भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग, स्वास्थ्य और परिवार
कल्याण मंत्रालय, भारत सरकार
Indian Council of Medical Research
Department of Health Research, Ministry of Health
and Family Welfare, Government of India

Date: 10/06/2021

Call for Expression of Intent

ICMR along with Drugs for Neglected Diseases Initiative (DNDi) is proposing to conduct a multi-centre, adaptive platform trial in mild COVID-19 patients, titled '***An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild cases of COVID-19***'.

An expression of intent from institutions, hospitals and and other organization interested with the facilities and capacity available to participate in the above-mentioned clinical trial, which will enroll participants from the community. The intervention arms to start with will be the following:

1. Oral Nitazoxanide + inhaled ciclesonide
2. Artesunate and Amodiaquine (ASAQ) + Ivermectin

The control arm will be standard of care arm.

The trial will be initiated only after obtaining requisite regulatory and ethical approvals. A brief synopsis of the study plan is attached herewith. Institutions which are interested to collaborate with ICMR on undertaking this trial, may express their interest by providing the details through the following link: https://forms.gle/4XmuP5Ba7vKaMUg2A

Please send your response on or before 15 June 2021, 05:30 PM.

For further details, please contact:

Dr. Aparna Mukherjee
Scientist E
Clinical Trial & Health Systems Research Unit
Epidemiology and Communicable Diseases
Indian Council of Medical Research
New Delhi - 110029
Email: aparna.sinha.deb@icmr.gov.in

SYNOPSIS

Title	An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild cases of COVID-19
Clinical Study Phase	III
Primary Objective	The primary objective is to compare the efficacy of alternative treatment strategies versus control on the risk of progression to moderate/ severe respiratory disease
Main Secondary Objectives	The secondary objectives are: • To compare the safety of each study arm to control, up to Day 21 of follow-up • To compare the rate of hospitalisations due to COVID-19 in each study arm versus control • To compare the time to hospitalisation due to COVID-19 in each study arm versus control • To compare the rate of hospitalisations for other reason than Covid-19 in each study arm versus control • To compare the disease-free rate in each study arm versus control • To compare the death rate in each study arm versus control • To compare time to worsening of SpO2 $\leq$ 93in each study arm versus control • To compare the capacity to prevent severe progression between study arms • To identify risk factors for severe progression
Investigational Products (IPs)	1. Oral Nitazoxanide (2000mg/day) + inhaled ciclesonide (640 mcg/day) + Paracetamol 500 mg qid per day 2. ASAQ (standard dose for malaria) + IVM (0,4,mg/kg per day – 5 days) + Paracetamol 500 mg qid per day 3. Paracetamol 500 mg qid per day
Study Duration	Patient participation will be for 22 days.
Indication	Mild COVID-19
Major Inclusion and Exclusion Criteria	***Inclusion Criteria*** 1. Male or female patients with Mild COVID and having pre-defined risk factors 2. COVID-19 confirmed by molecular biology or validated antigenic test available in India for SARS-Cov2 according to national guidelines, based on result within 24 hours prior to screening and maximum 48 hours after sampling. 3. Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO2) > 94%. 4. Signed written consent from the patient ***Exclusion Criteria*** 1. Abnormal physical examination findings: • respiratory rate >25 per minute. • blood pressure < 90/60 mmHg or > 160/100 mmHg. 2. End-organ compromise requiring admission to a resuscitation or continuous care unit or short-term life-threatening comorbidity with life expectancy < 3 months. 3. On-going treatment at screening with: • chronic systemic glucocorticosteroid > 40 mg daily; • immunosuppressive treatment;

	4. Known pulmonary arterial hypertension (PAH) or fibrosis. 5. Use of concomitant medications that are contraindicated with ciclesonide, known hypersensitivity to ciclesonide or any other ingredient in the formulation. 6. Known hypersensitivity to nitazoxanide/ ASAQ/Ivermectin or any other ingredient in the formulation. 7. Previous haematological event during treatment with amodiaquine, 8. Prior treatment with IVM within 6 months prior to screening 9. Patients vaccinated against SARS CoV-2
Study Design	Multicentre, randomised, open-label, adaptative master protocol / platform study
Number of Patients	Between 2000 and 3000 patients will be included, although the trial may be extended with the investigation of additional IPs. Approximately 700 partcipants will be enrolled per arm of intervention.
Primary Endpoint	The primary endpoint is SpO2 $\leq$ 93% within 21 days after randomisation to treatment, including death for any reason
Secondary Endpoints	The secondary endpoints are: • Mean number and incidence rate of serious adverse events (SAEs) • Mean number and incidence rate of severe adverse events • Mean number of discontinuations or temporary suspensions of IP • Number of hospitalisations due to severe progression • Time to hospitalisation • Disease-free status: disease-free based on normalisation of pre-existing symptoms (based on mMRC scale, scale of Clinical Improvement and clinical symptoms) and SpO2 $\geq$ 94% at Day 21 and no hospitalisation for COVID-19 • Time to worsening of SpO2 $\leq$ 93% within 21 days • Failure rate for each study arm • Occurrence of SpO2 $\leq$ 93% or death or hospitalisation due to COVID-19 • Sub-group analysis of failure rate for each study arm
Statistical Analyses	The following populations will be used in the statistical analyses. • Intent-to-treat (ITT): all patients who received at least one dose of IP, including • Per protocol (PP): all patients in the ITT population who were free from major protocol violations that could lead to bias • Safety: all patients who received at least one intake of IP *Efficacy Analyses* Interim analyses and the primary analysis of a treatment arm when it is declared either effective, ineffective or is dropped for futility will be based on the ITT population. The primary analysis will be a Bayesian comparison of the proportions experiencing progression to severe disease with the treatment versus control, with adjustments for site and temporal effects. Prior to the first interim analysis, a limited number of additional covariates may be specified for inclusion in the primary analysis, as predictors of outcome in ambulatory patients with COVID-19 become better understood.