Document prepared by Nerve Center of TFORD, Venture Center, Pune
Task Force on Repurposing of Drugs (TFORD) for COVID19
S&T Core Group on COVID19 constituted by PSA to GoI

Molecule Brief: Ulinastatin

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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 Ulinastatin

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Ulinastatin
Brand Name	Miraclid (Japan), Ulinase and U-Tryp (India)
Category/ Type	Immuno-modulatory
Drug Bank ID/Link	DB12038 https://www.drugbank.ca/drugs/DB12038
Mode of Action	Ulinastatin is a protease inhibitor extracted from human urine. Ulinastatin inhibits activity of several proteases - trypsin, pancreatic elastase, polymorphonuclear leukocyte elastase. It plays an anti-inflammatory role by decreasing the phosphorylation of p38 mitogen-activated protein kinase (p38-MAPK) and nuclear factor-κB (NF-κB) activation. It is known to inhibit production of TNF-α, IL-1β, IL-8, IL-6 and increase levels of IL-10 and IL-2. It inhibits coagulation and fibrinolysis and promotes microperfusion. https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf https://journal-inflammation.biomedcentral.com/articles/10.1186/s12950-017-0154-7 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893897/
Therapeutic Target	Serine proteases- Trypsin, Pancreatic Elastase, Polymorphonuclear Leukocyte Elastase
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Severe sepsis, Acute Pancreatitis (India, China, Japan, South Korea)
Approved Dose	1 to 2 vials of 100,000 I.U. of Ulinastatin (Reconstituted in 100 ml of Dextrose 5% or 100 ml of 0.9% Normal Saline) by intravenous infusion over 1 hour each time, 1-3 times per day for 3 to 5 days.
Route of Administration	Intravenous infusion

Safety Profile of drug (dose range in which it has been tested to be safe in humans)	50,000 I.U. / 1,00,000 I.U. https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf
Adverse events/Side effects reported at the current approved dose	Rare cases of rash, itching and pain at the site of injection, Rare cases of allergy, Rare cases of elevation of SGOT and SGPT, Rare cases of nausea, vomiting and diarrhea. https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Reported Drug-Drug Interactions	No drug interactions have been reported or noted. https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf
Link to Datasheet	https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf
Current TRL level of the Drug	TRL-9; Approved Drug
Has the drug been repurposed for any other indication before?	Data not available
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Bharat Serums & Vaccines Ltd. (Altius), Lupin, Urihk Pharmaceuticals
International Manufacturer(s)	Miraclid: Mochida Pharmaceuticals, Japan Roan: Techpool, China Ulistin: han Lim Pharm, Seoul, Korea
Price of the Drug in India	Rs. 2,250 (100000 IU/5ml)
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	Evidence indicates that several COVID-19 patients meet the diagnostic criteria for sepsis and septic shock according to the Sepsis-3 International Consensus. Evidence also indicates 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. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30920-X.pdf 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 Evidence from Clinical studies: 1. Sepsis • Trial in India (CTRI/2009/091/000650) with 122 randomized subjects, where 114 completed the study (55 subjects in the Ulinastatin group and 59 subjects in the control group). Mean hospital stay in the Ulinastatin group - 13.59±6.83 days vs. 26.21±5.36 days in the Placebo group (p=0.001). Number of ventilator free days up to day 28 end-of-study - 19.44±10.61 days in the Ulinastatin group and 10.18±12.54 days in the Placebo

	group (p=0.019). Authors conclude - Thus, treatment with Ulinastatin effectively reduced mortality in patients with severe sepsis when used as an adjunctive therapy in addition to standard therapy and ICU care. The reduction in mortality was accompanied by a shorter stay in the hospital and a shorter duration of ventilator and vasopressor usage with no side-effects seen in the study population. https://www.bharatserums.com/product/critical/U-Tryp%20(Liquid)%20Common%20Pack%20Insert%20for%20Domestic.pdf https://link.springer.com/article/10.1007/s00134-014-3278-8 • A meta-analysis study in which 13 randomized controlled trials and two prospective studies using Ulnistatin, that included 1358 patients with sepsis, severe sepsis, or septic shock were evaluated. Ulinastatin significantly decreased the all-cause mortality {odds ratio (OR) = 0.48, 95% confidence interval (CI) [0.35, 0.66], $p < 0.00001$, $I^2 = 13\%$}, Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score {mean difference (MD) = -3.18, 95%CI [-4.01, -2.35], $p < 0.00001$, $I^2 = 33\%$, and reduced the incidence of multiple organ dysfunction syndrome (MODS) (OR = 0.3, 95% CI [0.18, 0.49], $p < 0.00001$, $I^2 = 0\%$). Ulinastatin also decreased the serum levels of IL-6 (MD = -53.00, 95% CI [-95.56, -10.05], p = 0.02), TNF-a MD = -53.05, 95%CI [-68.36, -37.73], $p < 0.00001$, and increased the serum levels of IL-10 (MD = 37.73, 95% CI [16.92, 58.54], p = 0.0004). Ulinastatin administration did not lead to any difference in the occurrence of adverse events. https://www.frontiersin.org/articles/10.3389/fphar.2019.01370/full 2. ARDS: • Meta-analysis study done with 33 RCTs involving 2344 patients. Study shows, compared to conventional therapy, Ulinastatin has a significant benefit for ARDS patients by reducing mortality (RR = 0.51, 95% CI:0.43~0.61) and ventilator associated pneumonia rate (RR = 0.50, 95% CI: 0.36~0.69), and shortening duration of mechanical ventilation (SMD = -1.29, 95% CI: -1.76~-0.83), length of intensive care unit stay (SMD = -1.38, 95% CI: -1.95~-0.80), and hospital stay (SMD = -1.70, 95% CI:-2.63~−0.77). Ulinastatin significantly increased the patients' oxygenation index (SMD = 2.04, 95% CI: 1.62~2.46) and decreased respiratory rate (SMD = -1.08, 95% CI: -1.29~-0.88) and serum inflammatory factors (tumor necrosis factor-α: SMD = -3.06, 95% CI:-4.34~-1.78; interleukin-1β: SMD = -3.49, 95% CI: -4.64~-2.34; interleukin-6: SMD = -2.39, 95% CI: -3.34~-1.45; interleukin-8: SMD = -2.43, 95% CI: -3.86~-1.00). https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-019-0968-6
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	2 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 ?

NCT04393311	Multi-Center, Randomized, Double-Blind, Placebo Controlled Study	150	Ulinastatin Dose: IV infusion (200,000/infusion) Stage: COVID-19 Hospitalized Patients	Primary: Time to recovery Secondary: COVID-19 disease severity scale score on Day 8, day 15, day 22, day 29, incidence of mortality at day 29, incidence of in-hospital mortality, number of days alive and not on mechanical ventilator or ECMO in the 28 days following first dose, number of patients with resolution of symptoms defined as score of 8 on the 8-point ordinal scale at Day 29, number of patients alive and free of respiratory failure defined as score of 4, 5, 6, 7, or 8 on the 8-point ordinal scale at day 29, duration of mechanical ventilation, for patients requiring mechanical ventilation, duration of ECMO, duration of noninvasive ventilation, duration of ICU stay, duration of hospital stay	No
ChiCTR2000030779	Randomized, open-label, controlled trial	50	Ulinastatin Dose: Data not available Stage: Patients with severe novel coronavirus pneumonia	Primary: Blood gas, SOFA score Secondary: Natural survival rate, time to clinical improvement, days in hospital, duration of non-invasive / invasive ventilation, proportion of severe to light, Infection related data, frequency of serious adverse events	No
CTRI/2020/06/025704	Prospective, Randomized, Open Label, Comparative, Clinical Study	120	Ulinastatin Other Arms- SOC (HCQ+ AZT) Dose: IV infusion in a dose of 200,000 units (diluted in 100 ml of 0.9% saline) 3 times a day (Every 8 hours) for 7 days Stage: Hospitalized	Primary: 1. Number of days of use of Mechanical Ventilation 2. Change from baseline in PF ratio (PaO2/FiO2)	No

Key Data from Clinical Trials	No published data from clinical trials. A study with observations from 1 HIV+ve patient infected with SARS-Cov-2 mentions the use of Ulinastatin in combination with other drugs – Arbidol, Methylprednisone, Moxifloxacin, Human Serum Albumin, Thymosin, Tocilizumab. https://www.ijidonline.com/article/S1201-9712(20)30276-9/pdf
TRL Level for COVID19	TRL>7 (Phase III/IV trails)
IP Status	No relevant patent applications identified.
Other Key References	None

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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