FACT SHEET: Reelabs, India

1) **Project** Randomized placebo-controlled Phase I and II study of the treatment of patients with COVID-19 pneumonia using intravenous administration of mixture of umbilical cord and placenta mesenchymal stem cells

2) Institutes involved

Designated government institutes and ReeLabs Private Limited (stem cell provider).

3) Brief Description of ReeLabs, India.

ReeLabs, Mumbai, India (reelabs.com) is considered the largest, state-of-the-art stem cell enterprise of Asia covering over 5000 sq meter of laboratory space.

They have a distinguished list of doctors, researchers, philanthropists and entrepreneurs diligently involved in clinically relevant R&D in regenerative medicine and bio-banking along with production of niche food supplements and cytokine enhanced hair and skin rejuvenation products. With the advent of the COVID-19 pandemic the company has also recently procured FDA license for hand sanitizers and started mass production and distribution of the same.

Their promoter directors hold key influencer positions in numerous prestigious institutions of Regenerative Medicine and Bio-banking in India and overseas. They have also won numerous awards and accolades from various prestigious organizations, including the country's Honorable Health Ministry.

The company boosts of medical publications (over 250), peer reviews in international publications (over 500), authoring chapters in significant reference textbooks for postgraduate students of medicine (2), range of proprietary technologies (15), international patents (10), and key technology transfer services to listed enterprises overseas (2).

Their research team is geared to execute key FDA approved clinical trials in India using host of patent protected products.

Dr. Abhijit Bopardikar MD, Director ReeLabs says, "The sheer magnitude of the COVID-19 pandemic has sent shock waves throughout the world due to which ReeLabs has immediately recalibrated its priorities. We are now looking to fast-track a clinical trial in sync with the Indian health authorities using our patented product (mixture of cultured placental and Cord derived mesenchymal cells) against the COVID-19 virus. The world has started serious activity to overcome the devastation and India cannot be left behind. Once all permissions come through and the trial initiated, it shall be major milestone for the Asian subcontinent."

4) Urgent and unmet medical need

India is on the verge of shifting from phase 2 to phase 3 of COVID-19 pandemic. Should this happen there will be an exponential increase in the number of patients. Statistics show that about 8% of patients of COVID-19 develop respiratory distress and may require artificial ventilation. At present in our country, even major cities and major hospitals do not have large number of ventilators and intensive care beds that could possibly be needed to take this burden. It is here, the use of MSCs becomes important, as the paper from China clearly shows that MSCs prevent moderate and severe patients from progressing to critically severe stage.

Since there is no other proven medicine or vaccine available the use of MSCs will fill a major unmet medical need and significantly reduce the Death rate.

5) Scientific rationale for the treatment

(a) The reason why moderate to severe patients deteriorate clinically to become severely critical is due to the 'Cytokine storm'. MSCs by the virtue of their paracrine mechanisms reduce the harmful effect of the Cytokine storm by (i) reducing the level of the harmful pro-inflammatory cytokine TNF-alpha and (ii) increasing the level of the protective anti-inflammatory cytokines IL-10,

(b) Vascular endothelial growth factor and chemokine IP-10

(c) MSCs improve the pulmonary microenvironment and lung function by differentiating into different types of alveolar epithelial cells

(d) MSCs have immunomodulatory effect

(e) MSCs improve the microvasculature of the lung tissue

(f) It is well documented that the action of the COVID-19 virus is through ACE 2 receptors. MSCs are ACE 2 receptor negative and therefore cannot be infected by the virus.

(g) The MSCs have been used in H5N1 (Annexure 7) and H7N9 (Annexure 8) infection earlier which are similar to COVID-19 infection and efficacy results have been published.

6) Clinical Aspects of the project

a) The cells will be injected intravenously via an injection so there is no procedure involved.

b) In Phase I of the project out of 20 patients in the moderate and severe category 10 patients will get the intravenous MSCs and 10 patients will get a placebo.

All 20 patients will continue to get the standard treatments currently been given to them

c) In Phase I the inclusions criteria will be moderate and severe patients and exclusion criteria will be mild and critical patients.

d) Depending on the results of Phase I another 15/15 patients will get IV MSCs or Placebo.

e) Special informed consent will be taken from the patients.

7) Cells that will be used as an intervention

Cells used for this study are a mixture of MSCs derived from human umbilical cord blood and placenta. They will be obtained from ReeLabs, Mumbai which is a cGMP facility with a cord blood banking license and Form 29. 1 million cells/kg body weight will be injected intravenously over forty minutes with a speed of ~40 drops per minute.

8) Safety of Intravenous MSC

There are over 990 papers on safety and efficacy of MSCs in various clinical conditions and there are 4 published papers that also show safety and benefit in treating COVID – 19 and other respiratory conditions caused by Viruses like H7N9 and H5N1. Since the cells will be given intravenously there is no risk of any interventional procedure. The safety of this intervention is therefore assured.

8) Ethical aspects of the treatment

(a) Ethical approval will be taken from the IECs of all applicable institutes before initiation of the project.

(b) From the Ethical point of view, this is in complete alignment with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects Which states in paragraph 37 that

"In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."

9) Regulatory jurisdiction

I) Central regulatory authority (CDSCO)

a) Since the cells that we are using, umbilical cord and placental MSCs are more than minimally manipulated cells, which fall under the category of 'Stem Cell Derived Products'; therefore, they come under the jurisdiction of CDSCO.

b) In order no. F. No. DCGI/Misc./2014(132) of CDSCO, dated 5th September 2014 (attached as Annexure 9), it has been stated that new clinical trials should be evaluated in regard to 3 parameters

(i) Assessment of risk versus benefit to the patients

(ii) Innovation vis-à-vis existing therapeutic option

(iii) Unmet medical need in the country

Our proposal meets with all the three criteria as follows

(i) Assessment of risk versus benefit to the patients: There are over 990 papers on safety and efficacy of MSCs in various clinical conditions and there are 4 published papers that also show safety and benefit in treating COVID – 19 and other respiratory conditions caused by Viruses like H7N9 and H5N1. Also, since the cells are given intravenously there is almost no risk in injecting MSCs. The benefits described in the paper by Leng et. al. 2020 are significant and life-saving, and therefore this criteria is met.

(ii) Innovation vis-à-vis existing therapeutic option: Presently there are no existing therapeutic options for COVID-19 therefore this will be a significant medical innovation. Therefore, this criteria is met.

(iii)Unmet medical need in the country: In view of the increasing incidence of COVID-19 infection, the possibility of our shifting from phase 2 to phase 3, the likelihood for the need for significant ventilatory and intensive care which is presently not available; there is a definitive and significant unmet medical need in the country. Therefore, this criterion is met.

II) Local Authority

Permission will be required from local Bombay Municipal Corporation (BMC).

10) Cost implications:

The cells and the entire treatment will be done free of cost so there will be no financial implications on either the patients or the MCGM.

ReeLabs, India has offered to supply free stem cells to all patients of COVID-19 infection in the country even after completion of the study.

Summary:

In view of

(a) The serious situation that our country is facing in connection with the COVID-19 infection

(b) The major unmet medical need due to the lack of other treatment options

(c) The established safety of the use of MSCs

(d) The published results showing the efficacy of MSCs in COVID-19 infections in the paper published by Leng et. al. 2020

(e) The unique coming together of Municipal Hospitals and private entities

(f) The availability of a team of experienced professionals from the fields of regenerative medicine, stem cell manufacture, infectious diseases, intensive medical care, pulmonary care and basic sciences to conduct the treatment and study

(g) The offer of the stem cell manufacturer, ReeLabs, India to make these MSCs available Free of Cost to all patients in the country with COVID-19 infection even after completion of the study

This fast track approval is sought on compassionate grounds.