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: IFN-β

Ref: TFORD/MB/014	**Date:** 12 April 2020
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 IFN-β

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Interferon-beta (IFN-β)
Brand Name	Avonex / Rebif (IFNb-1a), Betaferon (IFN b1b).
Category/ Type	Adjuvants, Antivirals for systemic use - Antiviral agent, Antineoplastic agent, Immunostimulant
Drug Bank ID/Link	DBCAT000160 https://www.drugbank.ca/categories/DBCAT000160
Mode of Action	Interferon beta binds to type I interferon receptors (IFNAR1 and IFNAR2c) which, upon dimerization, activate two Jak (Janus kinase) tyrosine kinases (Jak1 and Tyk2). These transphosphorylate themselves and phosphorylate the receptors. The phosphorylated INFAR receptors then bind to Stat1 and Stat2 (signal transducers and activators of transcription) which dimerize and activate multiple (~100) immunomodulatory and antiviral proteins. Interferon beta binds more stably to type I interferon receptors than interferon alpha.IFN-β-1b exerts its therapeutic effects in part by targeting B cells' functions.
Therapeutic Target	Interferon alpha/beta Receptor-1 Interferon alpha/beta Receptor-2
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	To slow the progression of relapsing multiple sclerosis and to reduce the frequency of clinical symptoms.
Approved Dose	Avonex • 30 mcg IM qWk • May be titrated using the AVOSTARTGRIP titration kit with prefilled IM syringes starting with 7.5 mcg IM for first week, to reduce flu-like symptoms; increase by 7.5 mcg/week for next 3 weeks until recommended dose of 30 mcg/week Betaseron • 0.3 mg lyophilized powder in a single-use vial for reconstitution. • Initial dose: 0.0625 mg subcutaneously every other day, and increased (in 25% increments) every 2 weeks, over a 6

<table>
<tr><td></td><td>week period, to maintenance dose.
• Maintenance dose: 0.25 mg subcutaneously every other day
Schedule for Dose Titration
<table><tr><th></th><th>BETASERON Dose*</th><th>Percentage of Recommended dose</th><th>Volume</th></tr><tr><td>Weeks 1-2</td><td>0.0625 mg</td><td>25%</td><td>0.25 mL</td></tr><tr><td>Weeks 3-4</td><td>0.125 mg</td><td>50%</td><td>0.5 mL</td></tr><tr><td>Weeks 5-6</td><td>0.1875 mg</td><td>75%</td><td>0.75 mL</td></tr><tr><td>Week 7 and thereafter</td><td>0.25 mg</td><td>100%</td><td>1 mL</td></tr></table></td></tr>
<tr><td>Route of Administration</td><td>Avonex: Rotate IM injection sites between upper thighs and arms
Betaseron: Subcutaneous Injection.</td></tr>
<tr><td>Safety Profile of drug (dose range in which it has been tested to be safe in humans)</td><td>Avonex: Subjects received liquid HSA-tiee AvonexQ at 30 pg administered as one IM injection once per week (QW). The duration of subject participation was to be 24 months, where each month was defined as 4 weeks.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/103628s5021clinicalreview.pdf
https://clinicaltrials.gov/ct2/show/NCT00828204
Betaseron: Interferon Beta-1b (Betaferon® / Betaseron®) 250 µg given subcutaneously every other day for at least 36 months.
https://clinicaltrials.gov/ct2/show/study/NCT00185211
https://clinicaltrials.gov/ct2/show/NCT00317941</td></tr>
<tr><td>Adverse events/Side effects reported at the current approved dose</td><td>Avonex: Headache, Sweating, Fever, Chills, Flu-like symptoms
Betaseron: At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia), which is mainly due to the pharmacological effects of the medicinal product, and injection site reactions. Injection site reactions occurred frequently after administration of Betaferon. Redness, swelling, discolouration, inflammation, pain, hypersensitivity, necrosis and non-specific reactions were significantly associated with 250 microgram (8.0 million IU) Betaferon treatment.
https://www.medicines.org.uk/emc/product/1121/smpc#</td></tr>
<tr><td>Reported Drug-Drug Interactions</td><td>Avonex:
• 12 major drug interactions
• 272 moderate drug interactions
• 1 minor drug interaction
https://www.drugs.com/drug-interactions/interferon-beta-1a,avonex-pen.html
Betaseron:
• 12 major drug interactions
• 272 moderate drug interactions
• 1 minor drug interaction
https://www.drugs.com/drug-interactions/interferon-beta-1b,betaseron.html
(Clinicians need to note relevant drug-drug interactions depending on nature of use)</td></tr>
<tr><td>Link to Datasheet</td><td>Avonex:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103628s5189lbl.pdf
Rebif:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/ifnbser050203LB.pdf</td></tr>
</table>

	Betaseron: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/ifnbchi031403lb.pdf
Current TRL level of the Drug	TRL9; Approved Drug
Has the drug been repurposed for any other indication before?	No. However, clinical studies have been done with IFN β1a for Ebola, Alzhimers disease, CIDP, Glioma, human T cell leukaemia virus 1 associated myelopathy/tropical spastic paraparesis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321269/ https://pubmed.ncbi.nlm.nih.gov/31100209/
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Merck, Bayer
International Manufacturer(s)	Avonex: Biogen Idec Rebif: EMD Serono, Merck KGaA Betaferon: Bayer Healthcare API Manufacturer: Biotechnica Pharma Global, KinBio https://www.pharmacompass.com/active-pharmaceutical-ingredients/interferon-beta-1a/apis/suppliers
Price of the Drug in India	Avonex: Rs. 10000 INR/regimen Rebif: Rs. 6030 INR/regimen Betaferon: Rs. 6957 INR/regimen
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	1. Interferon beta is known to modulate the body's antiviral responses. There is evidence that deficiency in IFN-beta production by the lung could explain the enhanced susceptibility of these at-risk patient groups to developing severe lower respiratory tract (lung) disease during respiratory viral infections. Furthermore, viruses, including coronaviruses such as SARS-CoV-2 and MERS-CoV, have evolved mechanisms which suppress endogenous IFN-beta production, thereby helping the virus evade the innate immune system. The addition of exogenous IFN-beta before or during viral infection of lung cells either prevents or greatly diminishes cell damage and viral replication, respectively. • https://www.technologynetworks.com/drug-discovery/news/phase-ii-trial-of-sng001-in-covid-19-patients-set-to-start-332223 • https://www.europeanpharmaceuticalreview.com/news/115657/researchers-to-trial-sng001-therapeutic-in-covid-19-patients/ 2. In-vitro studies show that IFN-β1a potently inhibits SARS virus replication. • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322919/pdf/03-0482.pdf • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323075/ • https://pubmed.ncbi.nlm.nih.gov/15200845/ 3. Evidence from clinical studies: In a 147 patient Randomized Trial, efficacy and safety of inhaled IFN-β with placebo was determined. Drug was administered to people with asthma after onset of cold symptoms to prevent or attenuate asthma symptoms caused by respiratory viruses. Results: IFN-β treatment had no significant effect on this primary endpoint, although it enhanced morning peak expiratory flow recovery (P = 0.033), reduced the need for additional treatment,

	and boosted innate immunity as assessed by blood and sputum biomarkers.(NCT 01126177). https://www.europeanpharmaceuticalreview.com/news/115657/researchers-to-trial-sng001-therapeutic-in-covid-19-patients/
Proposed use as Primary or Adjuvant?	Adjuvant https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182113/
Pre-Clinical Data available for COVID-19	No published data for effect of IFN-β1a on SARS-CoV-2
Status of Clinical Trials	3 Ongoing 1 of the 4 drugs which are being tested in a WHO global multi-centric trial SOLIDARITY https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments https://science.sciencemag.org/content/367/6485/1412
Trial Details	See details below

Trial ID/Link	Type of Trial	Number of patients	Combination/Dose/Stage of Disease	Primary and Secondary Measures	Has data from the trial been published (Yes/No)
EudraCT Number: 2020-001023-14	Randomised double-blind placebo-controlled trial	400	No combination Dose - 6 million IU (nebulization) Stage - Not specified	Primary: 1. Change in condition measured using the Ordinal Scale for Clinical Improvement during the dosing period. 2. The Ordinal Scale for Clinical Improvement is a World Health Organisation recommended scale for use in COVID-19 trials. Secondary: a.Progression to pneumonia as diagnosed by chest x-ray, if no pneumonia is present at time of enrolment b. Evolution of pneumonia, as diagnosed by chest x-ray, if pneumonia is present at time of enrolment c. Time to clinical resolution ≥4 of 5 vital signs (temperature, O2 sats, Resp rate, heart rate, systolic blood pressure). d. LRT Symptoms (Changes in daily symptoms breathlessness, cough and sputum scale (BCSS) symptoms score during the study period (including disaggregated scores)) e. Virus clearance/load f. Safety and tolerability g. Blood and sputum biomarkers if samples are available	NO
NCT04276688	Open-label randomised controlled trial	127	Lopinavir/ Ritonavir, Ribavirin and Interferon Beta 1b Dose - 0.25mg subcutaneous injection	Primary: Time to negative NPS [Time Frame: Up to 1 month] Secondary: 1. Time to negative saliva [Time Frame: Up to 1 month] 2.Time to clinical improvement [Time Frame: Up to 1 month] 3.Hospitalisation Time Frame:	NO

			alternate day for 3 days Stage: Not specified	Up to 1 month] 4. Mortality [Time Frame: Up to 1 month] 5.Immune reaction [Time Frame: up to 1 month] 6.Adverse events [Time Frame: up to 1 month] 7.Time to negative all clinical specimens [Time Frame: up to 1 month]	
NCT04315948	Randomized, open clinical trial.	3100 (estimate)	Lopinavir/ritonavir plus Interferon ß-1a Dose - 44 µg for a total of 3 doses in 6 days (day 1, day 3, day 6). Stage - Not specified	Primary: Percentage of subjects reporting each severity rating on a 7-point ordinal scale [Time Frame: Day 1] Secondary: 1.Percentage of subjects reporting each severity rating on a 7-point on an ordinal scale [Time Frame: Days 3, 5, 8, 11, 15 and 29] 2. Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. [Time Frame: Days 3, 5, 8, 11, 15 and 29] 3. Number of oxygenation free days in the first 28 days [Time Frame: 29 days] 4. Incidence of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial. [Time Frame: 29 days] 5. Duration of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial. [Time Frame: 29 days] 6. Ventilator free days in the first 28 days [Time Frame: 29 days] 7. Incidence of new mechanical ventilation use during the trial. [Time Frame: 29 days] 8. Hospitalization [Time Frame: 29 days] 9. Rate of mortality 10. Cumulative incidence of serious adverse events (SAEs) [Time Frame: 29 days] 11. Cumulative incidence of Grade 3 and 4 adverse events (AEs) [Time Frame: 29 days] 12. Blood biochemistry and Haematological parameters.	NO

Key Data from Clinical Trials	No published data available. A UK based research group announced a study where a novel inhalable IFN-β formulation (SNG001) will be tested on 100 COVID-19 patients to see if it can prevent COVID-19 worsening in the most at-risk patients. Patients will receive the formulation for 14 days. SNG001, when tested previously in Phase II clinical trials in asthmatic patients has shown that it is well tolerated, enhances the lungs' antiviral defences and improves lung function during cold or flu infection. https://www.europeanpharmaceuticalreview.com/news/115657/researchers-to-trial-sng001-therapeutic-in-covid-19-patients/
TRL Level for COVID19	TRL – 6/7 (Phase I/II)

IP Status	Pending applications	22/MUMNP/2011 Title: Interferon Epsilon (Ifne1) As A Marker For Targeted Cancer Therapy Assignee: Piramal Lefe Sciences Limited (Assigned To Piramal Healthcare Ltd) Priority date: 10/06/2008 Publication date: 10/01/2014 1965/KOLNP/2007 Title: Deamidated Interferon-Beta Assignee: Chiron Corporation Priority date: 10/11/2004 (US) Publication date: 10/08/2007 Status: Refused for grant of patent under section 15 of the Patent act 111/MUM/2007 Title: Interferon Conjugates Assignee: Intas Biopharmaceuticals Limited Priority date: 19/01/2007 Publication date: 28/11/2008 Status: Refused to grant vide controller's decision 8915/DELNP/2013 Title: Method For Reducing Flu Like Symptoms Associated With Intramuscular Administration Of Interferon Using A Fast Titration Escalating Dosing Regimen Assignee: Biogen MA Inc. Priority date: 15/03/2011 Publication date: 19/12/2014 Status: Reply to FER submitted: 27/02/2019 5566/DELNP/2005 Title: A process comprising decreasing the ganglioside inhibitory activity in a composition Assignee: Schering Aktiengesellschaft Priority date: 11/07/2003 Publication date: 02/10/2009 Status: Refused 7041/DELNP/2006 Title: Intranasal Formulations Of Interferon Beta Free Of Stabilizers That Are Proteins Or Polypeptides Assignee: Nastech Pharmaceutical Company Inc. Priority Date: 07/06/2004 Publication date: 13/07/2007 Status: Abandoned u/s 21 of patent act 6465/DELNP/2006 Title: Hydrogel Interferon Formulations Assignee: Ares Trading S.A. Priority Date: 17/05/2004 Publication date: 31/08/2007 Status: Abandoned u/s 21 of patent act 311/MUMNP/2006 Title: Uses Of Interferons With Altered Spatial Structure Assignee: Huiyangtech (USA) Inc Priority Date: 28/08/2003 Publication date: 22/06/2007 Status: Refused u/s 15 of Patent act 2533/MUM/2007 Title: Stabilized Pharmaceutical Compositions Of Interferon Assignee: Wockhardt Ltd Filing Date: 24/12/2007 Publication date: 03/07/2009 538/DELNP/2009 Title: Recombinant Interferon-Beta With Enhanced Biological Activity Assignee: Novartis AG Priority Date: 08/08/2006 Publication date: 20/08/2010

Approved and Active applications	IN330155 Title: Modified Interferon Beta Polypeptides And Their UsES Assignee: Ambrx, Inc Priority date: 02/05/2007 Grant date: 24/01/2020 Expected expiry: 30/04/2028 IN253153 Title: Pharmaceutical Compositions Of Interferon Conjugates Assignee: Intas Biopharmaceuticals Limited Priority date: 01/12/2008 Grant date: 28/06/2012 Expected expiry: 01/12/2028 IN272565 Title: Process For The Preparation Of Glycosylated Interferon Beta Assignee: Ares Trading S.A Priority date: 26/08/2005 Grant date: 08/04/2016 Expected expiry: 26/08/2025 IN261198 Title: Method for Delivering Interferon ß Assignee: Biogen Idec Ma Inc Priority date: 12/01/2005 Grant date: 11/06/2014 Expected expiry: 11/01/2026 IN269295 Title: Human Interferon -Beta Mutein Assignee: Reference Biolabs Co Ltd Priority date: 02/11/2004 Grant date: 14/10/2015 Expected expiry: 02/11/2025 IN234633 Title: Interferon-β Complex Assignee: Toray Industries, Inc. & Tadatsugu Taniguchi Priority date: 25/08/2003 Grant date: 10/06/2009 Expected expiry: 24/08/2024 IN253210

	Expired or Lapsed application or status unknown IN226725 (No pdf available on WIPO site) Title: Polymer Conjugates Of Interferon-Beta With Enhanced Biological Potency Assignee: Mountain View Pharmaceuticals, Inc. Priority date: 20/06/2003 Grant date: 24/12/2008 Expected expiry: 23/12/2023 Legal Status :Ceased Date Of Cessation :24/12/2018 IN245460 Title: An Asialo-Interferon Pharmaceutical Composition Assignee: The General Hospital Corporation & The Gi Company, Inc Priority date: 05/09/2002 Grant date: 20/01/2011 Expected expiry: 03/09/2023 Legal Status :Ceased Date Of Cessation :20/04/2011 IN250476 (No pdf available on WIPO site) Title: Process For The Production Of Interferon Beta Assignee Cadila Healthcare Limited Priority date: 20/12/2004 Grant date: 05/01/2012 Expected expiry: 20/12/2024 Legal Status :Ceased Date Of Cessation :20/12/2016
Other Key References	1. WHO: Table of Therapeutics 2. https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A5236 3. https://www.smartpatients.com/trials/NCT03570359

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.

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