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: rhACE2

Ref: TFORD/MB/030	**Date:** 18 June 2020
About this document: *This document summarizes information available on drug candidates for COVID19. One Molecule Brief document covers one candidate at a time.*	
Circulation restrictions: *Non-confidential. Open Access. If you use this information in any other document or communication, please credit is as "Molecule Brief: rhACE2, Task Force on Repurposing of Drugs for COVID19, India, June 2020".*	

1. Summary Information on Recombinant Human Angiotensin-Converting Enzyme 2 (rhACE2)

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Recombinant human angiotensin-converting enzyme 2 (rhACE2)
Brand Name	APN01 (Investigational)
Category/ Type	Anti-viral
Drug Bank ID/Link	Data not available
Mode of Action	• Normalize ACE2 levels - Recombinant human angiotensin converting enzyme 2 APN01 may normalize ACE2 levels, cleaving angiotensin II to create angiotensin-(1-7) and restoring the function of the renin-angiotensin system (RAS). ACE2, a homolog of ACE1, appears to function as a negative regulator of the RAS system by converting angiotensin II to angiotensin-(1-7), a peptide with actions that counteract the cardiovascular actions of angiotensin II. In addition, angiotensin-(1-7) may inhibit cyclooxygenase 2 (COX-2) and the production of proinflammatory prostaglandins and may activate the angiotensin-(1-7) G protein-coupled receptor Mas, resulting in diminished tumor cell proliferation. • https://www.cancer.gov/publications/dictionaries/cancer-drug/def/recombinant-human-angiotensin-converting-enzyme-2-apn01 • Block viral entry - APN01 has a unique dual mode of action. APN01 imitates the human enzyme ACE2, which is used by the virus to enter cells. The virus binds to soluble ACE2/APN01, instead of ACE2 on the cell surface, which means that the virus can no longer infect the cells. At the same time, APN01 reduces the harmful inflammatory reactions in the lungs and protects against acute lung injury (ALI/acute respiratory distress syndrome (ARDS). • https://link.springer.com/article/10.1007/s13181-020-00777-5
Therapeutic Target	AT1 receptor
Is action Host or Virus directed?	Virus
Currently	Not approved, Investigational

Approved for which Indication(s)	Being developed by Apeiron Biologics and GlaxoSmithKline for Acute lung injury; COVID-19 infections; Pulmonary arterial hypertension https://www.apeiron-biologics.com/science/#apn01
Approved Dose	Data not available
Route of Administration	Intravenous
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	0.1 mg/kg to 0.8 mg/kg https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5588692/
Adverse events/Side effects reported at the current approved dose	Data not available
Reported Drug-Drug Interactions	Data not available
Link to Datasheet	Data not available
Current TRL level of the Drug	TRL< 5; Phase 1/2
Has the drug been repurposed for any other indication before?	Data not available
Is the Drug being sold in India?	Data not available
Indian Manufacturer(s)	Data not available
International Manufacturer(s)	Apeiron Biologics
Price of the Drug in India	Data not available
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	SARS-CoV-2 uses the ACE2 receptor to enter human host cells. ACE2 has a broad expression pattern with strong expression noted in the gastrointestinal system, heart, and kidney and lungs (type 2 alveolar cells). https://www.nature.com/articles/s41586-020-2012-7 https://jamanetwork.com/journals/jama/fullarticle/2763803 Evidence from Pre-clinical studies: • Recombinant ACE2 has a protective effect in lung injury animal models https://www.nature.com/articles/nm1267 https://www.sciencedirect.com/science/article/pii/S1871402120301417?via%3Dihub#bib23 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7094998/ • Binding studies show that soluble ACE2 binds to the SARS S protein with an affinity of 1.7nM. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC356985/ Soluble ACE2 blocks SARS-CoV S-bearing psedotypes from infecting VeroE6 cells in-vitro. • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7111153/ Evidence from Clinical studies: • ARDS patients infused with rhACE2 showed a trend for decrease in IL-6 levels, with no impact on other clinical parameters. https://doi.org/10.1186/s13054-017-1823-x
Proposed use as Primary or	Primary

Adjuvant?	
Pre-Clinical Data available for COVID-19	An in-vitro study shows clinical grade hrsACE2 can reduce SARS-CoV-2 recovery from VeroE6 cells by a factor of 1,000–5,000. Infection of engineered human blood vessel organoids and human kidney organoids by SARS-CoV-2 can be inhibited by hrsACE2. Authors conclude that hrsACE2 could block SARS-CoV-2 infection at an early stage https://doi.org/10.1016/j.cell.2020.04.004
Status of Clinical Trials	1 Ongoing trial
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?**
NCT04335136	Interventional, Randomized	200	RhACE2 APN01 Dose: IV twice daily – dose not mentioned Stage: Data not available	Primary: Cause of death or invasive mechanical ventilation [Time Frame: 28 days] Secondary: LDH level [Time Frame: Day 5] Mortality [Time Frame: 28 days] VFD [Time Frame: 28 days] Time to death [Time Frame: 28 days]	No

Key Data from Clinical Trials	Data not available
TRL Level for COVID19	TRL >7; (Phase III/IV Trials)
IP Status	
`Other Key References	• https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4229671/ • https://pipelinereview.com/index.php/2020022673884/Proteins-and-Peptides/APEIRONs-respiratory-drug-product-to-start-pilot-clinical-trial-to-treat-coronavirus-disease-COVID-19-in-China.html

IP Status

Status/ Molecule	Recombinant ACE
Pending applications	2149/KOLNP/2015 Title: Modified ACE2 polypeptides Assignee: Apeiron Biologics AG Priority date: 14/01/2013 Publication date: 29/01/2016 Status: FER has been issued on September 28, 2019
Approved and Active applications	288085 Title: A method of producing a coronavirus Assignee: Janssen Vaccines & Prevention B.V. Filing date:21/02/2008 Grant date:05/10/2017 Expected expiry date: 21/07/2026 286666 Title: ACE2 polypeptide Assignee: Apeiron Biologics AG. Priority date: 12/06/2007 Grant date: 28/08/2017 Expected expiry date: 12/06/2028
Expired or Lapsed application or examination request not filed	7271/DELNP/2006 Title: Nucleic acids, polypeptides, methods of expression, and

	immunogenic compositions associated with SARS corona virus spike protein Assignee: Institut Pasteur Priority date: 04/06/2004 Publication date: 27/04/2007 Status: Withdrawn u/S 11B(4) 4793/KOLNP/2010 Title: ACE2 as a target gene for the molecular identification of yeast and fungal species Assignee: National University Of Ireland, Galway Priority date: 13/06/2008 Publication date: 18/02/2011 Status: Application is refused under Section 15

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/ .

Disclaimer
This Molecule Brief is a compilation of information available openly with no opinions or judgments or recommendations. This document is meant to compile high-quality information that can form the basis for informed discussion and decision-making. It is not meant to reflect the Government's position or that of any specific organization or individual. This information should also not be interpreted as guidance for clinical case management.