dr Gopakumar Nair, GNAS and GnanLex.

About Advisory Group
The Nerve Center at TFORD-COVID19 has constituted an inter-disciplinary Advisory Group. This Advisory Group reviews the information compiled by the Nerve Center, provides suggestions on data, information sources, organization of data etc. while also providing inputs to refine the analysis and create a structured information base to support decision-making. The Advisory Group also provides expert input and opinions on certain selected points where experience-based inputs are needed. The members of the Advisory Group for each Discussion Paper are listed at https://nclinnovations.org/covid19/teams/ .

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