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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: Sarilumab

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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 Sarilumab

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Sarilumab
Brand Name	Kevzara
Category/ Type	Immunomodulator
Drug Bank ID/Link	DB11767 https://www.drugbank.ca/drugs/DB11767
Mode of Action	Interleukin-6 (IL-6) receptor antagonist. Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-and B-cells, lymphocytes, monocytes, and fibroblasts. https://www.drugbank.ca/drugs/DB11767
Therapeutic Target	Interleukin-6 receptor subunit α, High affinity immunoglobulin γ Fc receptor I, Low affinity immunoglobulin γ Fc region receptor II-a, Low affinity immunoglobulin γ Fc region receptor II-b, Low affinity immunoglobulin γ Fc region receptor III-A https://www.drugbank.ca/drugs/DB11767
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Rheumatoid arthritis https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf
Approved Dose	200 mg/ 1.14 mL & 150 mg/1.14 mL
Route of Administration	Subcutaneous injection
Safety Profile of drug (dose range in which it has been tested to be safe in	150-200mg https://www.ncbi.nlm.nih.gov/pubmed/31312844

humans)	
Adverse events/Side effects reported at the current approved dose	Most common adverse reactions (incidence at least 3%) are neutropenia, increased ALT, injection site erythema, upper respiratory infections and urinary tract infections. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf
Reported Drug-Drug Interactions	• Exercise caution when KEVZARA is co-administered with CYP substrates with a narrow therapeutic index (e.g. warfarin or theophylline), or with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the activity of the CYP3A4 substrate. • Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations. https://www.kevzarahcp.com/about-kevzara/safety *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	• https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf • https://www.ema.europa.eu/en/documents/product-information/kevzara-epar-product-information_en.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)	Data not available
International Manufacturer(s)	Sanofi
Price of the Drug in India	Data not available for price in India 700 $/ 150-200 mg -1.14 mL https://www.ncbi.nlm.nih.gov/books/NBK534399/table/pees.table1a/
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 indicates that CRS of varying degrees have occurred in severe patients with SARS and MERS. • Studies indicate that IL-6 is significantly up-regulated in patients with COVID-19, correlates with disease severity and viral load. The increase of baseline IL-6 level suggests that it may positively correlate with the severity of COVID-19 and could potentially be used as a disease biomarker. http://medrxiv.org/content/10.1101/2020.03.01.20029769v2.full.pdf https://www.medrxiv.org/content/10.1101/2020.02.29.20029520v1 https://www.medrxiv.org/content/10.1101/2020.02.25.20025643v1 • Tocilizumab (anti-IL-6 antibody) is undergoing clinical trials for COVID-19 and is also suggested for use in critically ill patients in a CRS situation.

Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	7 Ongoing trials
Trial Details	See the 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?
NCT04327388	Interventional (An Adaptive Phase 2/3, Randomized, Double-blind, Placebo Controlled Study)	300	Sarilumab SAR153191 Dose: IV. Data not available Stage: Hospitalized patients with COVID-19	Primary: Time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner [Time Frame: Baseline to Day 29] The percentage of patients reporting each severity rating on the 7-point ordinal scale [Time Frame: Baseline to Day 15] Secondary: The time to improvement in oxygenation [Time Frame: Baseline to Day 29] Mean change in 7-point ordinal scale from baseline to Day 15	No
NCT04324073	Interventional (Cohort Multiple Randomized Controlled Trials Open-label)	239	Sarilumab Dose: IV dose of 400 mg of sarilumab in a 1 hour-infusion at D1 Stage: Hospitalized with COVID-19 either diagnosed with moderate or severe pneumonia requiring no mechanical ventilation or critical pneumonia requiring mechanical ventilation	Primary: Survival without needs of ventilator utilization at day 14. [Time Frame: 14 days WHO progression scale <=5 at day 4 [Time Frame: 4 days] Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 WHO progression scale at day 4 Secondary: WHO progression scale [Time Frame: 7 and 14 days] Survival [Time Frame: 14, 28 and 90 days 28-day ventilator free-days [Time Frame: 28 days]	No
NCT04357808	Interventional (Randomized Open Pilot Study)	30	Sarilumab Dose: Single dose 2 x 200 mg subcutaneously Stage: Patients With Moderate-severe COVID-19 Infection	Primary: Mean change in clinical status assessment using the 7-point ordinal scale at day 7 after randomization [Time Frame: 7 days from enrolment] Duration of hospitalization (days) Death Secondary: Time to become afebrile	No

				Time to non-invasive mechanical ventilation (days) Time to invasive mechanical ventilation Time to independence from supplementary oxygen therapy (days) Mean change in clinical status assessment using the 7-point ordinal scale at day 14 after randomization.	
NCT04315298	Interventional (Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study)	400	Sarilumab Dose: Single intravenous dose (High and Low) Stage: Severe and Critically ill COVID-19 patients 1.	Primary: Percent change in C-reactive protein (CRP) levels [Time Frame: Day 4 Time to improvement (2 points) in clinical status assessment using the 7-point ordinal scale in patients with serum IL-6 levels greater than the upper limit of normal Secondary: Time to improvement (2 points) in clinical status assessment on the 7-point ordinal scale Time to resolution of fever for at least 48 hours without antipyretics by clinical severity Time to improvement in oxygenation for at least 48 hours	Yes (Updated on company website)
NCT04357860	Interventional, Open label	120	Sarilumab Dose: 200 MG/1.14ml Subcutaneous Solution Or 400 MG/2.28ml Subcutaneous Solution Stage: Hospitalized COVID-19 patients who have pulmonary infiltrates and are at high risk of unfavorable evolution	Primary: Ventilation requirements [Time Frame: At day 28 or when the subject is discharged (whichever occurs first) Secondary: Crude mortality [Time Frame: At day 28 or when the subject is discharged (whichever occurs first) Time to clinical improvement Time until improvement in oxygenation 4. Mean of serum cytokine levels	No
NCT04345289	Interventional (Adaptive, multi-arm)	1500	Sarilumab Other Arms - Convalescent anti-SARS-CoV-2 plasma, Baricitinib, Hydroxychloroquine Dose: 200 mg (1.14 mL) as a single dose Stage: Moderate to Severe Disease	Primary: All-cause mortality or need of invasive mechanical ventilation [Time Frame: 28 days] Secondary: Frequency of 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	No
NCT04322773	Interventional (Open-Label, Multicenter	200	Sarilumab Other Arms – Tocilizumab (IV),	Primary: Time to independence from supplementary oxygen therapy	No

	Sequential and Cluster Randomized Trial)		Toclizumab (SC) Dose: sarilumab 1 x 200 mg Stage: Patients With Severe SARS-CoV-2 Pneumonia	[Time Frame: days from enrolment up 28 days] Secondary: Number of deaths [Time Frame: 28 days from enrolment] Days out of hospital and alive [Time Frame: 28 days from enrolment] Ventilator free days alive and out of hospital [Time Frame: 28 days from enrolment] C-reactive protein (CRP) level [Time Frame: baseline]	
NCT04341870	Interventional, Randomized Control, Open-Label	27	Sarilumab Other Arms – Sarilumab + HCQ + Azithromycin Dose: Sarilumab - 400 mg in a 1 hour - I.V. infusion on D1 Stage: Adult Patients Hospitalized With Moderate to Severe COVID-19	Primary: Need for ventilation (including invasive and non invasive ventilation), intensive care or death [Time Frame: 14 days] Secondary: Early improvement: OMS progression scale <= 5 [Time Frame: 4 days] OMS progression scale [Time Frame: 4, 7 and 14 days] Survival [Time Frame: 14, 28 and 90 days] ICU-free days alive [Time Frame: 14, 28 and 90 days] Ventilation-free days alive [Time Frame: 14 and 28 days] Hospital-free days alive [Time Frame: 14, 28 and 90 days] Oxygen therapy-free days alive [Time Frame: 14 and 28 days] Time to negative viral excretion [Time Frame: 90 days] Immunophenotyping and multiplex cytokines [Time Frame: 8 days]	No
NCT04365764 (Observational)	Observational, Case Control	400	Sarilumab & other drugs Stage: Patients Hospitalized for Severe COVID-19 Pneumonia	Primary: Composite of death and mechanical ventilation [Time Frame: 14-days follow-up] Secondary: Death [Time Frame: 14-days follow-up] 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] World Health Organization score [Time Frame: 28-days follow-up]	No
NCT04366206 (Obeservational)	Observational, Cohort	143	Sarilumab & other drugs Stage: Patients Hospitalized for Covid-19	Primary: Composite of death and mechanical ventilation [Time Frame: At 14-days follow-up] Secondary: Need for mechanical ventilation [Time Frame: At 14-days follow-up] Death [Time Frame: At 14-days	No

				follow-up] Acute kidney injury [Time Frame: At 14-days follow-up] Acute respiratory distress syndrome [Time Frame: At 14-days follow-up] Cardiac arrhythmia and conduction disorder [Time Frame: At 14-days follow-up] Composite of death and mechanical ventilation [Time Frame: Up to 60 days after inclusion] 60-days mortality [Time Frame: Up to 60 days after inclusion] 60-days mechanical ventilation [Time Frame: Up to 60 days after inclusion]	
NCT04359901	Interventional, Randomized, Open-Label	120	Sarilumab Dose: Single dose of 200 mg subcutaneous Sarilumab Stage: Patients With Moderate COVID-19 Disease	Primary: Intubation or death [Time Frame: within 14 Days of enrollment] Secondary: Data not available	No

Key Data from Clinical Trials	No published data. On 27th April 2020, Sanofi & Regeneron released an update on their website from a Phase 2/3 trial NCT04315298 with Kevzara (Sarilumab). As per the update, in a preliminary analysis of the trial, Kevzara had no notable benefit on clinical outcomes when combining the "severe" and "critical" groups, versus placebo. However, there were negative trends for most outcomes in the "severe" group, while there were positive trends for all outcomes in the "critical" group. Kevzara rapidly lowered C-reactive protein, a key marker of inflammation, meeting the primary endpoint. Based on these observations, an Independent Data Monitoring Committee recommended continuing ongoing Phase 3 trial only in the more advanced "critical" group with Kevzara higher-dose versus placebo and discontinuing less advanced "severe" group. https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00
TRL Level for COVID19	TRL > 7; (Phase III Trials)
Other Key References	• https://pubchem.ncbi.nlm.nih.gov/substance/249565679 • https://doi.org/10.2217/imt-2017-0075 • http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19

IP Status

Status/ Molecule	Sarilumab
Pending applications	3738/KOLNP/2015 Title: Continuous multistep process for purifying antibodies Assignee: Sanofi Priority date: 06/05/2013 Publication date: 12/11/2014 Status: Reply to FER was submitted on 12/08/2019 201617011562 Title: Liquid protein formulations containing viscosity lowering agents Assignee: Eagle Biologics, Inc. Priority date: 11/09/2013

	Publication date: 12/08/2016 Status: Under examination (RFE filed on 07/09/2017) 201918052132 Title: Liquid protein formulations containing ionic liquids Assignee: Eagle Biologics, Inc Priority date: 11/09/2013 Publication date: 12/08/2016 Status: Under examination (RFE was filed on 16/12/2019) 201817020471 Title: Compositions comprising IL6R antibodies for the treatment of uveitis and macular edema and methods of using same Assignee: Sanofi Biotechnology, Regeneron Pharmaceuticals, Inc. Priority date: 03/11/2015 Publication date: 05/10/2018 Status: Under examination (RFE was filed on 30/09/2019)
Approved and Active applications	273688 Title: High Affinity Antibodies To Human Il-6 Receptor Assignee: Regeneron Pharmaceuticals, Inc. Priority date:02/06/2006 Grant date:23/06/2016 Expected expiry date: 01/06/2027
Expired or Lapsed application or examination request not filed	Not applicable

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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