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: Molnupiravir

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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 Molnupiravir

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Molnupiravir/ MK 4482/EIDD2801
Brand Name/Company	Molnupiravir/Merck and Co
Category/ Type	Anti-viral
Drug Bank ID/Link	Data not available
Mode of Action	It is a prodrug of the synthetic nucleoside derivative N4-hydroxycytidine, and exerts its antiviral action through introduction of copying errors during viral RNA replication. https://newdrugapprovals.org/2020/03/28/eidd-2801/
Currently Approved for which Indication(s)	Not approved. Developed as an experimental drug for Influenza https://newdrugapprovals.org/2020/03/28/eidd-2801/ https://www.guidetomalariapharmacology.org/GRAC/LigandDisplayForward?tab=refs&ligandId=10737
Approved Dose	Data not available
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Data not available
Adverse events/Side effects reported at the current approved dose	Data not available
Reported Drug-Drug Interactions	Data not available
Link to Datasheet	https://newdrugapprovals.org/2020/03/28/eidd-2801/ https://www.guidetomalariapharmacology.org/GRAC/LigandDisplayForward?tab=refs&ligandId=10737
Current TRL level of the Drug	< TRL 6
Has the drug been repurposed for any	No

other indication before?	
Is the Drug being sold in India?	No
Indian Manufacturer(s)	None
International Manufacturer(s)	Merck https://newdrugapprovals.org/2020/03/28/eidd-2801/
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Approval Status	Not Approved
Rationale for Repurposing for COVID-19/MoA?	1. Pre-clinical data showing Molnupiravir has broad anti-influenza activity in in-vitro and in-vivo (mice) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848974/ 2. Pre-clinical data showing Molnupiravir has anti- SARS, anti-SARS-CoV-2 and anti-MERS activity in in-vitro and in-vivo https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164393/
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID19	• NHC (Molnupiravir) potently inhibits SARS-CoV-2 replication in Vero cells with an IC50 of 0.3 μM and CC50 of >10 μM. Also causes dose-dependent reduction in SARS-CoV-2 titers with an IC50 of 0.08 μM in Calu-3 cells • NHC inhibits SARS-CoV-2 replication in human airway epithelial cells (> 3 log at 10 μM, average IC50 = 0.14 μM) • Prophylactic oral administration of drug was robustly antiviral and able to prevent SARS-CoV-2 replication and disease in mice • Therapeutic administration was potently antiviral against SARS-CoV-2 in mice but the degree of clinical benefit was dependent on the time of initiation post-infection. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164393/
Status of Clinical Trials	Completed (1 trial), Ongoing (4 trials)
Trial Details	See the table below

Trial ID/Link	Type of Trial	No. of patients	Drug Combination/Dose/ Stage of Disease	Primary Measures	Has data from the trial been published?
NCT04392219 Sponsor: Ridgeback Biotherapeutics Location: Data not available	Randomized, double-blind, placebo-controlled	130	PO/BID/5 days (dose not specified) Stage - Healthy volunteers	• Safety, Tolerability and PK	Yes (This is a safety trial)
NCT04575584 Sponsor: Merck Sharp & Dohme Location: Data not available	Phase 2/3 randomized, double blinded	1300	Molnupiravir – 200/400,800mg/PO/BID/ 5 days Stage - COVID 19+ve; Hospitalized	• Time-to-sustained recovery • Percentage of participants with an AE • Percentage of participants who discontinued study intervention due to an AE	No
NCT04575597 Sponsor: Merck Sharp & Dohme Location: Data not available	Phase 2/3 randomized, double blinded	1450	Molnupiravir – 200/400,800mg/PO/BID/ 5 days Stage - COVID 19+ve; Hospitalized	• Percentage of participants who are hospitalized and/or die • Percentage of participants with an AE • Percentage of participants who discontinued study	No

				intervention due to an AE	
NCT04405739 Sponsor: Ridgeback Biotherapeutics Location: Data not available	Phase 2a Randomized, Double blinded	89	Dose – PO/BID/5 days (dose not specified) Stage - COVID-19 +ve;	• Number of Participants that achieve Virologic Clearance • Number of Participants With any Serious Adverse Events • Number of Participants With any Adverse Events(AEs)	No
NCT04405570 Sponsor: Ridgeback Biotherapeutics Location: Data not available	Phase IIa, double-blind, placebo-controlled, randomized trial	108	Dose – PO/BID/5 days (dose not specified) Stage - COVID-19 +ve;	• Virologic Efficacy • Number of Participants with any Adverse Events (AEs) • Number of Participants With any Adverse Events (AEs), Grade 2 or higher	No

TRL Level for COVID19	>TRL 7 (Phase II/III Trials)
Clinical Trial Data	NCT04392219 (Pre-print), Phase 1, Safety Trial in healthy volunteers Results: Molnupiravir was well tolerated. Fewer than half of subjects reported an adverse event, the incidence of adverse events was higher following administration of placebo, and 93.3% of adverse events were mild. One discontinued early due to rash. There were no serious adverse events and there were no clinically significant findings in clinical laboratory, vital signs, or electrocardiography. Plasma exposures exceeded expected efficacious doses based on scaling from animal models. https://www.medrxiv.org/content/10.1101/2020.12.10.20235747v1
IP Status	See table below
Other Key References	None

Status/ Molecule	Molnupiravir
Pending applications	IN202017019418 Title: N4-hydroxycytidine and derivatives and anti-viral uses related thereto Assignee: Emory University Priority date:07/12/2017 Publication date: 14/08/2020 Status: FER issued IN201617001260 Title: Substituted nucleosides, nucleotides and analogs thereof Assignee: Alios Biopharma, Inc. Priority date:26/06/2013 Publication date: 22/07/2016 Status of patent: FER issued 4458/DELNP/2015 Title: Pyrimidine nucleotides and their monophosphate prodrugs for treatment of viral infections and cancer Assignee: Cocrystal Pharma Inc., Emory University Priority date:29/10/2012 Publication date: 22/11/2015 Status of patent: FER issued WO2017165489 Title: Antiviral agents for treating Zika and Dengue virus infections Assignee: Emory University Filing date:22/03/2017 Publication date:28/09/2017 Status: Not entered into national phase of Indian jurisdiction

	WO2019173602 Title: 4'-halogen containing nucleotide and nucleoside therapeutic compositions and uses related thereto Assignee: Emory University Filing date:07/03/2019 Publication date:12/09/2019 Status: Not entered into national phase of Indian jurisdiction
Approved and Active applications	NA
Expired or Lapsed application	WO2002032920 Title: Modified nucleosides for treatment of viral infections and abnormal cellular proliferation Assignee: Pharmasset Limited Filing date: 18/10/2001 Publication date: 25/04/2002 Status of patent: India has been designated. Not entered into national phase of Indian jurisdiction WO2006133353 Title: Methods of facilitating neural cell survival using non-peptide and peptide BDNF neurotrophin mimetics Assignee: The University Of North Carolina At Chapel Hill Filing date: 08/06/2006 Publication date: 14/12/2006 Status of patent: India has been designated. Not entered into national phase of Indian jurisdiction

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. Arati Ranade, Dr Vidula Walimbe, Dr Smita Kale, Dr KirteeWani, Dr Tejas Shah, Dr MugdhaLele, 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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