CLINICAL STUDY PROTOCOL

A Multi-center, Randomized, Double Blind, Placebo Controlled Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients

Investigational Medicinal Product:	AVIGAN® (Favipiravir or 6-fluoro-3-hydroxypyrazine-2-carboxamide)
Sponsor:	Dr. Reddy's Laboratories Limited 8-2-337, Road No. 3 Banjara Hills, Hyderabad Telangana 500034, India
Co-sponsor	G Response Aid FZCO ("GRA") Emirates Financial Tower, South Tower, Unit 704, Sheikh Zayed Road, Dubai, UAE
Protocol Number:	CVD-04-CD-001
Study Code:	NV-05-983-2020
Version No.:	Final Version 5.0
Date:	06 Jan 2021

PROTOCOL APPROVAL PAGE

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PROTOCOL NO.: CVD-04-CD-001

STUDY CODE: NV-05-983-2020

EudraCT Number: 2020-005485-34

Protocol Title: A Multi-center, Randomized, Double Blind, Placebo Controlled Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients

Protocol Number: CVD-04-CD-001

This study will be conducted according to the Guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Brazil, 2013), the International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (cGCP)

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PROTOCOL SYNOPSIS

EudraCT Number	2020-005485-34
Protocol Number:	CVD-04-CD-001
Investigational Medicinal Product:	AVIGAN® (Favipiravir) tablets
Active Ingredient(s)/INN:	Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide)
Study Sponsor	Dr. Reddy's Laboratories Limited 8-2-337, Road No. 3 Banjara Hills, Hyderabad Telangana 500034, India
Study Title:	A Multi-center, Randomized, Double Blind, Placebo Controlled Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients
Study Phase:	Phase III
Indication Under Investigation:	Acute treatment of moderate to severe COVID-19 caused by SARS-CoV-2 infection
Study Objectives:	Primary Objective: • To evaluate the efficacy of oral favipiravir in improving the time to resolution of hypoxia in moderate to severe COVID-19 patients Secondary Objectives • To evaluate the efficacy of oral favipiravir in improving the clinical and virological outcomes in moderate to severe COVID-19 patients • To assess the tolerability and safety of favipiravir in the targeted study population
Study Design:	• Prospective • Interventional • Randomized (ratio 1:1) • Double-blind • Placebo-controlled

	• As adjunct ('add on') to Supportive Care • Parallel assignment to treatment groups This study will be conducted in two parts; Stage I – Main study and Stage II – Extended Follow up. Once all the patients complete the Stage I of the study, the database will be locked, and analysis will be performed. Patients will enter Stage II of study after they complete the Day 28 assessment.
Inclusion/Exclusion Criteria:	Inclusion Criteria: Patients must satisfy all the following criteria to be included in the study: 1. Male and female patients aged 21 to 80 years (both inclusive) 2. Patients who have tested positive for SARS-CoV-2 by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay using a respiratory tract sample (either nasopharyngeal swab OR oropharyngeal swab OR nasal aspirate OR trachea-bronchial aspirate) collected within 72 hours prior to randomization 3. Patients should be hospitalized 4. Patients having 'moderate' or 'severe' COVID-19* with a score of > 4 on the 10-point ordinal scale of clinical status used by WHO in the SOLIDARITY trial at baseline assessment [i.e., patients with blood oxygen saturation (SpO2) <95% at rest on room air at sea level and requiring supplemental oxygen]. *Note: This includes patients clinically assigned as: I. 'moderate' COVID-19 a. symptoms which could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms or shortness of breath with exertion and/or clinical signs, such as respiratory rate ≥20 breaths per minute or heart rate ≥90 beats per minute AND b. blood oxygen saturation (SpO_2) of 94% at rest on room air at sea level II. 'severe' COVID-19

a. symptoms which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress and/or clinical signs, such as respiratory rate ≥30 per minute or heart rate ≥125 per minute

AND

b. blood oxygen saturation (SpO_2) ≤93% on room air at sea level or PaO_2/FiO_2 <300

**The above-mentioned definitions of COVID-19 severity are adapted from the FDA Guidance document COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry Final Document dated May 2020*

5. Female patients of childbearing potential*
   a. Must have a negative serum pregnancy test at screening.
   b. Should not be lactating; and not planning to become pregnant/breast feed during the treatment period and for 7 days after the last dose of study medication.
   c. Should commit to the use of **TWO** forms of study-acceptable contraception methods, including a barrier method (eg. diaphragm) along with one or more of the following methods of contraception for the duration of the treatment period and for 7 days after the last dose of study medication:
      i) hormonal methods [insertable, injectable, transdermal, or combination oral (estrogen+ progestin)] or
      ii) intrauterine contraceptive device

   Note: *Female patients who are sexually abstinent or whose male sexual partner has undergone vasectomy at least three months prior to the start of study treatment in the trial may be enrolled at the Investigator's discretion, provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting*

*pregnant during the study. Patients must also agree to use **TWO** forms of study-acceptable contraception methods should they become sexually active during the treatment period and for 7 days after the last dose of study medication.*

*Note: *A female patient is considered of childbearing potential unless she is*

a. postmenopausal for at least 12 months prior to study product administration, or

b. without a uterus and/or both ovaries; or has been surgically sterilized (ie, tubal ligation or has a fallopian tube blocking coil) for at least 6 months prior to study product administration.

6. Male patients should agree to abstain from sexual intercourse or to use double-barrier contraception (e.g. condom with spermicide) for the duration of the treatment period in the study and for at least 7 days after receiving the last dose of study medication. Male patients should also avoid semen donation or providing semen for *in-vitro* fertilization during the above-mentioned duration.
7. Able and willing to provide informed consent
8. Able to understand the trial requirements and comply with trial medications and assessments in the opinion of the Investigator
9. Should not have received investigational treatment from participation in another clinical trial within 30 days prior to randomization in the current trial and agrees not to participate in other clinical studies during the entire study period

Exclusion Criteria:

Patients who meet any of the following criteria will be disqualified from entering the study:

1. Critically ill patients, defined as those who are candidates for endotracheal intubation and mechanical ventilation, Extracorporeal Membrane Oxygenation (ECMO) , or clinical diagnosis of respiratory failure (i.e., clinical need for one of the

	preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) and those with shock (defined by systolic blood pressure (BP) <90 mm Hg, or diastolic BP <60 mm Hg or requiring vasopressors) or multi-organ dysfunction/failure, at baseline Note: *The above-mentioned definition of 'critically ill' COVID-19 patients is as defined in the FDA Guidance document COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry Final Document dated May 2020* 2. Patients in whom the first onset of symptoms/ signs suggestive of COVID-19 illness was observed >10 days earlier to the baseline assessment and randomization 3. Patients who have used interferon beta 1-a (IFN-β 1-a) preparations or drugs with reported anti-viral action against SARS-CoV-2 (hydroxychloroquine sulfate, phosphate, lopinavir-ritonavir combination drugs, ciclesonide, nafamostat mesylate, camostat mesylate) within 9 days after development of fever (≥37.5°C) Note: The above-mentioned exclusion criterion is not applicable in case of patients with history of human immunodeficiency virus infection or infective hepatitis in whom use of anti-viral drugs or interferons are prescribed for treatment of the underlying condition and who are currently receiving one or more of these medications (as maintenance treatment) at the time of randomization. The infection episode in question is a relapse of, or reinfection with SARS-CoV-2. 4. Patients suspected to have a complication of congestive cardiac failure based on Investigator's clinical judgement 5. Patients with moderate and severe hepatic dysfunction equivalent to Grade B and Grade C in the Child-Pugh classification respectively

	6. Patients with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels > 5 times upper limit of normal (ULN) at screening evaluation 7. Patients with renal impairment requiring dialysis 8. Patients with serum uric acid higher than the ULN at screening evaluation 9. Patients with history of hereditary xanthinuria 10. Patients who have been diagnosed with xanthine urinary calculus 11. Patients with a history of gout or patients who are currently being treated for gout 12. Patients who are taking immunosuppressants 13. Patients who were administered Favipiravir in the past 30 days 14. Patients with known hypersensitivity reaction to Favipiravir
Study Duration:	This study will be conducted in two parts; Stage I – Main study and Stage II – Extended Follow up **Stage I – Main Study:** It is estimated that the duration of the patient participation in the Stage I of the study will not exceed 33 days, including a maximum of 3 days of screening period, a treatment period of 10 days and a study data collection period of 28 (+2) days Study treatments Favipiravir/Placebo will be administered over 10 consecutive days. If the patient is discharged before Day 10, the patient will be required to continue the remainder of the treatment course at home. However, the above-mentioned treatment period will be shortened if it is necessary to discontinue administration of the study drug due to AEs or other circumstances. The patients will be discharged when the Principal Investigator or a medically qualified Sub Investigator judges that the patient is fit for discharge. Day 10 will be considered as the End of treatment (EOT) assessment.

1. If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 will be performed.
2. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home.
   a. On-site visit: If the patient is able to visit the hospital on Day 10, procedures for an unscheduled visit will be performed.

   OR

   b. At home: If the patient is unable to visit the hospital for the EOT, study nurse or phlebotomist will visit the patient at his/her residence to collect blood sample for safety assessments. A nasopharyngeal swab or oropharyngeal swab will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay based on Investigator's discretion for individual patients. A telephonic follow up will be performed to enquire on treatment emergent AEs experienced, concomitant medication and COVID-19 associated symptom for assessment of clinical relapse.

Day 28 will be considered the end of study visit.

If patient is discharged from the hospital before Day 28, the assessments mentioned in the end of study visit (Day 28) will be performed before the patient is discharged. After discharge, telephonic follow up will be performed on Day 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), Day 14, Day 21 and Day 28. The telephonic follow up will be as applicable for the individual patient, depending upon the actual day when (s)he is discharged. A 2-day window period is allowed for telephonic follow up.

In case the patient remains admitted in the hospital beyond Study Day 28, the end of study assessments will be performed for the patient on Day 28 (+2) days.

Stage II – Extended Follow Up:

	The duration of the patient participation in the Stage II of the study will not exceed 34 days. Two telephonic follow up assessments will be performed on Day 42 and Day 60. The patients will be followed up for AEs or for 'clinical relapse' of COVID 19. An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. A 2-day window period is allowed for telephonic follow up.
Administration of Study Treatments	Treatment group: Favipiravir + Supportive care Patients assigned to the 'Favipiravir + Supportive care' treatment group will receive AVIGAN® (favipiravir) 200 mg tablets at a dose of 1800 mg (9 tablets) orally twice daily (BID) on Day 1, followed by 800 mg (4 tablets) orally BID for 9 days. On Day 1, the second dose will be administered with at least a 4-hour interval from administration of the first dose. If the patient is discharged from hospital before Day 10, the patient will be required to continue the remainder of the treatment course of Favipiravir at home. Control group: Placebo + Supportive care Patients assigned to the 'Placebo + Supportive care' (control) treatment group will receive matching placebo, 9 tablets orally twice daily (BID) on Day 1, followed by 4 tablets orally BID for 9 days. On Day 1, the second dose will be administered with at least a 4-hour interval from administration of the first dose. If the patient is discharged from hospital before Day 10, the patient will be required to continue the remainder of the treatment course of Placebo at home. Patients in both the groups will receive supportive care, including symptomatic treatments. The Investigator may be guided by Management of COVID-19 as per the current local guidance or institutional practice, in his/her choice of supportive care for individual patients. Based on the individual patient's requirement, supportive care may be given for a longer period than favipiravir/matching placebo in the study.
Planned Sample Size:	Based on review of published literature, a hazard ratio of 1.25 is reported (adjusted for the stratification in

	randomization) for time to clinical improvement in COVID-19 patients receiving anti-viral interventions. The hazard ratio of 1.25 is also assumed to be constant throughout the study as per the assumptions of the Cox proportional hazards regression model with the expected average probability of the event over the course of the study to be 0.9 and 0.8 in test and control group respectively. Inequality testing of the hazard ratio using the Cox proportional hazards regression model with 371 subjects in Favipiravir group and 371 subjects in Placebo group achieves 80% power at the 0.05 significance level for an actual hazard ratio of 1.25 assuming the hazard ratio is 1 under the null hypothesis and that the total number of events achieved is 631. Based on the above assumption and considering the dropout rate to be 5%, overall, 390 patients will be randomized in each treatment group. i.e. 780 patients in total to be randomized in the study. The sample size is estimated using nQuery version 8.5.0.0 using Cox proportional hazard regression. Sample size will be re-estimated based on the analysis of results for the primary endpoint observed during interim analyses. . Details of the interim analysis and futility assessment are provided in the Statistical Analysis Plan (SAP) for the Interim Analysis.
Study Endpoints:	**Stage I:** **Efficacy Endpoints:** Primary Efficacy Endpoint: 1. Time to resolution of hypoxia (Time frame: Up to 28 days) This endpoint will be considered to have been met when the patient has attained a score of 4 or lower on the 10-point ordinal scale of clinical status and either of a) or b), and c) is met: a) Score is ≤ 4 on consecutive assessments over the next 5 days, if patient continues to remain in hospital (i.e., has not been discharged). OR

	b) Patient was discharged before five consecutive assessments (after reaching a score of 4). AND c) The patient has survived and has not been re-admitted to hospital for COVID-19 management through Day 28. Secondary Efficacy Endpoints: 1. Time to discharge from hospital. 2. Time (no. of days) from randomization to the earliest time when **ALL** COVID-19 associated symptoms (fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically diarrhoea and vomiting, shortness of breath or dyspnoea) are scored by the Investigator/trained study personnel as either '0=absent' or 'mild =1' in assessments over a period of 24 hours, when assessed from baseline to Day 28 or discharge from hospital (if discharge happens earlier than Day 28). 3. Percentage of patients with score of either '0=absent' or 'mild =1' over a period of 24 hours, for **ALL** COVID-19 associated symptoms, by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) Note*: Symptoms evaluated are fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically, diarrhoea and vomiting, shortness of breath or dyspnoea. The Investigator/trained study personnel will assess (including by enquiry with the patient, as necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical).* 4. Time to improvement in **EACH** of the symptoms of fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically diarrhoea and vomiting, shortness of breath or dyspnoea by at least 1 grade over baseline.

	Note: *Severity of symptoms will be evaluated once daily (preferably at or around the same clock time) on each day that the patient is admitted in the hospital. The Investigator/trained study personnel will assess (including by enquiry with the patient, as necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical). The improvement observed must be sustained at evaluations over a period of 24 hours, in order for this secondary efficacy endpoint to be reached.* 5. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 27 days after the day of randomization (Day 28). Note*: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge. This endpoint will be assessed only for those patients that were discharged before Day 28.* 6. Time (no. of days) to negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample, from randomization. 7. Percentage of patients showing negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample on Days 5, 10 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) 8. Changes over time in patient's clinical status on the 10-point ordinal scale used in the SOLIDARITY trial by WHO a. Changes in the 10-point ordinal scale score from baseline until discharge b. Proportion of patients in whom clinical status score of 4 ('hospitalized, no oxygen required') or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

	c. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline) d. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) 9. Changes over time in patient's clinical status on the 8-point ordinal scale a. Time (no. of days) from randomization to attain clinical status score of 4 or lower b. Proportion of patients in whom clinical status score of 4 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) c. Time (no. of days) from randomization to attain clinical status score of 3 or lower d. Proportion of patients in whom clinical status score of 3 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) e. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline) f. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) 10. Changes over time in findings on chest X-ray 11. Changes over time in the National Early Warning Score-2 (NEWS) 12. Percentage of patients requiring, until Day 28 or discharge from hospital (if discharge happens earlier) a. Management in intensive care unit

b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
c. Invasive mechanical ventilation

13. Time (no. of days) from randomization to:
    a. Management in intensive care unit
    b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

14. Duration (no. of days) the patient requires:
    a. Management in intensive care unit
    b. Oxygen supplementation
    c. High Flow Nasal Oxygen
    d. Non-Invasive Mechanical Ventilation
    e. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

15. Percentage of patients:
    a. dying from any cause
    b. dying from a COVID-19 associated complication

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

Safety endpoints:

1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term)
2. Changes of parameters at each assessment during the study/follow-up period, compared to baseline for:
   - Vital signs: body temperature, heart rate, respiratory rate, systolic/diastolic BP and oxygen saturation.
   - Clinical laboratory assessments: hematology, serum chemistry, urinalysis.

	▪ 12-lead ECG: Changes in heart rate, PR, QRS, QT and QT_cB intervals. **Stage II** **Efficacy endpoint:** 1. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 59 days after the day of randomization (Day 60). Note*: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge.* 2. Proportion of patients a. With disease worsening and requires: • Admission to ICU • High flow nasal oxygen • Non-invasive mechanical ventilation • Invasive mechanical ventilation AND b. Dying until Day 60 (regardless of whether patients are discharged from hospital before Day 28 or not) **Safety Endpoint:** 1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term) Secondary endpoints may be modified, or additional secondary endpoints may be defined in the SAP.
Statistical Analyses:	Unless otherwise specified, the primary efficacy analysis will be done using Intention to Treat (ITT) population. The statistical significance level is 0.05 by one sided or two-sided test, wherever appropriate. Mean/ Median (and other general statistics estimates such as Inter Quartile range, SD, min, max etc.) and the 95% CI for the estimates of the mean will be provided for the applicable efficacy endpoints.

	Endpoints will be analysed descriptively and inferentially wherever necessary. All AEs and TEAEs will be summarized in terms of severity, relationship to study treatment, action taken and patient outcome. The number and the proportion of patients who experienced AEs will be computed by treatment group, classified by Medical Dictionary for Regulatory Activities (MedDRA version 23.0) Primary System Organ Class and Preferred Terms. The AE data will be summarized using safety population. Detailed description on the statistical methods will be explained in the Statistical Analysis Plan which will be finalized before study database lock of Stage I of the study. If there is a discrepancy in the planned analysis between the protocol and SAP, the SAP takes precedence. An independent data monitoring committee (DMC) will review the results of the interim analyses to assess the efficacy and safety data emerging from the trial. The details of the interim analysis or futility assessment will be included in a separate Interim Analysis Plan, appended to the DMC charter. Sample size will be re-estimated based on the analysis of results for the primary endpoint observed during interim analyses. Details of the interim analysis and futility assessment are provided in the Statistical Analysis Plan (SAP) for the Interim Analysis.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACTT-1	Adaptive COVID-19 Treatment Trial-1
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Transaminase/Alanine Aminotransferase
AO	Aldehyde Oxidase
AST	Aspartate Transaminase/Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
AUCτ	AUC during repeated dose intervals
BD/BID	*Bis In Die* (Twice Daily)
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum observed Plasma Concentration
COVID-19	Novel Corona Virus Disease 2019
CYP	Cytochrome P-450
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CTCEA	Common Terminology Criteria for Adverse Events
DIC	Diffuse Intravascular Coagulation
DMC	Data Monitoring Committee
DMP	Data Management Plan
EC_{50}	Drug Concentration Producing 50% of Maximum Effect
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
ENT	Ear Nose Throat
EOT	End of Treatment
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
FPV	Favipiravir
GCP	Good Clinical Practice
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
Hb	Haemoglobin
IB	Investigator's Brochure
IC_{50}	Drug Concentration Producing 50% of Maximum Inhibition

ABBREVIATION	DEFINITION
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
IWRS	Interactive Web Response System
IFN	Interferon
JP321	Japanese Phase III clinical study
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mITT	Modified Intention to treat
MOI	Multiplicity of Infection
NEWS	National Early Warning Score
NIV	Non-invasive Ventilation
OTC	Over the Counter
PaO_2	Partial Pressure of Oxygen
PIC	Patient Identity Code
PP	Per Protocol
PPS	Per Protocol Set
RBC	Red Blood Corpuscles
RdRp	RNA-dependent RNA Polymerase
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcriptase – Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SFTS	Severe Fever with Thrombocytopenia Syndrome
SOC	System Organ Class
SpO_2	Peripheral Capillary Oxygen Saturation
T-705RMP	Favipiravir ibofuranosyl-5′-monophosphate
T-705RTP	Favipiravir ibofuranosyl-5′-triphosphate
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Corpuscles

ABBREVIATION	DEFINITION
WHO	World Health Organization
WHO-DG	World Health Organization Drug Global
XO	Xanthine oxidase

1 INTRODUCTION AND BACKGROUND INFORMATION

Background Information

The novel corona virus disease 2019 (COVID-19) is a global pandemic. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 29 June 2020, there have been 9,962,193 confirmed cases of COVID-19, including 498,723 deaths in 216 countries worldwide.[1]

The human-to-human transmission occurs through respiratory droplets with an incubation period ranging from 2 to 14 days. Fever, fatigue, dry cough, myalgia, dyspnoea, expectoration and diarrhea are the common symptoms reported among patients with the COVID-19 infection.[2] In addition to the respiratory system, this virus can infect the digestive system, the urinary system and the hematological system.[3] Inflammatory reactions occur in the all organs of the body, the microvascular system is damaged, leading to abnormal activation of the coagulation system, which pathologically manifests as generalised small vessel vasculitis and extensive micro thrombosis.[3] There is direct viral invasion of cardiomyocytes, hypoxia due to severe pneumonia leading to ischemic cardiac tissue, or an overwhelming inflammatory response leading to cytokine storm and myocardial dysfunction.[4] COVID-19 predispose to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation (DIC).[5]

The common laboratory abnormalities in patients with COVID-19 infection includes increased counts / levels of neutrophils, D-dimer, C-reactive protein, lactate dehydrogenase, alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine, creatine kinase, IgG and IgM. Decreased counts / levels of lymphocyte, platelet and albumin are also observed. The symptoms of SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) infections are similar to SARS-CoV-2 infection. The severity of the infection in patients with confirmed SARS-CoV-2 can be identified using radiological images of the lungs. The different abnormalities observed in the lungs of patients including ground-glass opacities, consolidation, centrilobular nodules, architectural distortion, bronchial wall thickening, vascular enlargement, traction bronchiectasis, reticulation, crazy paving pattern, intrathoracic lymph node enlargement and subpleural bands, that cause pulmonary discomfort and require rapid diagnosis and treatment.[6]

The main transmission routes for SARS-CoV-2 are respiratory droplets and close contact such as touching an infected person or the surfaces and fomites that the infected person has either touched, or on which large virus-containing droplets expired by the infected person have landed.[7]

SARS-CoV-2, a single-stranded positive sense RNA virus, targets cells through the viral structural spike (S) protein embedded in the viral membrane (M) that binds to the angiotensin-converting enzyme 2 receptor on target host cells. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes ribonucleic acid (RNA) via its RNA-dependent RNA polymerase (RdRp). Structural proteins are synthesized leading to completion of assembly and release of viral particles.[8]

Within six days of the onset of symptoms, patients with COVID-19 infections demonstrate high viral loads in their upper and lower respiratory tract. A nasopharyngeal swab and/or an oropharyngeal swab are often recommended for screening or diagnosis of early infection. For late detection and monitoring of patients with severe COVID-19 pneumonia, sputum or bronchoalveolar lavage should be used for collecting lower respiratory tract specimens.[9]

Clinical care of suspected patients with SARS-CoV-2 infection focuses on recognition of the disease condition at the earliest, isolation and adoption of proper infection control measures, and delivery of optimized supportive care toward the suspected/confirmed cases. For preventive measure, the WHO guideline "Clinical management of severe acute respiratory infection when novel coronavirus (COVID-19) infection is suspected" mainly focuses on avoiding close contact with persons suffering from acute respiratory infections, frequent hand washing, and avoidance of unwanted contact with wild animals. In case of patients with respiratory distress, the patient is to be evaluated for the presence of shock. Empirical antimicrobial coverage is to be given to cover the likely causative organisms, which may be responsible for severe acute respiratory infection. Special concern is to be given for other comorbid conditions. In case of hypoxemic respiratory failure, it needs to be managed aggressively with high-flow nasal oxygen or noninvasive ventilation or by endotracheal intubation and positive pressure ventilation as required. Special concern is to be taken for the identification and management of septic shock.[10]

The following drugs are being utilized as COVID-19 treatment in various clinical trials worldwide with varied results.

Selected Repurposed Drugs: Agents previously used to treat SARS and MERS

- Chloroquine phosphate
- Hydroxychloroquine sulfate
- Lopinavir/ritonavir
- Ribavirin
- Oseltamivir
- Umifenovir (Arbidol)

Investigational agents

- Remdesivir
- Favipiravir

Adjunctive therapy[8]

- Systematic corticosteroids
- Cytokines or Immunomodulators (Tocilizumab)
- IV immunoglobulin

In the current study, Investigator may be guided by the current local guidance for COVID-19 management or by the institutional practice, in his/her choice of supportive care for individual patients. The duration of supportive care will be based Investigator's judgement and as per individual patient's requirement.

1.1 Name of Investigational Product

AVIGAN® (Favipiravir) tablets

1.1.1 Description

Favipiravir (Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide), also known as T-705, is a selective nucleic acid (purine) analog that is converted to Favipiravir ibofuranosyl-5′-monophosphate (T-705RMP) and Favipiravir ibofuranosyl-5′-triphosphate (T-705RTP) by cellular kinases. Favipiravir is a novel nucleic acid (pyrazine molecule) analogue that interferes with viral ribonucleic acid (RNA) replication.[11] T-705RTP is recognized as a substrate by the viral RNA-dependent RNA polymerase (RdRP), and it selectively inhibits the latter.

1.1.2 Intended Use under Investigation

Favipiravir is being developed for the treatment of acute, uncomplicated, mild to moderate COVID-19 illness and to potentially reduce transmission by abbreviating the duration of viral shedding. An *in-vitro* study by Wang *et* al[12] found that SARS-CoV-2 was inhibited by favipiravir in Vero E6 cells with an EC_{50} of 61.88 µM. Favipiravir also inhibits growth in cells of pathogenic viruses from ten different RNA virus families and has been shown to be effective in animal models for RNA viral diseases including those caused by new and old world arenaviruses, Chikungunya virus, rabies virus, and Ebola virus. It has been used in compassionate use cases to treat people with Jamestown Canyon virus, Lassa fever, Ebola, norovirus and rabies.[11]

1.1.3 Nonclinical Studies

Nonclinical studies, single oral dose toxicity studies, repeated oral dose toxicity studies, genotoxicity studies and reproductive and developmental toxicity studies have been conducted using various species. Based on the results of these toxicity studies, it was identified that there are possibilities that adverse events (AEs) such as hepatic function disorder, renal impairment, anaemia symptoms, loss of appetite, queasy/vomiting, tissue discoloration, and testicular toxicity could occur in clinical studies.

Early embryonic deaths (in rats) and teratogenicity (in monkeys, mice, rats and rabbits) have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.

Also, the *in vitro* anti-viral effect of favipiravir on SARS-CoV-2 was confirmed. Vero E6 cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019 with a multiplicity of infection (MOI) of 0.05 in the presence of various concentrations of favipiravir. The virus copy number in the cell supernatant was evaluated via quantitative real-time reverse transcription-polymerase chain reaction, and the emergence of virus nucleoproteins in immunofluorescence microscopy over 48 hours after infection was visualized for confirmation. The EC_{50} of favipiravir was 61.88 µM) [12].

1.1.4 Clinical Experience

JP 120 study was a 22-Day repeated dose study on favipiravir investigation of the pharmacokinetics, safety and tolerability in healthy subjects. In the JP120 study, favipiravir was administered at 1,800/800 mg BID, which is the same dosage as in this clinical study, in repeated doses for 22 days, the maximum observed plasma concentration (C_{max}) was approximately 65 µg/mL after the first dose on Day 1 and approximately 100 µg/mL after the first dose on Day 12 and after administration on Day 22. The area under the plasma concentration-time curve (AUC) was approximately 720 µg·hr/mL after the first dose on Day 1, the AUC during repeated dose intervals (AUCτ) after the first dose on Day 12 and after administration on Day 22 was approximately 950 µg·hr/mL. The C_{min} remained at approximately 56 to 75 µg/mL after the second dose on Day 1 and onward.

Also, in the JP120 study, there were no serious adverse events (SAEs) including death or any significant AEs. The incidence of AEs was 100% (8/8 subjects, 16 events) in the favipiravir group and 1/2 subjects (1 event) in the placebo group. The incidence of AEs that occurred was as follows. In the favipiravir group: blood uric acid increase was 100% (8/8 subjects, 8 events), alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and white blood cells urine positive were each 25.0% (2/8 subjects, 2 events), and abdominal pain upper and rash were each 12.5% (1/8 subjects, 1 events). In the placebo group: the incidence of protein urine present was 1/2 subjects (1 event). The AEs that occurred in the JP120 study were all AEs for which a causal relationship with the investigational drug cannot be ruled out, except for white blood cells urine positive, which occurred in the favipiravir group. All AEs that occurred were mild in severity and resolved without any treatment. Based on the above, the safety and tolerability of favipiravir administered for 22 days were confirmed.

In the Japanese Phase III clinical study (JP321), in which favipiravir was administered at 1,800/800 mg BID, which is the same dosage as in this clinical study, in repeated doses for 10 days in patients with severe fever with thrombocytopenia syndrome (SFTS), three AEs (SFTS) that resulted in death occurred in three patients and six other SAEs (liver function test increased, Factor XIII deficiency, sepsis, myocarditis, seizure and respiratory arrest, one event each) in five patients. All these AEs, except for liver function test increased and seizure, were judged by the Principal Investigator to be unrelated to the study drug. The incidence of AEs was 86.7% (26/30 patients, 116 events). Adverse events with an incidence of ≥ 10% were hyperglycemia and hyperuricemia each in 23.3% (7/30 patients), insomnia and blood uric acid increased each in 20.0% (6/30 patients), constipation and rash each in 16.7% (5/30 patients), back pain in 13.3% (4/30 patients), oral candidiasis, SFTS, hypertriglyceridemia and pneumonia aspiration each in 10.0% (3/30 patients). The incidence of AEs for which a causal relationship with the study drug could not be ruled out was 70.0% (21/30 patients, 40 events). Adverse events with an incidence of ≥ 10% were hyperuricemia in 23.3% (7/30 patients), blood uric acid increased in 20.0% (6/30 patients), and hypertriglyceridemia in 10.0% (3/30 patients).

In a prospective, randomized, controlled, open-label study[13] conducted on adult patients with COVID-19, 116 patients received Favipiravir (twice daily) and 120 patients received Umifenovir (thrice daily) plus standard care. Favipiravir was started with 1600 mg on the first day followed

by 600 mg for the following days upto a maximum of 10 days. In the comparator arm Umifenovir was given at 200 mg combined with standard care for 7 days. On Day 7, the clinical recovery rate in Favipiravir group was 71/116 and Umifenovir group was 62/120. There was no significant difference between the 2 groups. In Favipiravir group there was a significant improvement with respect to relief for fever and cough. But there was an increase in serum uric acid observed in 16 patients receiving Favipiravir.

Favipiravir was compared with Lopinavir/Ritonavir an open label study on patients with confirmed COVID-19. Oral Favipiravir (1600 mg twice daily on first day followed by 600 mg twice daily for the following days until Day 14) was given to 35 patients. In the control arm, 45 patients received oral tablet with combination of Lopinavir (400 mg)/Ritonavir (100 mg) twice daily for 14 days. Both the groups received interferon (IFN)-α by aerosol inhalation (5 million U twice daily). Viral clearance rate was shorter and improvement in chest imaging was significant in Favipiravir group compared to control group.[14]

An observational study on Favipiravir registered 2,158 COVID-19 cases. These patients received orally 1800 mg Favipiravir twice daily on first day followed by 800 mg twice daily for the successive days for a mean duration of 11 days. The clinical improvement rates were 79% on Day 7 and 92.4% on Day 14 in patients aged 59 years or younger. The same were 55% and 73.8% respectively in patients aged 60 years or older.[15]

1.2 Study Rationale

Favipiravir is an antiviral drug that was discovered by FUJIFILM Toyama Chemical Co., Ltd. (previously, Toyama Chemical Co., Ltd.). At the time of initial registration, its indication was limited to "novel or re-emerging influenza virus infection (only for cases in which other anti-influenza virus agents were not effective or were insufficiently effective)," and the drug was approved for marketing in Japan in March 2014. The mechanism of action of favipiravir is that the ribosyl triphosphate form (T-705RTP) converted *in vivo* selectively suppresses the viral RNA polymerase, and it has been shown in preclinical studies tobe effective on RNA viruses in addition to the influenza virus. Favipiravir has been reported to have an effect *in vitro* and *in vivo* against Ebola virus and viruses of the families Arenaviridae and Bunyaviridae, which are RNA viruses [16, 17, 18].

There is a Licensing agreement between Fujifilm and Dr Reddy's Laboratories and Global Response Aid on development, manufacture and sale of Favipiravir tablets. Fujifilm authorises Dr Reddy's Laboratories and Global Response Aid to implement clinical studies targeting COVID-19 patients in India and Middle East and other regions where infections has been spreading.

The novel coronavirus[19] (SARS-CoV-2) first reported in China at the end of 2019 is an RNA virus, which belongs to the family Coronaviridae, order Nidovirales [20]. When infected with this virus, fever and acute respiratory symptoms including cough and dyspnea develop, [19] and when the condition is exacerbated, pneumonia develops. COVID-19 is a multi-system disease that results from uncontrolled immune reaction ('cytokine storm') and clotting in smaller blood vessels.[21]

The drug concentration producing 50% of maximum effect (EC_{50}) of favipiravir on SARS-CoV-2 using Vero E6 cells reported by Wang et al. in the journal Cell Research was 61.88 μM[12]. This corresponded to 9.72 μg/mL and was almost equivalent to the drug concentration producing 50% of maximum inhibition (IC_{50}) of 10.5 μg/mL (67 μM) [18] against Ebola virus.

In a clinical study conducted in Ebola virus-infected patients in Sierra Leone, [22]favipiravir was administered at 1,600 mg twice a day (BID) on Day 1 and 600 mg BID from Day 2 (1,600/600 mg BID), which are the current approved doses for influenza virus infections, for 3 to 11 days. The survival rate with favipiravir (except for patients who were transferred to other hospitals within 2 days after the treatment initiation) was 56.4% while with the conventional therapy (historical control) it was 35.3% (except for patients who were transferred to other hospitals within 2 days after the treatment initiation), demonstrating a significant difference ($p = 0.027$). Following co-administration of interferon alpha-1b with favipiravir to COVID-19 patients in Shenzhen, China, the median time to elimination of SARS-CoV-2 was 4 days. The rate of improvement in findings from chest imaging was 56.25% (18/32 patients) on Day 9 and 91.43% (32/35 patients) on Day 14. Co-administration of interferon alpha-1b with favipiravir showed earlier therapeutic effect compared with that of co-administration of interferon alpha-1b with a lopinavir-ritonavir combination drug [14].

In a 22-day multiple dose study (JP120)[11] in which favipiravir was administered at 1,800 mg BID on Day 1 and 800 mg BID from Day 2 (1,800/800 mg BID) to Japanese healthy adult males aged 20 to ≤ 39 years, the peak plasma concentration of favipiravir remained at approximately 87 to 104 μg/mL on Day 5 and onward and the minimum plasma concentration after peak (C_{min}) remained at approximately 56 to 75 μg/mL following the second dose on Day 1 and onward. This value was higher than the abovementioned EC_{50} of favipiravir, 9.72 μg/mL, on SARS-CoV-2 even taking into consideration the human protein binding ratio of favipiravir, which is approximately 55%. These results showed that favipiravir may be effective in COVID-19 patients.

Based on the fact a positive signal is seen with 1800/800 mg dose in COVID-19 patients with Favipiravir and safety has been established with this regimen for upto 22 days, 1800/800 mg dose has been chosen for the phase III study.

There is no established treatment method for COVID-19, and a continuous increase in the number of COVID-19 patients is a concern based on epidemiological surveys to date. Given the relatively high contagiousness of SARS-CoV-2 and continuous outbreaks, the development of a treatment that is effective for COVID-19 is urgent. This clinical study was planned because if the therapeutic efficacy of favipiravir against COVID-19 in humans is demonstrated, it can significantly contribute to the treatment of COVID-19.

Patients will be randomized to each treatment group and the study will be conducted in a 'double-blind' fashion in order to minimize bias. The study will compare the safety and efficacy of favipiravir when administered as adjunct ('add-on') to supportive care as per local guidance to that of placebo added on to supportive care, and will enroll moderate to severe COVID-19 patients (those having a blood oxygen saturation < 95% at rest and requiring Oxygen supplementation). Given that there is currently no established treatment for moderate to severe COVID-19, it is

reasonable to use placebo as control, while using supportive care as per local guidance and management practices in both treatment groups as appropriate, to ensure patients receive the medical care they need.

1.3 Risks and Benefits for Study Patients

Many medicinal treatments for COVID-19 disease are being administered off-label, or in the experimental setting. In this study, we are evaluating one such potential treatment, favipiravir, which has demonstrated some indirect and direct evidence of efficacy in the management of COVID-19 patients over and above the standard of care in accordance with the institutional guidelines.

Patients will have clinical assessments, assays for detection of the SARS-CoV-2, other clinical laboratory evaluations and chest imaging performed, at more than one time points during the course of this study, at no cost to them, and may benefit from close medical oversight in the course of safety assessments in the trial. Finally, they would have altruistic satisfaction of having directly contributed to medical scientific research against an infectious disease that has emerged as a major current challenge to the human race, as well their immediate personal health.

The risks to the study patients from study participation are that, they could possibly experience one or more adverse effects from any medications used as and from favipiravir such as blood uric acid increased, diarrhea, neutrophil count decreased, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT)increased.

Serious adverse events reported in subjects taking this drug are hepatic function abnormality, hematochezia, colitis, seizure and acute kidney injury. It is not known if all are attributable favipiravir administration.

The clinically significant adverse reactions of similar (anti-influenza) drugs requiring particular attention include shock, anaphylaxis, pneumonia, hepatitis fulminant, hepatic function disorder, jaundice, TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute renal failure, neurological and psychiatric symptoms (consciousness disturbed, abnormal behavior, delirium, hallucination, delusion, convulsion, etc.), and colitis hemorrhagic.

1.4 Route, Dosage, Dosage Regimen, Treatment Period

AVIGAN® (Favipiravir) is supplied as 200 mg tablets to be administered orally. The proposed dosing regimen for this study is 1,800 mg twice a day (BID) for 1 day followed by 800 mg BID for a maximum of 9 days.

1.5 Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) of Food and Drug Administration (FDA) GCP Regulations: Code of

Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or local regulations.

An approval must be obtained from applicable regulatory agencies and ethics committees.

Patient's written informed consent will be taken prior to any study procedure being conducted.

1.5.1 Patient Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all patients taking part in the study, in accordance with GCP and local and applicable data protection regulations.

The Investigator must ensure that the patient's anonymity is maintained. On the electronic Case Report Forms (eCRFs) or other documents submitted to Sponsor/CRO, patients should be identified by a unique patient identifier as designated by the Sponsor. Documents that are not for submission to Sponsor/CRO (eg, signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor companies or CRO, of the Regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) direct access to review the patient's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the patient that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

1.5.2 Informed Consent Procedure

Before a patient's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the patient or legally acceptable representative (LAR) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential patient population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IEC or IRB prior to being provided to potential patients.

The patient's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the patient's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the patient or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the patient or legal representative. The date and time (if applicable) that informed consent was administered to the patient/legal representative should be recorded on the Case Report Form.

If the patient or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the patient or the legally acceptable representative has orally consented to the patient's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the patient or the legally acceptable representative and that informed consent was freely given by the patient or the legally acceptable representative.

1.5.3 Regulatory Compliance

The study protocol, patient information and consent form, the Investigator's Brochure, any written instructions to be given to the patient, available safety information, patient recruitment procedures (eg, advertisements), information about payments and compensation available to the patients, and documentation evidencing the Investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB and/ or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor or Contract Research Organization (CRO) in accordance with local procedures.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

Primary Objective:

- To evaluate the efficacy of oral favipiravir in improving the time to resolution of hypoxia in moderate to severe COVID-19 patients

Secondary Objectives

- To evaluate the efficacy of oral favipiravir in improving the clinical and virological outcomes in moderate to severe COVID-19 patients
- To assess the tolerability and safety of favipiravir in the targeted study population

3 STUDY DESIGN

3.1 Overall Study Design

3.1.1 Study Type

This is a prospective, interventional, multi-centre, phase III, randomized, double blind, placebo-controlled, parallel design trial to evaluate the efficacy, safety and tolerability of favipiravir as adjunct ('add on') to supportive care, in comparison to placebo with supportive care, in the acute treatment of patients who have tested positive for SARS-CoV-2, presenting with moderate to severe COVID-19 and require hospitalization.

This study will be conducted in two parts; Stage I – Main study and Stage II – Extended Follow up.

Stage I – Main Study:

All the eligible patients will be randomized to receive either favipiravir + supportive care or placebo + supportive care. The treatment duration with the IMP will be for a period of 10 consecutive days. If the patient is discharged before Day 10, the patient will be required to continue the remainder of the treatment course of the assigned IMP at home. Patients in both the groups will receive supportive care, as appropriate. The duration of supportive care will be based Investigator's judgement and as per individual patient's requirement. The study data collection period will be up to 28 (+2) days.

Day 10 will be considered as the End of treatment (EOT) assessment.

1. If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 will be performed (details mentioned in Section 6.3.1.3).
2. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home (details mentioned in Section 6.3.1.4).
   a. On-site visit: If the patient is able to visit the hospital on Day 10, procedures for an unscheduled visit will be performed.

   OR

   b. At home: If the patient is unable to visit the hospital for the EOT, study nurse or phlebotomist will visit the patient at his/her residence to collect blood sample for safety assessments. A nasopharyngeal swab or oropharyngeal swab will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay based on Investigator's discretion for individual patients. A telephonic follow up will be performed to enquire on treatment emergent AEs experienced, concomitant medication and COVID-19 associated symptom for assessment of clinical relapse.

Day 28 will be considered the end of study visit.

If patient is discharged from the hospital before Day 28, the assessments mentioned in the end of study visit (Day 28) will be performed before the patient is discharged. After discharge, telephonic

follow up will be performed on Day 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), Day 14, Day 21 and Day 28. The telephonic follow up will be as applicable for the individual patient, depending upon the actual day when (s)he is discharged. A 2-day window period is allowed for telephonic follow up.

In case the patient remains admitted in the hospital beyond Study Day 28, the end of study assessments will be performed for the patient on Day 28 (+2) days.

Stage I of the study will be completed when the 'Day 28' assessment is completed either as an in-patient assessment if the patient is still hospitalized, or as a telephonic follow up assessment if the patients are discharged earlier to Day 28.

Once all the patients complete the Stage I of the study, the database would be locked, and analysis will be performed.

Stage II – Extended Follow Up:

All the patients will be followed up for AEs or for 'clinical relapse' of COVID 19. Two telephonic follow up assessments will be performed on Day 42 and Day 60. An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. A 2-day window period is allowed for telephonic follow up.

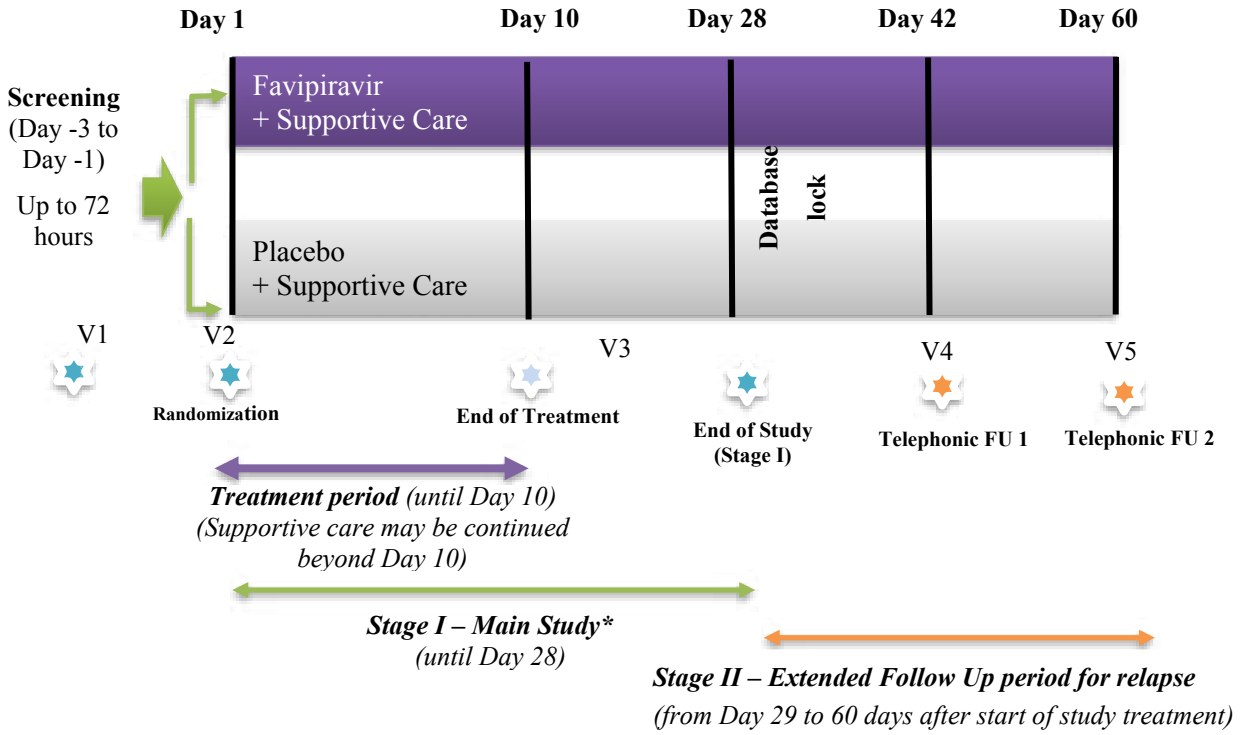
3.1.2 Treatment Groups

The study population will consist of patients of either sex, aged between 21 and 80 years (both inclusive) that have tested positive for SARS-CoV-2 by Reverse Transcriptase -Polymerase Chain Reaction (RT-PCR) assay using a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate) and clinically assessed to have moderate to severe COVID-19. The study will be conducted in Middle East and Europe. An adequate number of patients will be screened in order to randomize 780 patients into two treatment groups at a 1:1 ratio, so as to have approximately 390 patients in favipiravir + supportive care group and 390 patients in placebo + supportive care group.

An interim analysis and/or assessment futility and/or harm will be performed. An independent data monitoring committee (DMC) will review the results of the interim analysis to assess the efficacy and safety data emerging from the trial. The details of the interim analysis and/or futility/harm assessment will be included in a separate Interim Analysis Statistical Analysis Plan (SAP), that will be appended to the DMC charter. Sample size will be re-estimated based on the analysis of results for the primary endpoint observed during interim analyses. Details of the interim analysis and futility assessment are provided in the Statistical Analysis Plan (SAP) for the Interim Analysis. If there is a discrepancy in the planned analysis between the protocol and SAP, the SAP takes precedence.

The study population will consist of patients admitted/ requiring admission in hospital. Figure 1 provides a schematic overview about the study design.

Figure 1: Schematic diagram of study design



* If patient is discharged from the hospital before Day 28, a telephonic follow up will be performed on Day 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), Day 14, Day 21 and Day 28 as applicable for the individual patient.

The screening period will be for a maximum of 3 days. Although the duration of screening period is for a maximum of 3 days, once the results of the screening assessments are available and the patient successfully fulfils the eligibility criteria for the study, the Day 1 visit will be scheduled.

On Day 1, once the pre-dose assessments are completed and the patient is found to be eligible to participate in the study, patients will receive either favipiravir + supportive care or placebo + supportive care as per the randomization schedule. Given the current pandemic situation, wherein patients reporting to the hospital sites with a suspicion of COVID-19 are undergoing specific evaluations/ investigations as part of their medical care which overlap those that are mentioned as part of screening procedure for this study, these specific investigations conducted within 72 hours prior to Randomization/Baseline Visit (Visit 2 /Day 1) may be accepted for determining study eligibility and not repeated again as part of Screening Procedure. Refer to Section 6 for further details.

In both the treatment groups, patients will receive favipiravir/matching placebo for 10 consecutive days. If the patient is discharged from hospital before Day 10, the patient will be required to continue the remainder of the treatment course of favipiravir/matching placebo at home. Changes

to the medications used in supportive care are permitted during the treatment period. The Investigator will record all changes to the medications (medication, dose, frequency, regimen, route of administration) in the dedicated eCRF page. As per Investigator's clinical discretion, supportive care may be continued for individual patients beyond Study Day 10, as necessary; however, favipiravir/matching placebo will not be continued beyond Study Day 10 under any circumstance. Stage I of the study will be completed on Day 28. Stage II of the study will be extended follow up for safety and clinical relapse until Day 60.

3.1.3 Study Endpoints

3.1.3.1 Stage I

3.1.3.1.1 Efficacy Endpoints

Primary Efficacy Endpoint:

Time to resolution of hypoxia (Time frame: Up to 28 days)

This endpoint will be considered to have been met when the patient has attained a score of 4 or lower on the 10-point ordinal scale of clinical status and either of a) or b), and c) is met:

a) Score is ≤ 4 on consecutive assessments over the next 5 days, if patient continues to remain in hospital (i.e., has not been discharged).

OR

b) Patient was discharged before five consecutive assessments (after reaching a score of 4).

AND

c) The patient has survived and has not been re-admitted to hospital for COVID-19 management through Day 28.

Secondary Efficacy Endpoints:

1. Time to discharge from hospital
2. Time (no. of days) from randomization to the earliest time when **ALL** COVID-19 associated symptoms (fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms – specifically diarrhoea and vomiting, shortness of breath or dyspnoea) are scored by the Investigator/trained study personnel as either '0=absent' or 'mild =1' in assessments over a period of 24 hours, when assessed from baseline to Day 28 or discharge from hospital (if discharge happens earlier than Day 28).
3. Percentage of patients with score of either '0=absent' or 'mild =1' over a period of 24 hours, for **ALL** COVID-19 associated symptoms, by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

Note*: Symptoms evaluated are fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically, diarrhoea and vomiting, shortness of breath or dyspnoea. The Investigator/trained study personnel will assess (including by enquiry with the patient, as*

necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical).

4. Time to improvement in **EACH** of the symptoms of fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically diarrhoea and vomiting, shortness of breath or dyspnoea by at least 1 grade over baseline.

Note*: Severity of symptoms will be evaluated once daily (preferably at or around the same clock time) on each day that the patient is admitted in the hospital. The Investigator/trained study personnel will assess (including by enquiry with the patient, as necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical). The improvement observed must be sustained at evaluations over a period of 24-hours, in order for this secondary efficacy endpoint to be reached.*

5. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 27 days after randomization (Day 28).

Note*: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge. This endpoint will be assessed only for those patients that were discharged before Day 28.*

6. Time (no. of days) to negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample, from randomization.
7. Percentage of patients showing negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample on Days 5, 10 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
8. Changes over time in patient's clinical status on the 10-point ordinal scale used in the SOLIDARITY trial by WHO
    a. Changes in the 10-point ordinal scale score from baseline until discharge
    b. Proportion of patients in whom clinical status score of 4 ('hospitalized, no oxygen required') or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
    c. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline)
    d. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

9. Changes over time in patient's clinical status on the 8-point ordinal scale
    a. Time (no. of days) from randomization to attain clinical status score of 4 or lower
    b. Proportion of patients in whom clinical status score of 4 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

c. Time (no. of days) from randomization to attain clinical status score of 3 or lower
d. Proportion of patients in whom clinical status score of 3 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
e. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline)
f. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

10. Changes over time in findings on chest X-ray
11. Changes over time in the National Early Warning Score-2 (NEWS)
12. Percentage of patients requiring, until Day 28 or discharge from hospital (if discharge happens earlier)
    a. Management in intensive care unit
    b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c. Invasive mechanical ventilation
13. Time (no. of days) from randomization to:
    a. Management in intensive care unit
    b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

14. Duration (no. of days) the patient requires:
    a. Management in intensive care unit
    b. Oxygen supplementation
    c. High Flow Nasal Oxygen
    d. Non-invasive mechanical ventilation
    e. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

15. Percentage of patients:
    a. dying from any cause
    b. dying from a COVID-19 associated complication

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

3.1.3.1.2 Safety endpoints

1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term)
2. Changes of parameters at each assessment during the study/follow-up period, compared to baseline for:
   - Vital signs: body temperature, heart rate, respiratory rate, systolic/diastolic blood pressure (BP) and oxygen saturation.
   - Clinical laboratory assessments: hematology, serum chemistry, urinalysis.
   - 12-lead ECG: Changes in heart rate, PR, QRS, QT and QT_cB intervals.

3.1.3.2 Stage II

3.1.3.2.1 Efficacy Endpoints:

1. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 59 days after randomization (Day 60).

   Note*: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge.*

2. Proportion of patients
   a. With disease worsening and requires:
      - Admission to ICU
      - High flow nasal oxygen
      - Non-invasive mechanical ventilation
      - Invasive mechanical ventilation

   AND

   b. Dying

until Day 60 (regardless of whether patients are discharged from hospital before Day 28 or not)

3.1.3.2.2 Safety Endpoints:

1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term)

Secondary endpoints may be modified, or additional secondary endpoints may be defined in the SAP.

3.1.4 Duration of the Study

The overall duration of the study from First-patient-First-Visit to Last-Patient-Last-Follow-up, including the recruitment period will be approximately 5 months.

3.1.5 Duration of Patient Participation

It is estimated that the total duration of the patient participation in the current study will not exceed 67 days.

Stage I: The duration of the patient participation in the Stage I of the study will not exceed 33 days, including a maximum of 3 days of screening period, a treatment period of 10 consecutive days and a study data collection period of 28 (+2) days.

Study treatments Favipiravir/Placebo will be administered over 10 consecutive days. If the patient is discharged before Day 10, the patient will be required to continue the remainder of the treatment course at home. However, the above-mentioned treatment period will be shortened if it is necessary to discontinue administration of the study drug due to AEs or other circumstances.

The patients will be discharged when the Principal Investigator or a medically qualified Sub Investigator judges that the patient is fit for discharge.

Day 10 will be considered as the EOT assessment.

1. If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 will be performed (details mentioned in Section 6.3.1.3).
2. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home (details mentioned in Section 6.3.1.4).
   c. On-site visit: If the patient is able to visit the hospital on Day 10, procedures for an unscheduled visit will be performed.

   OR

   d. At home: If the patient is unable to visit the hospital for the EOT, study nurse or phlebotomist will visit the patient at his/her residence to collect blood sample for safety assessments. A nasopharyngeal swab or oropharyngeal swab will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay based on Investigator's discretion for individual patients. A telephonic follow up will be performed to enquire on treatment emergent AEs experienced, concomitant medication and COVID-19 associated symptom for assessment of clinical relapse.

Day 28 will be considered the end of study visit.

If patient is discharged from the hospital before Day 28, the assessments mentioned in the end of study visit (Day 28) will be performed before the patient is discharged. After discharge, telephonic follow up will be performed on Day 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), Day 14, Day 21 and Day 28. The telephonic follow up will be as applicable for the individual patient, depending upon the actual day when (s)he is discharged. A 2-day window period is allowed for telephonic follow up.

In case the patient remains admitted in the hospital beyond Study Day 28, the end of study assessments will be performed for the patient on Day 28 (+2) days.

Stage II:

The duration of the patient participation in the Stage II of the study will not exceed 34 days. Two telephonic follow up assessments will be performed on Day 42 and Day 60. The patients will be followed up for AEs or for 'clinical relapse' of COVID 19. An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. A 2-day window period is allowed for telephonic follow up.

3.1.6 Completion or Discontinuation of the Clinical Study and Discontinuation of Administration of the Study Drug (Completion or Discontinuation by Individual Patient)

3.1.6.1 Study Discontinuation

3.1.6.1.1 Study discontinuation criteria

When a patient meets any of the following criteria, the Principal Investigator or a Sub-Investigator will discontinue the patient from the study.

a. The patient requests withdrawal from the clinical study
b. The patient died
c. The patient is lost to follow-up
d. The patient is otherwise deemed ineligible to continue in the study by the Principal Investigator or a Sub-Investigator (e.g adverse event or pregnancy)
e. Upon request by the CRO or Sponsor Medical Monitor (with appropriate justification)

3.1.6.1.2 Study discontinuation procedures

If the patient is discontinued from the clinical study based on criteria mentioned in Section 3.1.6.1.1, the Principal Investigator or a Sub-Investigator is to take appropriate action and conduct the assessments scheduled for Day 28 as specified in Section 6.3.1.5 before the patient is discharged.

The date of discontinuation from the clinical study, the reason for discontinuing the patient from clinical study, and other details are to be investigated. One of applicable reason for discontinuation from the list below will be entered in the eCRF.

When the patient misses the scheduled visits, the Principal Investigator or a Sub-Investigator will confirm the patient's condition using methods such as telephone calls and mail and encourage the patient to visit the site. A follow-up investigation regarding the subsequent course of symptoms, and the presence or absence of AEs, will also be conducted within the scope of the patient's cooperation, and the results will be recorded. When a follow-up investigation is impossible (because of a change of residence or other factors), such situations will also be recorded. A patient will be called 'lost to follow-up' if there is no response from the patient even after 3 documented telephone contact attempts on 3 different days.

3.1.6.2 Study Treatment Discontinuation

3.1.6.2.1 Study treatment discontinuation criteria

When a patient meets any of the following criteria, the Principal Investigator or a Sub-Investigator will discontinue administering the study drug to that patient.

a. The patient requests withdrawal from the clinical study
b. If the patient requests discontinuation of administration of the study drug
c. The patient died
d. The patient is lost to follow-up
e. If an AE occurs and the Principal Investigator or a medically qualified Sub-Investigator judges that continuing with the administration of the study drug would not be in the interest of patient's safety or well-being
f. If a patient experiences a serious adverse event assessed by Investigator and/or Medical Monitor to be reasonably causally related to the IMP (FPV/Placebo)
g. If a patient becomes pregnant while receiving IMP (FPV/Placebo)
h. If patient's serum uric acid or hepatic transaminases levels are assessed as Grade 3 severity by National Institutes of Health (NIH) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[23], at any timepoint during the treatment period
i. If a patient is otherwise deemed ineligible to continue in the study by the Principal Investigator or a Sub-Investigator
j. Upon request by the CRO or Sponsor Medical Monitor (with appropriate justification)

3.1.6.2.2 Study treatment discontinuation procedures

If the study drug administration is discontinued based on Section 3.1.6.2.1, the Principal Investigator or a Sub-Investigator need to take appropriate action. The date of, and reasons for, discontinuing administration of the study drug and the details (including actions taken after discontinuation of drug administration and the outcome, if the study drug was discontinued due to an AE) are to be investigated and captured in the eCRF. One of applicable reason for discontinuation from the list below will be entered in the eCRF.

Even if the administration of study treatment is stopped, patients will be encouraged to continue in the study and provide the applicable scheduled assessments, as specified in Section 6.3 until the patients are discharged, as long as they do not meet the criteria for study discontinuation.

4 STUDY POPULATION

The study population will consist of patients of either sex, 21 to 80 years of age, who test positive for SARS-CoV-2 by RT-PCR assay using a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate), have moderate to severe clinical presentations of COVID-19 and require hospitalization. An adequate number of patients will be screened to randomize 780 patients in a 1:1 ratio, so as to have approximately 390 patients in favipiravir + supportive care group and 390 patients in placebo + supportive care group.

4.1 Enrollment

Patients are eligible for enrolment into the study if they meet all the inclusion criteria and do not meet any of the exclusion criteria.

4.1.1 Inclusion Criteria

Patients must satisfy all the following criteria to be included in the study:

1. Male and female patients aged 21 to 80 years (both inclusive)
2. Patients who have tested positive for SARS-CoV-2 by RT-PCR assay using a respiratory tract sample (either nasopharyngeal swab OR oropharyngeal swab OR nasal aspirate OR tracheobronchial aspirate) collected within 72 hours prior to randomization
3. Patients should be hospitalized
4. Patients having moderate or severe COVID-19* with a score of > 4 on the 10-point ordinal scale of clinical status used by WHO in the SOLIDARITY trial, at baseline assessment [i.e., patients with blood oxygen saturation (SpO_2) <95% at rest on room air at sea level and requiring supplemental oxygen].

*Note: This includes patients clinically assigned as:

I. 'moderate' COVID-19
   a. symptoms which could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms or shortness of breath with exertion and/or clinical signs, such as respiratory rate ≥20 breaths per minute or heart rate ≥90 beats per minute

   AND

   b. blood oxygen saturation (SpO_2) of 94% at rest on room air at sea level

II. 'severe' COVID-19
   a. symptoms which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress and/or clinical signs, such as respiratory rate ≥30 per minute or heart rate ≥125 per minute

   AND

   b. blood oxygen saturation (SpO_2) ≤93% on room air at sea level or PaO_2/FiO_2 <300*

The above-mentioned definitions of COVID-19 severity are adapted from the FDA Guidance document COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry Final Document dated May 2020[24]

5. Female patients of childbearing potential*
    a. must have a negative serum pregnancy test at screening
    b. should not be lactating; and not planning to become pregnant/breast feed during the treatment period and for 7 days after the last dose of study medication.
    c. should commit to the use of **TWO** forms of study-acceptable contraception methods, including a barrier method (eg. diaphragm) along with one or more of the following methods of contraception for the duration of the treatment period and for 7 days after the last dose of study medication:
        i) hormonal methods [insertable, injectable, transdermal, or combination oral (estrogen+ progestin)] or
        ii) intrauterine contraceptive device

    Note: *Female patients who are sexually abstinent or whose male sexual partner has undergone vasectomy at least three months prior to the start of study treatment in the trial may be enrolled at the Investigator's discretion, provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. Patients must also agree to use **TWO** forms of study-acceptable contraception methods should they become sexually active during the treatment period and for 7 days after the last dose of study medication.*

*Note: *A female patient is considered of childbearing potential unless she is:*

a. postmenopausal for at least 12 months prior to study product administration, or
b. without a uterus and/or both ovaries or has been surgically sterilized (ie, tubal ligation or has a fallopian tube blocking coil) for at least 6 months prior to study product administration.

6. Male patients should agree to abstain from sexual intercourse or to use double-barrier contraception (e.g. condom with spermicide) for the duration of the treatment period in the study and for at least 7 days after receiving the last dose of study medication. Male patients should also avoid semen donation or providing semen for *in-vitro* fertilization during the above-mentioned duration.
7. Able and willing to provide informed consent
8. Able to understand the trial requirements and comply with trial medications and assessments in the opinion of the Investigator
9. Should not have received investigational treatment from participation in another clinical trial within 30 days prior to randomization in the current trial and agrees not to participate in other clinical studies during the entire study period

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be disqualified from entering the study:

1. Critically ill patients, defined as those who are candidates for endotracheal intubation and mechanical ventilation, Extracorporeal Membrane Oxygenation (ECMO), or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) and those with shock (defined by systolic BP <90 mm Hg, or diastolic BP <60 mm Hg or requiring vasopressors) or multi-organ dysfunction/failure at baseline

Note: *The above-mentioned definition of 'critically ill' COVID-19 patients is as defined in the FDA Guidance document COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry Final Document dated May 2020*[24]

2. Patients in whom the first onset of symptoms/signs suggestive of COVID-19 illness was observed >10 days earlier to the baseline assessment and randomization
3. Patients who have used interferon beta 1-a (IFN-β-1a) preparations or drugs with reported anti-viral action against SARS-CoV-2 (hydroxychloroquine sulfate, chloroquine phosphate, lopinavir-ritonavir combination drugs, ciclesonide, nafamostat mesylate, camostat mesylate) within 9 days after development of fever (≥37.5°C)

Note: The above-mentioned exclusion criterion is not applicable in case of patients with history of human immunodeficiency virus infection or infective hepatitis in whom use of anti-viral drugs or interferons are prescribed for treatment of the underlying condition and who are currently receiving one or more of these medications (as maintenance treatment) at the time of randomization. The infection episode in question is a relapse of, or reinfection with SARS-CoV-2

4. Patients suspected to have a complication of congestive cardiac failure based on Investigator's clinical judgement
5. Patients with moderate and severe hepatic dysfunction equivalent to Grade B and Grade C in the Child-Pugh classification respectively
6. Patients with ALT and AST levels > 5 times upper limit of normal (ULN) at screening evaluation
7. Patients with renal impairment requiring dialysis
8. Patients with serum uric acid higher than the ULN at screening evaluation
9. Patients with history of hereditary xanthinuria
10. Patients who have been diagnosed with xanthine urinary calculus
11. Patients with a history of gout or patients who are currently being treated for gout
12. Patients who are taking immunosuppressants
13. Patients who were administered Favipiravir in the past 30 days
14. Patients with known hypersensitivity reaction to Favipiravir

4.2 Removal of Patients from Therapy

4.2.1 Withdrawal Procedures

Patients who drop out will be asked about the reason(s) for their discontinuation and about the presence of any AEs. If a patient withdraws consent or is discontinued from the study before completion, every effort should be made to complete the assessments scheduled for Day 28. The PI must provide a written report on the appropriate eCRF page describing the reason for discontinuation. The primary reason for the discontinuation must also be recorded in patient's medical record along with eCRF. Adverse events should be followed up and all investigational products should be returned by the patient.

If the Principal Investigator or a medically qualified Sub-Investigator judges that the patient is fit for discharge, the assessment specified on Day 28 (Section 6.3.1.5) will be performed.

4.2.2 Patient Replacement

Patients who drop out from the study after enrolment will not be replaced.

4.2.3 Patient Re-screening Procedures

Not applicable.

5 TREATMENTS ADMINISTERED

5.1 Investigational Product(s)

The Investigator must ensure that the investigational medicinal products (IMP) will be used only in accordance with the protocol. The IMP will be manufactured complying with all required regulations. Sufficient quantities of the IMP will be supplied to the clinical study facility by the Sponsor. Batch numbers and expiration dates will be filed in the study documents when available. See the Table 1 below for ingredient list of each product.

Table 1: Investigational Medicinal Product Details

	Treatment	Comparator
Active Ingredient	Favipiravir (+ supportive care [a])	Placebo (+ supportive care [a])
Brand name	AVIGAN® (T-705)	Placebo
Dosage form	Tablets	Tablets
Strength	200 mg	Not Applicable
Dosage	1,800 mg BID on Day 1 + 800 mg BID for next 9 days (maximum) On Day 1, the second dose will be administered with at least a 4-hour interval from administration of the first dose.	9 tablets for BID on Day 1 + 4 tablets BID for next 9 days (maximum) On Day 1, the second dose will be administered with at least a 4-hour interval from administration of the first dose.
Frequency	Twice daily (morning and evening)	Twice daily (morning and evening)
Route of administration [b]	Oral	Oral
Supplied by [c]	FUJIFILM Toyama Chemical Co., Ltd. 4-1, Shimookui 2-chome, Toyama-shi, Toyama (Japan) - 930-8508	FUJIFILM Toyama Chemical Co., Ltd. 4-1, Shimookui 2-chome, Toyama-shi, Toyama (Japan) - 930-8508

[a] Patients in both the groups will receive supportive care, as appropriate. The Investigator may be guided by the current local guidance for COVID-19 management or by the institutional practice, in his/her choice supportive care for individual patients. The duration of supportive care will be based Investigator's judgement and as per individual patient's requirement.

COVID management guidelines of Kuwait: https://www.moh.gov.kw/UserRefs/Technical%20Dept/AdultC19.pdf

COVID management guidelines of United Arab Emirates: https://covidaba.com/wp-content/uploads/2020/06/National-Guidelines-for-Clinical-Management-and-Treatment-of-COVID-19-Version-4-1-June-2020.pdf

	Treatment	Comparator
[b] During the study period, in case of patient's clinical status deteriorates as to require invasive mechanical ventilation and patient is not able to take IP orally, IP can be powdered and administered as a suspension in water through Ryle's tube, if patient continues in the study as per Investigator's judgement. [c] Dr. Reddy Ltd. is an Authorised Licensee of Avigan (Favipiravir) with FUJIFILM.		

Note: *For the purpose of this trial, Investigational Medicinal Product/ IMP refers to favipiravir and matching placebo. The use of terms study medication / study drug / study treatment is non-standard and in certain contexts may refer to IMP and the medications prescribed as part of supportive care (including symptomatic treatments) for individual patients*.

5.1.1 Method of Assigning Patients to Treatments

A total of 780 eligible patients will be assigned randomly to one of two treatment groups in 1:1 ratio, so as to have approximately 390 patients in favipiravir + supportive care group and 390 patients in placebo + supportive care group. Details of the interim analysis and futility assessment are provided in the Statistical Analysis Plan (SAP) for the Interim Analysis.

Patients will be randomized to the favipiravir + supportive care group or placebo + supportive care group in a 1:1 ratio and a conditional stratification will be performed to include at least 15% of female patients, at least 30% of patients with either category of baseline disease severity (i.e., moderate and severe) and at least 30% of patients aged more than 50 years randomized in each of the treatment groups. If there is an impact on the patient recruitment rate due to limits enforced by the stratification of patients based on the category of baseline disease severity, a decision may be made to waive the stratification based on disease severity. The percentage of stratification may be adjusted according to the re-estimated sample size. The randomization schedule will be generated by CRO statistical team, in SAS, (version 9.4 or higher), according to CRO's standard operating procedures (SOPs).

All patients who sign an IRB/IEC approved informed consent form and authorization for the use and disclosure of protected health information will be assigned a unique patient identity code (PIC) consisting of 03-digit center/site code and three digits (004) patient specific code. The randomization code will be captured separately as an additional identity.

5.1.2 Method of Assessing Treatment Compliance

Compliance to study treatment will be assessed every day the treatment is administered.

If patient is in the hospital for 10 days, compliance will be assessed by supervised administration/ intake history of all supportive medications and the IMP dose (as per the prescribed regimen) and also by periodic IMP pill counts. Patients judged to be non-compliant will be counselled on the importance of daily intake of study medication, as prescribed. Patients who are repeatedly or severely non-compliant may be discontinued, at Investigator's discretion.

If the patient is discharged before Day 10, the patient will be required to continue the remainder of the IMP treatment course at home. The compliance for the medication taken at home will be evaluated based on the details in the patient diary. The patients will be counselled on the

importance of daily intake of study medication, as prescribed, and instructed to comply to instructions provided by study personnel on how and when to s(he) should take IMP (and any SoC medications) at the time of discharge.

The number of days the treatment was taken overall and the number of days the treatment was taken in compliance with the prescribed regimen (for supportive care) and the protocol (for IMP) will be assessed.

This information will be recorded in the eCRF.

5.1.3 Labeling and Packaging

It will be the Sponsor' responsibility to provide the IMP (favipiravir and placebo). Packaging and labelling will be done in accordance with the principle of Good Manufacturing Practice (GMP) and the applicable national and/or local regulatory requirements by the Sponsor/designated vendor.

The following general information will be provided on the clinical trial supply label:

- Protocol Number
- Product Name and Strength
- Brief Instructions for use
- Storage Instructions
- Batch or Lot #
- Expiry date
- Supplier of drug

Cautionary Statement – "For clinical trial purpose only"

Note: *Sponsor will not supply any medications that are prescribed as part of supportive care for the patients*.

5.1.4 Preparation

A pharmacist or designated site staff personnel, delegated by the Investigator, will dispense sufficient IMP to each individual patient.

When the patient is at the site, a delegated pharmacist/ staff personnel will maintain comprehensive and accurate records of the dispensing and dose administration for the IMP dispensed and dosed to each individual patient, date and time of dispensing of each dose of IMP, any IMP units that were dispensed but not dosed to patients, at each designated treatment administration timepoint. Details of medication administered as part of supportive care (medication name [brand and generic] dosage form, strength, dose, frequency, route of administration, time[s] of administrations) will also be recorded on a daily basis for each individual patient or Investigator decides no further supportive treatment is necessary for the individual patient, whichever is earlier.

(*This would also include any medication that might be used to treat one or more of the core symptoms of COVID-19 ([eg. analgesics or antipyretics]*)

If the patient is discharged before Day 10, the remaining treatment course will be continued at home. Delegated pharmacist/ staff personnel will dispense the study drug to each individual patient to be taken at home at the time of discharge. Delegated pharmacist/ staff personnel will maintain comprehensive and accurate records of the dispensing of IMP.

Note*: Any IMP units that was dispensed but not dosed to patients at a designated timepoint (for whatever reason) should not be re-dispensed in the trial. Instead such IMP units should be labelled appropriately and stored separately (from undispensed IMP) at the site, until return to Sponsor/ CRO/ designated vendor for destruction.*

5.1.5 Drug Accountability

When IMP shipment is received, the Investigator or designated site staff personnel (preferably a pharmacist) will check the amount and condition of the IMP (including temperature during transit), check drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be scanned by the site and shared with Sponsor/CRO/designated vendor. The original Form will be retained at the site. In addition, the Investigator or designee shall contact site clinical research associate (CRA) as soon as possible if there is a problem with the shipment.

An Investigator designated site staff personnel, preferably a pharmacist outside the isolation ward, will be responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the designated site staff (study pharmacist) will maintain accurate study drug accountability records throughout the course of the study. An electronic or manual drug accountability log for recording the receipt, dispensing and return of study drug will be maintained to document the amount of drug received, and the amount of drug used in the study. Study medication requests, receipts and dispensing records as well as study medication inventory forms will be examined and reconciled during and at the end of the study by the Sponsor/CRO/designated vendor personnel. The reconciliation can happen remotely whilst checking scanned documents and electronic documents and possibly with on-site monitoring visit, as appropriate.

If the patient is discharged before Day 10, the details of treatment regimen completed at home will captured in the patient diary and transcribed to the eCRF and IMP accountability log. If the patients continue to be on supportive care, the details of medication administered as part of supportive care will enquired during the telephonic follow up and also be recorded in the eCRF. The IMP accountability will also be checked using the empty blisters and unused IMP returned during the Day 10 visit.

All unused or partially used IMP must be returned to the Sponsor/designated vendor at the end of the study for destruction. Reconciliation between the amounts of IMP supplied, used and returned to the Sponsor/designated vendor must be performed and any discrepancies accounted for. This reconciliation will be logged on the study IMP reconciliation form, signed and dated. The study drug destroyed on site, if any and as appropriate, will be documented in the study files. A Drug

Accountability electronic or manual record will be provided for the study drug and should be maintained. The details for the Drug accountability will be included within the Clinical Monitoring Plan.

5.1.6 Blinding and Unblinding

This will be a double-blind randomized study. All investigators, patients, site personnel, Sponsor and CRO study team (except persons involved in preparation of the codes and the safety monitoring group and unblinded biostatistician involved in the interim analysis and to present data to DMC for closed sessions), will be blinded to the medication codes. The medication codes will not be available to the investigators, patients, site personnel, Sponsor and CRO study team (except persons involved in preparation of the codes and the safety monitoring group) until completion of the study and final data review (clinical database lock) except in case of an emergency.

A treating physician may request unblinding of study medication for an individual patient, if it is essential for the clinical management of the patient's health, or to ensure safety. If a treating physician requires unblinding of study medication on a patient, e.g. for management of a SAE, the investigators will be able to access this information via IWRS. The Sponsor and CRO medical monitor should be contacted immediately (preferably before unblinding takes place).

As back up to the IWRS, sealed envelopes containing the randomized study treatment (Favipiravir or Placebo) for each patient in the trial will be held in the secure custody (under 'lock and key') by a designated third party vendor, who would be accessible round the clock to the Investigator in case unblinding of treatment becomes necessary for individual patients (in the event of a medical emergency where knowledge of the treatment administered is essential).

The date and reason for unblinding has to be documented in the source document (medical record) and CRF, accordingly. The CRO medical monitor or designee is required to contact and inform the Sponsor regarding unblinding of the patient's treatment.

5.1.7 Dosing Schedule, Selection and Timing of dosing

Dosing schedule of study medications is mentioned under Section 5.1.

5.1.8 Instructions for Patients

Patients will be instructed as follows:

1. Patients have to take the medicines regularly, as per the treatment group they are assigned and the dosage regimen prescribed.
2. Patients have to comply with all other requirements of the study protocol.
3. Patients must try and adhere to any oral or written instructions provided by the Investigator on how the study treatment is to be taken.
4. Patients should inform the Investigator if they believe they are not able to tolerate study medication or develop severe side effects.
5. Patients must inform the Investigator or site staff if they develop any side effects or experience any symptoms after discharge and until Day 60.

6. If the patient is discharged before Day 10, the patients will be dispensed the remainder of the treatment course to be taken at home. Patients will be instructed to return the empty blister and unused IMP to the site.

5.1.9 Concomitant Medications

Concomitant treatment with other medications (other than the investigational products and prohibited medications) for the control of AEs or other conditions identified during screening (medical history) are permitted during the study.

The medications provided to treat the core symptoms of COVID-19 (e.g., analgesics or antipyretics) will be recorded daily, including name of medication, dose, unit, frequency, route and date(s) of administration in a separate module in the eCRF.

5.1.10 Drug-Drug Interaction

Favipiravir is not metabolized by cytochrome P-450 (CYP). It is metabolized by aldehyde oxidase (AO) and partially metabolized by xanthine oxidase (XO). Also, it inhibits AO and CYP2C8, but no CYP-induction has been observed.

Favipiravir may show drug-drug interactions with the following medications and caution must be exercised when co-administering favipiravir with these drugs.

1. **Pyrazinamide**

   Pyrazinamide additively promotes reabsorption of uric acid in the renal tubular, increasing blood uric acid levels.

2. **Repaglinide**

   Inhibition of CYP2C8 by favipiravir increases blood concentrations of repaglinide, increasing the risk of adverse reactions associated with repaglinide.

3. **Theophylline**

   Theophylline increases the blood concentration of favipiravir via XO, increasing the risk of adverse reactions associated with favipiravir.

4. **Famciclovir**

   Inhibition of AO by favipiravir may reduce famciclovir's efficacy.

5. **Sulindac**

   Inhibition of AO by favipiravir may reduce sulindac's efficacy.

Patients should not be administered or take acetaminiphen/paracetamol at doses of ≥ 3000 mg per day whilst receiving favipiravir.

5.1.11 **Prohibited concomitant drugs**

Use of the following medications is prohibited during the study period because they may affect the efficacy evaluation of the study drug.

1. Other drugs under development for treatment of COVID-19
2. Interferon alpha or beta preparations
3. Drugs with anti-viral effect (those that directly inhibit the virus grown and multiplication) are not permitted eg., zanamivir, oseltamivir, lopinavir/ritonavir, ribavirin, umifenovir, etc.
4. The following drugs whose anti-viral action against SARS-CoV-2 has been reported
    a. Hydroxychloroquine sulfate, chloroquine phosphate
    b. Ciclesonide
    c. Nafamostat mesylate
    d. Camostat mesylate

Exceptions will be made in case of patients with human immunodeficiency virus infection or infective hepatitis, in whom use of anti-viral drugs or interferons are prescribed for treatment of the underlying condition and these medications may be permitted.

5.1.12 Rescue Medications

Acute deterioration of disease conditions has been reported in some COVID-19 patients. In such cases, further treatment management will be as per the Principal Investigator's or a medically qualified Sub-Investigator's discretion and hospital protocol or practice for treating COVID-19.

Study treatment with the IMPs (Favipiravir/Placebo) will be permanently discontinued before starting treatment with convalescent plasma. In such cases, the Principal Investigator or a Sub-Investigator will record assessment specified in Section 6.3.1.5 in accordance with Section 3.1.6.2.2.

Study treatment with the IMPs can be continued with rescue treatment like remdesivir, and IL-6 pathway antagonists like tocilizumab. The details of rescue medication (medication, dose, route, start date, frequency of administration, end date etc.) will be captured.

The use of low molecular weight heparin, vasopressors, rehydration fluids is allowed as per patient's clinical status and local management guidelines/hospital practice.

6 STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 2. All study assessments (with the exception of telephonic follow up assessments on Study days 10, 14, 21, 28 (as applicable) and on Days 42 and 60) will be performed on an in-patient basis.

6.1 Stage I – Main Study

6.1.1 Visit 1 - Screening (Day -3 to Day -1)

An adequate number of patients will be screened to ensure enrolment of 780 patients into the study. The duration of screening period will be from Day -3 to Day -1. The Principal Investigator or his designee will explain the nature of the study, give full details and obtain a written informed consent from the patient prior to their participation in any study related procedures.

All inclusion/exclusion criteria will be assessed. Demographic characteristics including age, gender, nationality, race, height and weight will be assessed. A detailed medical history will be elicited regarding symptoms and prior medical/surgical therapies in the past 1 year prior to date of screening. Prior medications will include all medications that the patient has received in the past 1 month prior to date of screening and those which are still ongoing will be recorded at this visit. COVID-19 associated symptom severity assessment will be performed. A respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate) will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay. The patient's clinical severity will be assessed. The clinical status by WHO 10-point ordinal scale, 8-point ordinal scale and NEWS-2 score will be evaluated and recorded. Safety assessments [vital signs, complete physical examination, serum pregnancy test for women of childbearing potential, 12-lead ECG, clinical laboratory evaluations (hematology, serum biochemistry, urinalysis)] will be performed. Chest X-ray will be performed at this visit. AEs reported after signing the informed consent and before receiving the first dose of study drug will be recorded as pre-treatment AEs.

Although the duration of screening period is for a maximum of 3 days, once the results of the screening assessments are available and the patient successfully fulfills the eligibility criteria for the study, the next visit (Day 1) will be scheduled.

Screening investigations, including clinical laboratory evaluations (hematology, serum biochemistry, urinalysis, serum pregnancy test), chest X ray, ECG and RT-PCR assay for detection of SARS-CoV-2 RNA, performed within 72 hours prior to Randomization/Baseline Visit (Visit 2 /Day 1) can be considered for eligibility assessments. This sample/investigation might have been collected/performed as a part of routine work up at the hospital for detection/ evaluation of COVID -19 prior to patient having signed the informed consent for participation in the current trial. The sample/investigation collection/performed date and time will be considered for calculating the time gap between screening procedures and day of randomization. If any evaluations which are part of the screening procedures according to the protocol, have not been conducted previously, then those investigations would need to be performed for confirming the eligibility status.

However, if there is delay in randomizing the patient (i.e., time gap between sample collection / investigation and randomization is greater than 72 hours), then all the investigations mentioned under screening will be performed again to check the eligibility status.

If the patients do not meet the eligibility criteria, they will be considered as screen failures. The Investigator will maintain a log of all the patients screened for study participation and will record the reason(s) for screen failure.

6.1.2 Visit 2- Randomization/Baseline Visit [Day 1 (Pre-dose and post-dose)]

The patients who successfully pass the screening tests and meet the eligibility criteria will be enrolled in the study and will be randomized to one of the two treatment groups by IWRS.

The clinical status by WHO 10-point ordinal scale, 8-point ordinal scale, NEWS-2 score and COVID-19 associated symptom severity assessment (i.e., presence or absence, and if present, the severity of individual COVID-19 related symptoms) will be evaluated and recorded. To confirm patient eligibility for randomization (i.e., whether or not [s]he meets inclusion criterion no. 4), the patient's blood oxygen saturation (SpO_2) will be measured once at rest on room air (i.e., without O_2 supplementation). In case of patients with 'severe' (or suspicion of 'severe') COVID-19 disease at baseline, for whom it is not possible to record the SpO_2 on room air, the estimated SpO_2 / FiO_2 ratio (as a surrogate for PaO_2/ FiO_2 ratio) while receiving supplemental oxygen will be used for determining eligibility. Safety assessments (vital signs, partial physical examination, 12-lead ECG will be performed. A chest X-ray will be performed. Pre-treatment AEs will be recorded.

Patients will be administered the study medication as per the treatment group to which (s)he is allocated to by the IWRS system. On Day 1, the second dose will be administered with at least a 4-hour interval from administration of the first dose. Treatment emergent AEs and concomitant medication will be recorded.

The status of each individual patient with respect to admission to the Intensive care unit (ICU) of the hospital (with date of admission), supplemental oxygen (standard or high flow) and mechanical ventilation will be collected.

The investigations (chest X ray and 12 lead ECG) mentioned in Visit 2 - Randomization/Baseline Visit can be waived off if Randomization/Baseline Visit (Visit 2) is being performed on the same day of screening or if the investigations were performed within 72 hours before Randomization/Baseline Visit.

6.1.3 Study Period (Day 2 to Day 27)

The study period will be for a duration of 28 consecutive days. The patients will be discharged when the Principal Investigator or a medically qualified Sub Investigator judges that the patient is fit for discharge. All assessments mentioned in Section 6.3.1.5 will be completed before the patient is discharged from the hospital.

The below assessments will be performed as applicable until discharge or Day 28, whichever is earlier.

The clinical status by WHO 10-point ordinal scale and 8-point ordinal scale, NEWS-2 score and COVID-19 associated symptom severity assessment will be evaluated and recorded every day during the study period (until discharge or Day 28, whichever is earlier). Vital signs will be assessed, partial physical examination will be performed every day (until discharge or Day 28, whichever is earlier).

A respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR on Day 5, Day 10 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints).

Safety assessments [clinical laboratory evaluations (hematology, serum biochemistry, urinalysis)] and 12-lead ECG will be performed on Day 4, Day 7, Day 10, Day 14 and Day 21 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints). Chest X-ray will be performed on Day 4, Day 7, Day 10 and Day 14 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints).

Treatment emergent AEs and concomitant medication will be recorded every day.

The status of each individual patient with respect to admission to the Intensive care unit (ICU) of the hospital (with dates of admission and discharge), details of supplemental oxygen received (standard and/or high flow) and details of any mechanical ventilation will be collected every day during the study period (until discharge or Day 28, whichever is earlier).

In case the patient is hospitalized until Day 10, the IMP (Favipiravir/Placebo) will be dispensed for each individual patient in the morning and evening on every study day for 10 days. Patient will take/ be administered the dispensed IMP and treatment compliance will be assessed in the morning and evening on every study day for 10 consecutive days.

If the patient is discharged before Day 10, the required IMP (Favipiravir/Placebo) to complete the remainder of the IMP treatment course will be dispensed to patient at the time of discharge. The patient will be required to continue the remainder of the IMP treatment course at home. The compliance will be evaluated based on details recorded in the patient diary.

End of Treatment (EOT) assessment:

The EOT assessment will be performed on Day 10 (+2 days). A window period of 2 days is applicable only if the patient is discharged before Day 10.

1. If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 will be performed (details mentioned in Section 6.3.1.3).
2. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home.
    a. On-site visit: If the patient is able to visit the hospital on Day 10, procedures for an unscheduled visit will be performed. Empty blister packs and /or unused IMP will be collected.

OR

b. At home: If the patient is unable to visit the hospital for the EOT, study nurse or phlebotomist will visit the patient at his/her residence to collect blood sample for safety assessments. A nasopharyngeal swab or oropharyngeal swab will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay based on Investigator's discretion for individual patients. Empty blister packs and /or unused IMP will be collected. A telephonic follow up will be performed to enquire on treatment emergent AEs experienced, concomitant medication and COVID-19 associated symptom for assessment of clinical relapse.

6.1.4 End of Study-Day 28 (+2 days) or discharge or study discontinuation whichever is earlier

The end of study assessments will be performed on Day 28 or earlier if the patient is discontinued from study or is considered fit for discharge earlier. If the Principal Investigator or a Sub-Investigator judges that the patient is fit for discharge, patient should undergo assessments scheduled for End of Study – Day 28 (+2 days) visit.

The clinical status by WHO 10-point ordinal scale and 8-point ordinal scale, NEWS-2 score and COVID-19 associated symptom severity assessment will be evaluated. Vital signs will be assessed, and partial physical examination will be performed. A respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay. Safety assessments [serum pregnancy test for female patients of child-bearing potential, 12-Lead ECG, clinical laboratory evaluations (hematology, serum biochemistry, urinalysis)] will be performed. A chest X-ray will be performed. Treatment emergent AEs and concomitant medication will be recorded.

The status of each individual patient with respect to admission to the Intensive care unit (ICU) of the hospital (with date of discharge, if discharged from ICU), details of supplemental oxygen received (standard and/or high flow), and details of any mechanical ventilation will be collected.

Note: *Principal Investigator or a medically qualified Sub Investigator may discharge a patient if (s)he considers the patient to be clinically fit and eligible (per applicable National Regulations/ Hospital practice) for discharge. After discharge, a telephonic follow up will be performed on Day 10, Day 14, Day 21 and Day 28 (as applicable for the individual patient, depending on the actual day of his/her discharge).*

6.1.5 Telephonic follow up on Day 10, Day 14, Day 21 and Day 28, as applicable for the individual patient

For patients who are discharged before Day 28, a telephonic follow up assessment will be performed on Day 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), Day 14, Day 21 and Day 28 ***as applicable***

for the individual patient (window period for telephonic follow up is +2 days from scheduled day of follow up). The patients will be followed-up for:

a. safety reasons (eg. follow-up on AEs),

b. to report a clinical relapse of COVID-19 (the patient will be asked if they have had any of the symptoms of COVID 19 after they were discharged).

An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. Details of concomitant medication will be recorded. The assessments to be performed at an unscheduled visit are mentioned in Section 6.3.2.3 and Table 2.

6.2 Stage II – Extended Follow Up

6.2.1 Telephonic Follow Up on Day 42 (+2 days) and Day 60 (+2 days)

During the extended follow up period, the patients will be followed up for AEs or for 'clinical relapse' of COVID 19. An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. Details of concomitant medication will be recorded. The assessments to be performed at an unscheduled visit are mentioned in Section 6.3.2.3 and Table 2.

During the telephonic follow up, the patients will be followed-up for the following reasons:

a) safety reasons (eg. follow-up on AEs),

b) to report a clinical relapse of COVID-19 (the patient will be asked if they have had any of the symptoms of COVID-19 after they were discharged).

6.3 Measurements and Evaluations

6.3.1 Stage I – Main Study

6.3.1.1 Visit 1: Screening Visit (Day -3 to Day -1)

- Written informed consent.
- Demographic data (age, gender, nationality, race, height and weight)
- Medical history
- Collection of respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay)*
- Serum Pregnancy Test (only for female patients of childbearing potential)*
- Complete physical examination

- Vital signs (SpO_2, body temperature, systolic BP, diastolic BP, pulse rate, and respiratory rate)
- Clinical Status by WHO 10-point ordinal scale
- Clinical Status by 8-point ordinal scale
- NEWS-2 score
- Severity of COVID-19 associated symptoms
- Prior medications
- Chest X-ray*
- 12-Lead ECG*
- Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis)*
- Pre-treatment AEs
- Apply Inclusion and Exclusion Criteria

**Note: Screening investigations, including clinical laboratory evaluations (hematology, serum biochemistry, urinalysis, serum pregnancy test), chest X ray, ECG and RT-PCR assay for detection of SARS-CoV-2 RNA, performed within 72 hours prior to Randomization Day (Day 1) can be considered for eligibility assessments. Refer to Section 6.3.1.1 for further details.*

6.3.1.2 Visit 2: Randomization/Baseline Visit (Day 1)

- Clinical Status by 10-point ordinal scale
- Clinical Status by 8-point ordinal scale
- NEWS-2 score
- Blood oxygen saturation (SpO_2) measurement at rest on room air (i.e., without O_2 supplementation) or alternatively SpO_2/ FiO_2 will be estimated if the patient is on supplemental oxygen, for confirmation of patient eligibility
- Presence/ Absence, and if present, then COVID-19 associated symptom severity assessment
- ICU admission status, supplemental oxygen and mechanical ventilation details
- Partial physical examination
- Vital signs
- Chest X-ray*
- 12 Lead ECG*

- Pre-treatment AEs
- Randomization of patients
- Dosing and compliance assessment
- Treatment emergent AEs
- Concomitant medication

**Note: The investigations (chest X ray and 12 lead ECG) mentioned in Visit 2 - Randomization/Baseline Visit can be waived off if Randomization/Baseline Visit (Visit 2) is being performed on the same day of screening or if the investigations were performed within 72 hours before Randomization/Baseline Visit.*

6.3.1.3 Study period: (Day 2 to Day 27 or discharge, whichever is earlier)

- Clinical Status by 10-point ordinal scale (assessment to be performed once daily on each study day until Day 27 or discharge)
- Clinical Status by 8-point ordinal scale (assessment to be performed once daily on each study day until Day 27 or discharge)
- NEWS-2 score (assessment to be performed once daily on each study day until Day 27 or discharge)
- COVID-19 associated symptom severity assessment (assessment to be performed once daily on each study day until Day 27 or discharge)
- ICU admission status, supplemental oxygen (standard and/or high flow) and mechanical ventilation details (to be collected once daily on each study day until Day 27 or discharge)
- Partial physical examination
- Vital signs
- Treatment emergent AEs
- Concomitant medication
- Dosing (two times in a day) of IMP and assessment of treatment compliance, on each study day until Day 10 or discharge. (Note: *If the patient is discharged before Day 10, the patient will be required to continue the remainder of the IMP treatment course at home. The compliance will be evaluated based on the details in the patient diary)*
- Collection of a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay) on Day 5 and Day 10 or discharge

(if discharge happens earlier than one or more of the above-mentioned assessment timepoints)

- Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis) on Day 4, Day 7, Day 10, Day 14 and Day 21 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints)
- 12 Lead ECG on Day 4, Day 7, Day 10, Day 14 and Day 21 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints)
- Chest X-ray on Day 4, Day 7, Day 10 and Day 14 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints)

6.3.1.4 End of treatment assessment [Day 10 (+2 days)]

1. If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 mentioned in Section 6.3.1.3 will be performed.
2. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home.

   a. On-site visit:

   If the patient is able to visit the hospital on Day 10, procedures for an unscheduled visit will be performed.

   - COVID-19 associated symptom severity assessment
   - Collection of a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay)*
   - Partial physical examination*
   - Vital signs*
   - Chest X-ray*
   - 12 Lead ECG*
   - Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis)*
   - Treatment emergent AEs
   - Concomitant medication*
   - ICU admission status, supplemental oxygen (standard and/or high flow) and mechanical ventilation details*
   - Return of empty blister packs and /or unused IMP

** Assessments maybe performed at Investigator's discretion for individual patients for evaluation of patient safety or follow up of adverse events.*

OR

b. At home:

If the patient is unable to visit the hospital for the EOT, the below procedures will be performed.

- Study nurse or phlebotomist will visit the patient at his/her residence
- Blood sample collection for clinical laboratory assessments (haematology, serum biochemistry)
- A nasopharyngeal swab or oropharyngeal swab will be collected from the patient and sent for detection (qualitative) of SARS-CoV-2 RNA by RT-PCR assay based on Investigator's discretion for individual patients
- Collection of empty blister packs and /or unused IMP
- A telephonic follow up will be performed to assess the below
    - Treatment emergent AEs
    - COVID-19 associated symptom enquiry for assessment of clinical relapse
    - Concomitant medication

6.3.1.5 Visit 3: End of Study-Day 28 (+2 days) or discharge or study discontinuation whichever is earlier

- Serum Pregnancy Test (only for female patients of childbearing potential)
- Clinical Status by 10-point ordinal scale
- Clinical Status by 8-point ordinal scale
- NEWS-2 score
- COVID-19 associated symptom severity assessment
- ICU admission status, supplemental oxygen (standard and/or high flow) and mechanical ventilation details
- Collection of a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay)
- Partial physical examination
- Vital signs
- Chest X-ray

- 12 Lead ECG
- Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis)
- Treatment emergent AEs
- Concomitant medication

6.3.1.6 Telephonic follow up on Day 10, Day 14, Day 21 and Day 28, as applicable for the individual patient

For patients who are discharged before Day 28, a telephonic follow up assessment will be performed on Days 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), 14, 21 and 28 ***as applicable for the individual patient*** (window period for telephonic follow up is +2 days from scheduled day of follow up).

- Treatment emergent AEs
- COVID-19 associated symptom enquiry for assessment of clinical relapse
- Concomitant medication

6.3.1.7 Unscheduled Visit: If further assessment is found to be necessary on Telephonic Follow up

- COVID-19 associated symptom severity assessment
- Collection of a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay)*
- Partial physical examination*
- Vital signs*
- Chest X-ray*
- 12 Lead ECG*
- Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis)*
- Treatment emergent AEs
- Concomitant medication*
- ICU admission status, supplemental oxygen (standard and/or high flow) and mechanical ventilation details*

* *Assessments maybe performed at Investigator's discretion for individual patients for evaluation of patient safety or follow up of adverse events.*

6.3.2 Stage II - Extended Follow Up

6.3.2.1 Telephonic follow up on Day 42 (+2 days)

- Treatment emergent AEs
- COVID-19 associated symptom enquiry for assessment of clinical relapse
- Concomitant medication

6.3.2.2 Telephonic follow up on Day 60 (+2 days)

- Treatment emergent AEs
- COVID-19 associated symptom enquiry for assessment of clinical relapse
- Concomitant medication

6.3.2.3 Unscheduled Visit: If further assessment is found to be necessary on Telephonic Follow up

- COVID-19 associated symptom severity assessment
- Collection of a respiratory tract sample (nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate or bronchial lavage) for detection (qualitative) of SARS-CoV-2 (by RT-PCR assay)*
- Partial physical examination*
- Vital signs*
- Chest X-ray*
- 12 Lead ECG*
- Clinical Laboratory assessments (haematology, serum biochemistry and urinalysis)*
- Treatment emergent AEs
- Concomitant medication*
- ICU admission status, supplemental oxygen (standard and/or high flow) and mechanical ventilation details*

* *Assessments maybe performed at Investigator's discretion for individual patients for evaluation of patient safety or follow up of adverse events.*

Table 2: Study Assessment Schedule

Assessments	STAGE I – Main Study[1]												Stage II – Extended Follow Up[2]		Unscheduled Visit
	Screening[3]	Randomization (Baseline)[4]						EOT[5]			End of Study	Data base Lock			
Day	-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
Window Period	N/A	0	0	N/A	N/A	0	0	0	0/+2	0/+2	0/+2	0/+2		+2	+2	

[1] Stage I of the study includes a treatment period of 10 consecutive days and a study data collection period until Day 28. The treatment period may be shortened if it is necessary to discontinue administration of the study drug due to AEs or other circumstances. Principal Investigator or a medically qualified Sub Investigator may discharge a patient, if (s)he considers the patient to be clinically fit and eligible (per applicable National Regulations/ Hospital practice) for discharge. After discharge, telephonic follow up will be performed on Days 10, 14, 21 and 28 (as applicable for the individual patient, depending on actual day of discharge). For patients who remain admitted in the hospital until Study Day 28, the End of Study assessments will be performed on Day 28. A window period of 2 days will be allowed for the telephonic follow ups.

[2] During the Stage II of the study, the patients will be followed up for AEs or for 'clinical relapse' of COVID 19, on Day 42 and Day 60. An additional visit to the hospital (for further assessment) may be scheduled for such patients, if required. A window period of 2 days will be allowed for the telephonic follow ups.

[3] Screening investigations, including clinical laboratory evaluations (hematology, serum biochemistry, urinalysis, serum pregnancy test), chest X ray, ECG and RT-PCR assay for detection of SARS-CoV-2 RNA, performed within 72 hours prior to Randomization Day (Day 1) can be considered for eligibility assessments. Refer to Section 6.1.1 for further details.

[4] The investigations (chest X ray and 12 lead ECG) mentioned in Visit 2 - Randomization/Baseline Visit can be waived off if Randomization/Baseline Visit (Visit 2) is being performed on the same day of screening or if the investigations were performed within 72 hours before Randomization/Baseline Visit. Refer to Section 6.1.2 for further details

[5] The EOT assessment will be performed on Day 10 (+2 days). If the patient remains in the hospital until Day 10, the EOT will be performed at the site and all the scheduled assessments for Day 10 will be performed. If the patient is discharged before Day 10, the EOT can be performed either as an onsite visit or will be performed at the patient's home (refer to Section 6.3.1.4).

Assessments	STAGE I – Main Study[1]												Data base Lock	Stage II – Extended Follow Up[2]		Unscheduled Visit
	Screening[3]	Randomization (Baseline)[4]							EOT[5]			End of Study				
Day	-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
(Days)[6]													[redacted]			
Obtaining informed consent	●															
Baseline patient characteristics[7]	●															
Medical history	●	●														
Pregnancy test[8]	●											●				
Assessment of inclusion/exclusion criteria	●	●														
Measurement of Blood Oxygen Saturation at rest on room air (without oxygen		●														

[6] If patient is discharged before Day 28, a telephonic follow up assessment will be performed on Days 10 (applicable only for patients who are discharged earlier than Day 10 and if patients are unable to visit the site for EOT on Day 10), 14, 21 and 28 (as applicable for the individual patient). A window period for telephonic follow up will be +2 days from scheduled day of follow up.

[7] Includes age, gender, nationality, race, height and weight.

[8] Pregnancy test only for female subjects of childbearing potential. Serum pregnancy will be performed at Screening and End of Study (Day 28 or discharge, whichever is earlier).

Assessments		STAGE I – Main Study[1]											Data base Lock	Stage II – Extended Follow Up[2]		Unscheduled Visit
		Screening[3]	Randomization (Baseline)[4]						EOT[5]			End of Study				
Day		-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
supplementation) or SpO_2/ FiO_2 estimated on supplemental oxygen for confirmation of eligibility																	
Randomization			●														
Dosing and compliance status[9]	Morning			●		●											
	Evening			●		●											
COVID-19 associated symptom severity assessment[10]		●	●		●											●[11]	

[9] IMPs will be administered twice daily (in the morning and evening) from Day 1 to Day 10. If the patient is discharged before Day 10, the patient will be required to continue the remainder of the IMP treatment course at home. Dosing compliance status will be checked for 10 days. Compliance will be assessed daily assessment if the patient is the hospital or based on the details in the patient diary and the empty blister packs and / unused IMP in case of patients discharged before study Day 10.

[10] COVID-19 associated symptom severity assessment will be done on all days (Day 1 up to Day 28 or until discharge, whichever is earlier).

[11] COVID-19 associated symptom severity assessment will be done and recorded in case of patients in whom the follow up (unscheduled) visit was necessitated for reporting of clinical relapse

Assessments	STAGE I – Main Study[1]												Data base Lock	Stage II – Extended Follow Up[2]		Unscheduled Visit
	Screening[3]	Randomization (Baseline)[4]							EOT[5]			End of Study				
Day	-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
RT-PCR (qualitative)[12]	●						●		●			●				●
Clinical Status by 10-point ordinal scale (SOLIDARITY SCALE)[13]	●	●		●												
Clinical Status by 8-point ordinal scale [14]	●	●		●												
NEWS-2 score[15]	●	●		●												

[12] Qualitative RT-PCR assay for detection of SARS-CoV-2 RNA in a respiratory tract sample will be performed at Screening, on Day 5, Day 10 and Day 28, or discharge (i.e., if the patient happens to be discharged before one or more of the mentioned timepoints, then the sample will be collected at discharge). No sample will be collected from patients at any timepoint after discharge, EXCEPT if individual patients are scheduled for an additional (unscheduled) visit, either to follow up on an AE or to report a possible 'clinical relapse' of COVID-19 or based on Investigator's discretion during the Day 10 - home visit. A sample for RT-PCR will be collected during the unscheduled visit in such cases.

[13] Clinical Status by 10-point ordinal scale (SOLIDARITY SCALE) will be assessed once daily at screening, on all days (Day 1 up to Day 28 or until discharge, whichever is earlier).

[14] Clinical Status by 8-point ordinal scale will be assessed once daily at screening, on all days (Day 1 up to Day 28 or until discharge, whichever is earlier).

[15] NEWS-2 score will be assessed once daily on all days (Day 1 up to Day 28 or until discharge, whichever is earlier).

Assessments	STAGE I – Main Study[1]											Data base Lock	Stage II – Extended Follow Up[2]		Unscheduled Visit
	Screening[3]	Randomization (Baseline)[4]							EOT[5]		End of Study				
Day	-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
Clinical Laboratory Evaluations (Hematology, Serum Biochemistry, Urinalysis)	●					●		●	●	●	●	●				●
Chest X-ray	●	●				●		●	●	●		●				●
12-lead ECG	●	●				●		●	●	●	●	●				●
Vital signs[16]	●	●		●					●							●
Complete Physical Examination[17]	●															
Partial Physical Examination[18]		●		●												●
Hospitalization period[19]	●	●	●	●												
Prior Medications	●															

[16] Vital signs will be assessed on all days (Day 1 to Day 28 or until discharge, whichever is earlier). Includes SpO_2, body temperature (axillary), systolic BP, diastolic BP, pulse rate, and respiratory rate. Vital signs will be measured at pre-dose only on Day 1 and at least twice, morning and afternoon, daily from Day 2 to Day 28 or until discharge, whichever is earlier.

[17] Includes general appearance, skin, head, neck, ENT, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes

[18] Includes general appearance, ENT, heart, lungs and lymph nodes.

[19] The patients will be discharged when the Principal Investigator or a medically qualified Sub Investigator judges that the patient is fit for discharge. If the patient is discharged before Day 10, the remaining treatment course will be continued at home.

Assessments	STAGE I – Main Study[1]												Data base Lock	Stage II – Extended Follow Up[2]		Unscheduled Visit
	Screening[3]	Randomization (Baseline)[4]							EOT[5]			End of Study				
Day	-3 to -1 (72 hrs)	1 (Pre-dose)	1 (Post-dose)	On all days until discharge	On all days until Day 10	4	5	7	10	14	21	28 or discharge		42	60	
Concomitant Medications		●	●	●						●	●	●		●	●	●
Pre-treatment Adverse Events	●	●														
Treatment Emergent Adverse events			●	●						●	●	●		●	●	●[20]
ICU admission status, supplemental oxygen and mechanical ventilation details [21]			●	●												●
Clinical relapse[22]									●	●	●	●		●	●	

[20] Treatment Emergent Adverse Events will be assessed and recorded in case of patients in whom the follow up (unscheduled) visit was necessitated for follow up of an adverse event/reporting of a new Treatment Emergent Adverse Event after discharge.

[21] Will be evaluated on all days during the study period (until Day 28 or discharge, whichever is earlier) and also may be evaluated when patient retiurns for additional visit

[22] Patients will be asked if they experience any COVID-19 symptoms after discharge.

6.4 Protocol Deviations

The Investigator shall conduct the study in compliance with the study protocol. Waivers to deviate from the protocol will not be granted neither by the Sponsor nor by the Medical Lead of the CRO acting on behalf of the Sponsor. All protocol deviations occurring will be tracked in the clinical database and classified as major or minor protocol deviations.

7 EVALUATION CRITERIA

7.1 Efficacy Evaluation Criteria

7.1.1 Stage I

7.1.1.1 Evaluation Criteria for the Primary Endpoint

Primary Efficacy Endpoint:

1. Time to resolution of hypoxia (Time frame: Up to 28 days)

This endpoint will be considered to have been met when the patient has attained a score of 4 or lower on the 10-point ordinal scale of clinical status and either of a) or b), and c) is met:

a) Score is ≤ 4 on consecutive assessments over the next 5 days, if patient continues to remain in hospital (i.e., has not been discharged).

OR

b) Patient was discharged before five consecutive assessments (after reaching a score of 4).

AND

c) The patient has survived and has not been re-admitted to hospital for COVID-19 management through Day 28.

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7.1.1.2 Evaluation Criteria for the Secondary Endpoints

1. Time to discharge from hospital.
2. Time (no. of days) from randomization to the earliest time when **ALL** COVID-19 associated symptoms (fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms – specifically diarrhoea and vomiting, shortness of breath or dyspnoea) are scored by the Investigator/trained study personnel as either '0=absent' or 'mild =1' in assessments over a period of 24 hours, when assessed from baseline to Day 28 or discharge from hospital (if discharge happens earlier than Day 28).
3. Percentage of patients with score of either '0=absent' or 'mild =1' over a period of 24 hours, for **ALL** COVID-19 associated symptoms, by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
   Note*: Symptoms evaluated are fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically, diarrhoea and vomiting, shortness of breath or dyspnoea. The Investigator/trained study personnel will assess (including by enquiry with the patient, as necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical).*
4. Time to improvement in **EACH** of the symptoms of fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms- specifically diarrhoea and vomiting, shortness of breath or dyspnoea by at least 1 grade over baseline.

Note: Severity of symptoms will be evaluated once daily (preferably at or around the same clock time) on each day that the patient is admitted in the hospital. The Investigator/trained study personnel will assess (including by enquiry with the patient, as necessary) and score the severity of each COVID-19 associated symptom on a 5-point Likert-type scale (0= absent, 1= mild, 2=moderate, 3= severe, 4= very severe/critical). The improvement observed must be sustained at evaluations over a period of 24hours, in order for this secondary efficacy endpoint to be reached.

5. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 27 days after the day of randomization (Day 28).

Note: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge. This endpoint will be assessed only for those patients that were discharged before Day 28.

6. Time (no. of days) to negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample, from randomization
7. Percentage of patients showing negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory sample on Days 5, 10 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned time points)

Patients who have tested positive for SARS-CoV-2 on a RT-PCR assay will be enrolled in this study. The RT-PCR assay will be evaluated at screening, on Day 5, Day 10, and Day 28, or discharge (i.e., if the patient happens to be discharged before one or more of the mentioned timepoints, then the sample will be collected at discharge). No sample will be collected from patients at any timepoint after discharge, EXCEPT if individual patients are scheduled for an additional (unscheduled) visit, either to follow up on an AE or to report a possible 'clinical relapse' of COVID-19. A sample will be collected during the unscheduled visit in such cases.

8. Changes over time in patient's clinical status on the 10-point ordinal scale used in the SOLIDARITY trial by WHO
    a. Changes in the 10-point ordinal scale score from baseline until discharge
    b. Proportion of patients in whom clinical status score of 4 ('hospitalized, no oxygen required') or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
    c. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline)
    d. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

For the SOLIDARITY trial, a COVID-19 specific ordinal scale has been developed by WHO to assess the clinical status of the patient at baseline and to monitor over time the changes of the clinical status. Table 3 shows the scores assigned on an ordinal level to each status.

Table 3: The 10-point ordinal scale used in the WHO SOLIDARITY trial for assessment of patients' clinical status

Score	Description
0	Uninfected, no viral RNA
1	Asymptomatic, viral RNA detected
2	Symptomatic, independent
3	Symptomatic, Assistance Needed
4	Hospitalized: no oxygen therapy
5	Hospitalized, on oxygen
6	Hospitalized, Oxygen by NIV or high-flow
7	Mechanical ventilation, p/f>150 or s/f >200
8	Mechanical ventilation, p/f<150 or s/f<200 OR vasopressors
9	Mechanical ventilation, p/f<150 AND vasopressors, dialysis, or ECMO
10	Death

Note: *Score categories 3,2,1 and 0 apply even if the patient continues to remain in the hospital.*

9. Changes over time in patient's clinical status on the 8-point ordinal scale
    a. Time (no. of days) from randomization to attain clinical status score of 4 or lower
    b. Proportion of patients in whom clinical status score of 4 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
    c. Time (no. of days) from randomization to attain clinical status score of 3 or lower
    d. Proportion of patients in whom clinical status score of 3 or lower has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)
    e. Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline)
    f. Proportion of patients for whom clinical status score improvement by 1 and by 2 points has been attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints)

The 8-point ordinal scale of Clinical Status is adapted from the one used in the Adaptive COVID-19 Treatment Trial- 1 (ACTT-1) that formed basis of approval for Veklury® (Remdesivir or RDV) in moderate to severe COVID-19 in the United States. Table 4 shows the scores assigned on an ordinal level to each status.

Table 4: Modified 8-point ordinal scale of Clinical Status

Category Score	Clinical Status Category Description
1	Not hospitalized, no limitation of activities
2	Not hospitalized, limitation of activities
3	Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care* (*used if hospitalization was extended for infection-control reasons*)
4	Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19– related or other medical conditions)
5	Hospitalized, requiring any supplemental oxygen
6	Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices
7	Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8	Death
*Patients receiving vitamins, minerals or other supplements, symptomatic treatments (e.g. analgesics, antitussives), treatments for non-COVID-19 related ailments and antibiotics or treatment for secondary infections will not be considered as requiring 'ongoing medical care'	

10. Changes over time in findings on chest X-ray

Chest X-ray will be performed at screening, on Days 1 (pre-dose), 4, 7, 10, 14, and Day 28 or discharge or Study Discontinuation, whichever is earlier.

The Principal Investigator or a Sub-Investigator will assess improvement in chest images.

Radiographic Assessment of Lung Edema (RALE) score will be used to evaluate the changes in the chest X-ray. Each radiograph will be divided into quadrants, defined vertically by the vertebral column and horizontally by the first branch of the left main bronchus. Each quadrant will be assigned a consolidation score from 0–4 to quantify the extent of alveolar opacities, based on the percentage of the quadrant with opacification and a density score from 1–3 to quantify the overall density of alveolar opacities, unless the consolidation score for that quadrant was 0. The density score (1=hazy, 2=moderate, 3=dense) allows for more quantitative assessment of the density of opacification by quadrant. To calculate the final RALE score, the product of the consolidation and density score for each quadrant will be summed for a final RALE score ranging from 0 (no infiltrates) to 48 (dense consolidation in >75% of each quadrant).[25]

Table 5: Consolidation and density scoring in the Radiographic Assessment of Lung Edema (RALE) score

Consolidation[a]	
Consolidation score	**Extent of alveolar opacities**
0	None
1	<25%
2	25 to 50%

3	50 to 75%
4	> 75%
Density[b]	
Density score	**Density of alveolar opacities**
1	Hazy
2	Moderate
3	Dense
Final RALE Score	
Right Lung	**Left Lung**
Upper Quadrant Consolidation score × Density score = **Q1 score**	Upper Quadrant Consolidation score × Density score = **Q3 score**
Lower Quadrant Consolidation score × Density score = **Q2 score**	Lower Quadrant Consolidation score × Density score = **Q4 score**
Total RALE = Q1 + Q2 + Q3 + Q4	
[a] Consolidation is scored for each quadrant b Density is scored for each quadrant that has a consolidation score ≥1	

11. Changes over time in the National Early Warning Score-2 (NEWS) on

NEWS-2 is the latest version of the National Early Warning Score (NEWS), first produced in 2012 and updated in December 2017, which advocates a system to standardise the assessment and response to acute illness. In this second edition, NEWS has received further improvements to become the early warning system for identifying acutely ill patients – including those with sepsis – in hospitals.

Table 6 shows the NEWS-2 chart in which the specific variables will be scored.

The NEWS-2 is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

1. Respiration rate
2. Oxygen saturation
3. Systolic blood pressure
4. Pulse rate
5. Level of consciousness or new confusion*
6. Temperature

**The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some*

confusion, disorientation and/or agitation. This would score 3 or 4 on the GCS (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.

A score is allocated to each parameter as they are measured, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated and uplifted by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation.

Table 6: National Early Warning Score 2 (NEWS-2)

Variable		Points
Respiratory rate, breaths per minute	≤8	3
	9-11	1
	12-20	0
	21-24	2
	≥25	3
SpO_2 (on room air or supplemental)	≤91%	3
	92-93%	2
	94-95%	1
	≥96%	0
SpO_2 (if patient has hypercapnic respiratory failure)	≤83%	3
	84-85%	2
	86-87%	1
	88-92%, ≥93% on room air	0
	93-94% on supplemental oxygen	1
	95-96% on supplemental oxygen	2
	≥97% on supplemental oxygen	3
Room air or supplemental oxygen	Supplemental oxygen	2
	Room air	0
Temperature	≤35.0°C (95°F)	3
	35.1-36.0°C (95.1-96.8°F)	1

Variable		Points
	36.1-38.0°C (96.9-100.4°F)	0
	38.1-39.0°C (100.5-102.2°F)	1
	≥39.1°C (102.3°F)	2
Systolic BP, mmHg	≤90	3
	91-100	2
	101-110	1
	111-219	0
	≥220	3
Pulse, beats per minute	≤40	3
	41-50	1
	51-90	0
	91-110	1
	111-130	2
	≥131	3
Consciousness	Alert	0
	New-onset confusion (or disorientation/agitation), responds to voice, responds to pain, or unresponsive	3

Note: *Interpretation of NEW score:*

NEW Score	Clinical risk	Frequency of monitoring	Response
0-4	Low	Minimum every 12 hrs if score of 0 Minimum every 4-6 hrs if score 1-4	Assessment by a competent registered nurse or equivalent, to decide change in frequency of clinical monitoring or escalation of care
Score of 3 in any individual parameter	Low-medium	Minimum every hr	Urgent review by a ward-based doctor, to decide change in frequency of clinical monitoring or escalation of care
5-6	Medium		Urgent review by a ward-based doctor or acute team nurse, to decide if critical care team assessment is needed

NEW Score	Clinical risk	Frequency of monitoring	Response
≥7	High	Continuous monitoring of vital signs	Emergent assessment by a clinical team or critical care team and usually transfer to higher level of care

12. Percentage of patients requiring, until Day 28 or discharge from hospital (if discharge happens earlier)
    a. Management in intensive care unit
    b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c. Invasive mechanical ventilation
13. Time (no. of days) from randomization to:
    a. Management in intensive care unit
    b. High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)
14. Duration (no. of days) the patient requires:
    a. Management in intensive care unit
    b. Oxygen supplementation
    c. High Flow Nasal Oxygen
    d. Non-invasive mechanical ventilation
    e. Invasive mechanical ventilation

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)
15. Percentage of patients:
    a. dying from any cause
    b. dying from a COVID-19 associated complication

    over an assessment period from randomization until Day 28 or discharge from hospital (if discharge happens earlier)

Details about management in the intensive care unit, patients requiring supplemental oxygen, (standard or by high flow nasal cannula) non-invasive and invasive mechanical ventilation will be collected daily during the study along with the duration that these are required.

7.1.2 Stage II

7.1.2.1 Evaluation Criteria for the Efficacy Endpoint

1. Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 59 days after the day of randomization (Day 60).

Note: 'Clinical relapse' is defined as either the reappearance or worsening of severity (over the assessment on the day of discharge) of one or more of the above-mentioned COVID-19 associated symptoms, or the appearance of any of these symptoms (due to COVID-19 infection) for the first time after discharge.

2. Proportion of patients
    a. With disease worsening and requires:
        - Admission to ICU
        - High flow nasal oxygen
        - Non-invasive mechanical ventilation
        - Invasive mechanical ventilation

    AND

    b. Dying

until Day 60 (regardless of whether patients are discharged from hospital before Day 28 or not)

7.2 Safety Evaluation Criteria

7.2.1 Stage I

1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term)

The AEs and SAEs occurring throughout the study will be collected irrespective of whether they are related to investigational product or not and will be presented as per the System Organ Class (SOC). The number of patients with treatment-emergent AEs will be collected and summarized based on the SOC and preferred term.

2. Changes of parameters at each assessment during the study/follow-up period, compared to baseline for:
    - Vital signs: body temperature, heart rate, respiratory rate, systolic/diastolic BP and oxygen saturation.
    - Clinical laboratory assessments: hematology, serum chemistry, urinalysis.
    - 12 Lead ECG: Changes in heart rate, PR, QRS, QT and QT_cB intervals.

Vital signs will be measured at screening, at pre-dose only on Day 1 and at least twice, morning and afternoon, daily from Day 2 to Day 28 or discharge or discontinuation form the study. Laboratory assessments will be performed at screening, Day 4, Day 7, Day 10, Day 14, Day 21, and Day 28 or discharge or discontinuation. 12-Lead ECG will be performed at screening, Day 1

(pre-dose), Day 4, Day 7, Day 10, Day 14, Day 21 and Day 28 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints or study discontinuation (whichever is earlier). Pre-dose measurement will act as the baseline for vital signs, laboratory assessments and 12-Lead ECG parameters. The changes in these parameters will be compared between the treatment groups for each of these assessments.

7.2.2 Stage II

1. Number (and percentage) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term)

The AEs and SAEs occurring throughout the study will be collected irrespective of whether they are related to investigational product or not and will be presented as per the System Organ Class (SOC). The number of patients with treatment-emergent AEs will be collected and summarized based on the SOC and preferred term.

8 PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Not applicable.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

All clinical AEs occurring after the patient signs the Informed Consent Form and up to Day 60 or study discontinuation, whichever is earlier whether observed by the Investigator or reported by the patient, will be recorded on the AE electronic case report form (eCRF) page. All SAEs are to be reported according to the procedures in Section 9.2 SAE Reporting-Procedure for Investigators. Pre-planned procedure or hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.1.1 for Definitions).

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator must be recorded in the AE page of the eCRF.

Investigator should follow patients with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.1.1 Definitions

9.1.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE is therefore any unfavorable and unintended sign (an abnormal ophthalmic finding, for example), symptom (including physical, psychological or behavioral effect), or disease temporally associated with the use of a medicinal (investigational or marketed) product, experienced by a patient during their participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not considered product-related.

This includes any untoward signs, symptoms, illness or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, experienced by the patient from the time of signing the informed consent until completion of the study. Throughout the patient's participation in the study, any new clinically significant findings/abnormalities that meet the definition of an AE must be recorded and documented as an AE.

9.1.1.2 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note*: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situation, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient's safety or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note*:*

- *A procedure is not an AE or SAE, but the reason for the procedure may be an AE.*
- *Pre-planned surgeries or hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.*
- *Routine treatment or monitoring of the studied indication not associated with deterioration in condition should not be considered as SAE. For example, in the patient population for the current study, administration of supplemental oxygen should not in itself be considered as SAE, unless it is associated with a significant deterioration in subject's condition (such as development of ARDS and/or respiratory failure requiring invasive mechanical ventilation).*
- *. Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE should not be considered as SAE.*
- *Abnormal clinically significant laboratory values should not be reported as SAEs, unless they lead to prolongation of hospitalization on their own, while the underlying disease condition merited a discharge from the hospital.*

Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the time patient signs the Informed Consent Form to Day 60 or study discontinuation, whichever is earlier. If follow up is required beyond Day 60 for safety related reasons, additional visit(s) may be scheduled for individual patients.

Medical History Condition

A medical history condition is any clinically significant medical/surgical condition already present at the time of informed consent.

Pre-treatment Adverse Events

Any clinically significant abnormality between the time of informed consent and intake of the first dose of the study drug in the trial, which meets the definition of AE, should be recorded as a pre-treatment AE (or non-Treatment Emergent Adverse Event). Any new clinically significant event or worsening of existing medical history condition between the time of informed consent and intake of the first dose of the study drug in the trial, which meets the definition of AE will also be considered as pre-treatment AE.

Treatment Emergent Adverse Events

All AEs recorded after the first dose of study drug (on Day 1) until Day 30 or study discontinuation, whichever is earlier will be considered as Treatment Emergent Adverse Events (TEAEs). Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the product will not be considered as adverse experiences after treatment (TEAEs) unless they reoccur after the patient has recovered from the pre-treatment condition or they represent an exacerbation in intensity or frequency, or the character of the condition worsens during the study period.

Post Treatment Adverse Events

All AEs recorded after Day 30 until Day 60 or study discontinuation, whichever is earlier will be considered as post treatment AEs.

Physical Examination Findings

At screening assessment, any clinically significant abnormality detected on physical examination should be recorded as a pre-existing condition. During the visits that fall within the treatment period and after the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must be recorded and documented as an AE.

Abnormal Laboratory Values

A clinically significant laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity, then the underlying condition should be captured as an AE.
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Lab abnormalities found during the screening assessments will not be considered as AE but will be used by the Investigator in determining eligibility of the individual patient for study participation and included as part of the medical history.

Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

a) Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

b) Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

c) Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical Investigator.

9.1.1.3 AE Severity

The intensity or severity of AEs will be done by two methods:

a. The severity of the respective AEs will be graded using the NIH NCI CTCAE Version 5.0. Published: November 27, 2017[23].

b. Additionally, the following definitions should be used to assess severity of AEs:

- Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate: minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.1.1.4 Causality Assessment

The relationship between an AE and the study drugs will be determined by the Investigator on the basis or his/her medical/ pharmacological knowledge and clinical judgment and the following definitions:

- Not Related: The event is clearly due to extraneous causes (e.g., diseases, environment, etc.) (specify if known) or, the event is most probably produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study product.
- Possibly Related: The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.
- Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.
- Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product, and could not have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study product administration or improves on stopping the product, or there is a positive reaction at the application site

9.1.1.5 Action Taken Regarding the Study Product

The action taken regarding the study product will be categorized as below;

Grading	Category	Definition
1	None	No change in study drug dosage was made
2	Discontinued Permanently	The study product was permanently stopped
3	Reduced	The dosage of study product was reduced
4	Interrupted	The study product was temporarily stopped.
5	Increased	The study product dosage was increased

9.1.1.6 Adverse Event Outcome

The outcome of the AE will be categorized as below;

Grading	Category	Definition
1	Recovered/Resolved	The patient fully recovered from the AE with no residual effect observed
2	Recovered/Resolved with Sequelae	The residual effects of the AE are still present and observable. Identify sequelae/residual effects
3	Not Recovered/Not Resolved	The AE itself is still present and observable
4	Fatal	The AE resulted in death of the patient or contributed significantly to it
5	Unknown	The outcome of the AE in the patient is not known or cannot be determined.

9.1.1.7 Other Action Taken for Event

The other action taken for the AE will be categorized as below;

Grading	Category	Definition
1	None	No treatment was required
2	Medication required	Prescription and/or OTC medication was required to treat the AE
3	Hospitalization or prolongation of hospitalization required	Hospitalization was required or prolonged due to the AE, whether or not medication was required
4	Other	

9.2 Serious Adverse Event Reporting

Procedure for Investigator

All serious adverse events (SAEs) should be reported immediately to the CRO (at the below mentioned e-mail address), who will relay it to Sponsor. The Investigator will report the SAEs using SAE form via email, regardless of the Investigator's determination of causality at least within 24 hours of the Investigator becoming aware of the event on dedicated SAE Reporting Form.

SAE Reporting Contact Information
DRLPV@navitaslifesciences.com

In particular, if the SAE is fatal or life-threatening, the CRO must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports.

At a minimum, the Investigator must provide the following information: protocol number, site ID, patient initials, patient number and date of event initiation, event term and causality in the initial SAE form.

The Investigator is obligated to pursue and provide information to Sponsor and the responsible CRO on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor and the responsible CRO to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on eCRF. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

The initial reports should be followed promptly by detailed written reports. The initial and follow-up reports should identify patients by unique code numbers assigned to the trial patients rather than by the patients' names, personal identification numbers, and/or addresses.

All SAEs will be followed until event resolution or stabilization (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that does not fully resolve until years later, the outcome should be reported as "resolved with sequelae" as soon as the event has stabilized or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

All pre-treatment events (see Section 9.1.1) which are assessed as being serious according to the criteria listed in Section 9.1.1.2 , have to be reported in the same way.

Procedure for Sponsor/CRO

Sponsor will follow expedited reporting procedures according to local and international regulations as appropriate. The Sponsor will promptly notify SAE to the applicable regulatory authorities, Ethics Committee and other investigators of the trial within applicable timelines as per the applicable regulatory requirement.

9.2.1 SUSARs

Procedure for Investigator

Investigator will inform the responsible CRO (who in turn will inform the Sponsor) about the occurrence of the SAE via email within 24 hours of the occurrence of the SAE. The investigator should comply with the local regulatory requirements related to the reporting of unexpected serious adverse drug reactions (SUSARs) to the regulatory authority and IRB.

Procedure for Sponsor

In case of fatal or life threatening unexpected ADRs will be notified to regulatory agencies as soon as possible or no later than 7 calendar days. The follow up report will be submitted within 8 additional calendar days after the first knowledge by the Sponsor that a case qualifies.

In case of serious, unexpected reactions (ADRs) that are not fatal or life-threatening will be filed as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that the case meets the minimum criteria for expedited reporting.

For unexpected SAE, the Sponsor considers the Investigator's causality assessment but submits an IND safety report to the applicable regulatory authority for those events for which the Sponsor determines there is a reasonable possibility that the drug caused the event (a Suspected Adverse Reaction), regardless of the investigator's causality assessment.

9.3 Exposure *In Utero* During Clinical Studies

If a patient becomes pregnant during the treatment period or within 7 days after the last dose of study treatment, she must not receive additional study drug or treatment and must be promptly discontinued from the study. The patient must be followed up until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator must notify the responsible CRO (at the below mentioned e-mail address) within 24 hours of first learning of the occurrence of pregnancy using the Pregnancy Notification Form providing as much information as possible. The Investigator must notify the responsible CRO about reported complications within 24 hours using the same procedure. Outcome of pregnancy, once known by the Investigator, must also be reported to the responsible CRO within 24 hours using the Pregnancy Outcome Form. Pregnancy communications will be directed to:

Pregnancy Reporting Contact Details Email
DRLPV@navitaslifesciences.com

CRO who will relay pregnancy notifications to Sponsor. Please note that pregnancy in and of itself is not an AE or SAE. Pregnancy should not be entered into the CRF as an AE unless the Investigator suspects an interaction between the study treatment and contraceptive method. Pregnancy will be documented as the reason for study discontinuation.

CRO will direct the pregnancy communication to Sponsor (Pharmacovigilance and Medical Monitor) as soon as it is received.

9.4 Clinical Laboratory Evaluations

All laboratory values outside the normal range will be evaluated for clinical significance by the Investigator and annotated as clinically significant or not clinically significant. Patients with values

outside of the normal range (at the screening visit) may continue in the study at the Investigator's discretion, provided they do not meet any of the exclusion criteria of the study.

Laboratory tests mentioned in Table 7 will be evaluated at the local laboratory as described in Section 6.3.

When a change in a laboratory test value constitutes an AE, the event should be followed-up until the change resolves or improves even after the end of the study period, within the scope of the patient's cooperation.

Table 7: Clinical / Diagnostic Laboratory Tests

Haematology	Serum chemistry	Urine analysis
▪ Haemoglobin ▪ Haematocrit ▪ Total WBC count ▪ Differential WBC count ▪ Platelet count ▪ RBC count ▪ Absolute neutrophil count	▪ Total Cholesterol ▪ Triglycerides ▪ Total Protein ▪ Albumin ▪ Albumin/Globulin ratio ▪ Blood Urea Nitrogen ▪ Uric acid ▪ Creatinine ▪ Total Bilirubin ▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Gamma-glutamyl transferase ▪ Alkaline phosphatase ▪ Lactate dehydrogenase ▪ Creatine Kinase ▪ Calcium ▪ Phosphate ▪ Sodium ▪ Potassium ▪ Chloride ▪ C-Reactive Protein ▪ Glucose ▪ D-dimer ▪ Ferritin	▪ Colour ▪ Transparency ▪ pH ▪ Specific gravity ▪ Protein ▪ Glucose ▪ Ketone bodies ▪ Bilirubin ▪ Blood ▪ Nitrite ▪ Urobilinogen ▪ Microscopic examination

9.5 RT-PCR (Qualitative)

Sample collection

The respiratory tract sample will be collected through nasopharyngeal swab or oropharyngeal swab or nasal aspirate or tracheobronchial aspirate (or bronchial lavage at post-baseline assessments) for the RT-PCR (qualitative) assay for SARS-CoV-2 RNA. The sample will be collected at screening, on Day 5, Day 10 and Day 28, or discharge (i.e., if the patient happens to be discharged before one or more of the mentioned timepoints, then the sample will be collected at discharge). No sample will be collected from patients at any timepoint after discharge, EXCEPT if individual patients are scheduled for an additional (unscheduled) visit, either to follow up on an AE or to report a possible 'clinical relapse' of COVID-19 or based on Investigator's discretion during the Day 10 - home visit. A sample will be collected during the unscheduled visit in such cases. The time of sample collection will be recorded.

However, the test may be performed on other days at the Principal Investigator's or a Sub-Investigator's discretion.

Testing of samples

The test will be performed at the site laboratory, if the site laboratory is not capable of performing RT-PCR assay, the testing will be conducted in an approved laboratory.

9.6 Vital Signs

SpO_2, body temperature (axillary), systolic BP, diastolic BP, pulse rate, and respiratory rate will be measured at pre-dose only on Day 1 and at least twice, morning and evening, daily from Day 2 to Day 28 or discharge or discontinuation form the study (whichever is earlier), and the results will be recorded with time of measurement (one measurement of each vital sign is accepted at Study Discontinuation). If more than one measurement is performed in both the morning and evening, the worst value will be recorded. SpO_2 will be measured without oxygen therapy as much as possible. If SpO_2 is measured under oxygen therapy, it should be recorded. If body temperature is $\leq 37.4°C$, whether the measurement in question occurred within 4 hours after the use of antipyretic analgesic drugs should be recorded.

9.7 Electrocardiograms

12-lead electrocardiogram (ECG) will be recorded with the patient at rest in the supine position at screening, once daily (preferably at the same time on each day) on Day 1, Day 4, Day 7, Day 10, Day 14, Day 21 and Day 28 or discharge (if discharge happens earlier than one or more of the above-mentioned assessment timepoints) or Study Discontinuation, whichever is earlier, and heart rate (HR), RR, PR, QRS, QT and QT_cB intervals, and the presence or absence of clinically significant abnormalities will be recorded. Changes in ECG parameters will be recorded as AEs if the Investigator judges these as being clinically significant.

9.8 Physical Examination Findings

The Physical Examination will be performed, and results will be documented at visits as described in Section 6.3. Changes to physical examination from screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

A complete physical examination includes general appearance, skin, head, neck, ENT, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes.

A partial physical examination includes general appearance, ENT, heart, lungs and lymph nodes.

9.9 Other Safety Assessments

Serum pregnancy test will be conducted in case of women of childbearing potential at screening and End of Study (Day 28 or discharge, whichever is earlier).

10 OTHER ASSESSMENTS

Not applicable.

11 STATISTICAL METHODS

11.1 Analysis Sets

Four Analysis populations will be considered for this study which are defined as below.

Screened Population: All participants who signed the informed consent form.

Safety Population (SAF): All randomized patients who received at least one dose of the study medication.

Intention-to-treat (ITT): All randomized patients who received at least one dose of the study medication.

Modified Intention to treat (mITT): All randomized patients who received at least one dose of the study medication and has at least one post dose primary efficacy endpoint assessment available.

(Note: If there is a greater than 5% difference in the number of patients in the ITT and mITT populations, then analyses for mITT population will be provided additionally)

Per protocol set (PPS): All patients included in the ITT who complete the study without major protocol deviation which would affect the primary endpoint of the study.

11.2 General Statistical Considerations

Adverse events and medical history will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA Version 23.0) terminology. Prior and concomitant medications (including medications which are a part of supportive care) will be coded with the World Health Organization Drug Global (WHO-DG, version March 1, 2020) dictionary as applicable.

Unless otherwise specified, the primary efficacy analysis will be done using ITT population. The statistical significance level is 0.05 by one sided or two-sided test, wherever appropriate. Mean/ Median estimate (and other general statistics such as Inter quartile range, SD, min, max) and the 95% CI for the estimates of the mean will be provided for the applicable efficacy endpoint. Endpoints will be analysed descriptively and inferentially wherever necessary. Details of the statistical methods will be described in the SAP, which will be finalized before study database lock of Stage I of the study.

Description of statistics:

The primary indicators collected in this study will be described by appropriate statistical methods. To briefly mention, Quantitative indicators will be described by arithmetic mean, standard deviation, median, inter quartile range, maximum, minimum etc.; qualitative indicators will be described by frequency and percentage.

11.2.1 Missing data

Efficacy

Missing data imputation will be done for the for the primary endpoint analysis. Method to be used will described on SAP.

Furthermore, a sensitivity analysis will be done for the method of handling missing values, if the number of missing values is substantial.

Safety

No imputation will be done on missing safety data, unless for partially incomplete dates for remote events such as AE, concomitant medication etc. The detailed information on imputing partial dates will be detailed in SAP.

11.3 Study Population Data

The safety data will be analysed using safety population; the summaries for disposition will be presented using screened population; demographics and other baseline characteristics will be presented using safety and ITT population and efficacy analysis will be analysed using ITT and PP population as required.

11.4 Efficacy Analyses

11.4.1 Primary Efficacy Analyses

Analysis of the primary endpoint:

The time from the start of administration of the study drug to time to ***resolution of hypoxia*** as described in the Section 3.1.3.1.1 will be compared between the treatment groups using the Cox proportional hazard model with age, gender and disease severity (moderate and severe) as factors and baseline WHO ordinal score at the start of administration of the study drug as baseline covariates. The hazard ratio and its corresponding 95% confidence interval (CI) and p-value will be obtained from the above Cox proportional hazard model; Also Median time, Inter quartile range estimate etc. will be presented and Kaplan-Meier plot will be plotted. All the efficacy analysis mentioned will be performed using ITT and PP population.

For censored patients who died of any cause, discontinued or were lost to follow-up due to treatment-related adverse events or lack of efficacy, they will be censored at Day 28. However, censored patients who discontinued or were lost to follow-up for reasons that were independent of the study medication will be censored at the day of discontinuation of lost to follow-up. Censored patients who were still in the study follow-up at the time of the analysis will be censored at the last day of available follow-up data.

11.4.2 Secondary Efficacy Analyses

All the secondary endpoints will be analysed descriptively and inferentially wherever necessary and more details on statistical analysis will be explained in the SAP. If there is a discrepancy in the planned analysis between the protocol and SAP, the SAP takes precedence.

11.4.3 Exploratory Efficacy Analyses

Based on the data availability and feasibility, exploratory analysis may be planned if required for this study and will be detailed in the SAP.

11.5 Pharmacokinetic/Pharmacodynamic Analyses

Not applicable

11.6 Safety Analyses

11.6.1 Adverse Event Analyses

All AEs and TEAEs will be summarized in terms of severity, relationship to study treatment, action taken and patient outcome. The number and the proportion of patients who experienced AEs will be computed by treatment arm, classified by Medical Dictionary for Regulatory Activities (MedDRA version 23.0) Primary System Organ Class and Preferred Terms. The AE data will be summarized using safety population.

11.6.2 Clinical Laboratory Evaluation Analyses

Continuous Laboratory data will be summarized using descriptive statistics, such as arithmetic mean, standard deviation, median, minimum and maximum values; while the categorical variable will be summarized using frequency and percentage. Descriptive statistical summaries will be generated for each assessment timepoint as well as change from baseline at each timepoint Clinically significant abnormal lab data will be summarized using frequency and percentage.

The lab data will be summarized using safety population.

11.6.3 Vital Sign Analyses

Descriptive statistics such as arithmetic mean, standard deviation, median, minimum and maximum values will be summarized for vital sign parameters using Safety population. Clinically significant abnormal vital data will be summarized using frequency and percentage. Descriptive statistical summaries will be generated for each assessment timepoint as well as change from baseline at each timepoint

11.6.4 Electrocardiogram Analyses

Descriptive statistics, such as arithmetic mean, standard deviation, median, minimum and maximum values will be provided for the continuous variables and the number of observations and percentage will be provided for the categorical variables. Descriptive statistical summaries will be generated for each assessment timepoint as well as change from baseline at each timepoint The 12 Lead ECG analysis will be summarized using safety population.

11.6.5 Physical Finding Analyses

The physical examination findings will be summarized by number of observation and percentage using safety population

11.6.6 Other Safety Analyses

Other safety analysis if required will be detailed in the SAP

11.7 Other Analyses

Other analysis if required will be detailed in the SAP.

11.8 Interim Analyses

Based on the data availability and feasibility, an interim analyses and/or assessment for futility and/or harm will be performed. During the interim analyses and/or assessment for futility and/or harm, re-estimation of sample size will be considered. The details of the interim analysis and futility/harm assessment will be included in a separate SAP for Interim analyses, appended to the DMC charter. If there is a discrepancy in the planned analysis between the protocol and SAP, the SAP takes precedence.

11.9 Independent Data Monitoring Committee

An independent data monitoring committee will review the results of the interim analyses to assess the efficacy and safety data emerging from the trial. The details appended to the DMC charter of the interim analysis and/or futility and/or harm assessment will be included in a separate SAP. If there is a discrepancy in the planned analysis between the protocol and SAP, the SAP takes precedence.

11.10 Sample Size Determination

Based on review of published literature,[26] a hazard ratio of 1.25 is reported (adjusted for the stratification in randomization) for time to clinical improvement in COVID-19 patients receiving anti-viral intervention. The hazard ratio of 1.25 is also assumed to be constant throughout the study as per the assumptions of the Cox proportional hazards regression model with the expected average probability of the event over the course of the study to be 0.9 and 0.8 in test and control group respectively. Inequality testing of the hazard ratio using the Cox proportional hazards regression model with 371 subjects in Favipiravir group and 371 subjects in Placebo group achieves 80% power at the 0.05 significance level for an actual hazard ratio of 1.25 assuming the hazard ratio is 1 under the null hypothesis and that the total number of events achieved is 631. Based on the above assumption and considering the dropout rate to be 5%, overall, 390 patients will be randomized in each treatment group. i.e. 780 patients in total to be randomized in the study. The sample size is estimated using nQuery version 8.5.0.0 using Cox proportional hazard regression.

Sample size will be re-estimated based on the analysis of results for the primary endpoint observed during interim analyses. Details of the interim analysis and futility assessment are provided in the Statistical Analysis Plan (SAP) for the Interim Analysis.

12 DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related in-person or remote monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source documents and remote access to source data. Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of a clinical study. Remote access to source data is applicable when on site access is not possible or restricted.

This will be carried out giving due consideration to applicable data protection and medical confidentiality.

12.1 Study Monitoring Plan

Before the first patient is recruited into the study, the monitor(s) of CRO will remotely review and confirm the selection of clinical study facilities to:

- Determine the adequacy of the clinical study facility
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and other responsibilities

During the progress of the study, the monitor(s) from CRO will have regular telephonic contacts, online discussions with the clinical study facility, or an in-person visit (if permissible and necessary) at agreed interval depending on the requirement and the situation to:

- Provide information and support to Investigator(s)
- Confirm the continued adequacy of the clinical study facility
- Confirm that the investigational team is adhering to the protocol, GCP, and applicable regulatory requirements
- Perform remote source data review (a comparison of the data in the CRFs with the patient's medical records, and other records relevant to the study).
- Check that the data are being accurately and completely recorded in the CRFs, and that drug accountability checks are being performed
- Verify the protection of the rights and wellbeing of the patients

During these remote contacts, online discussions or in-person visit (if permissible), CRFs and supporting documentation or scanned copies with redacted patient details as per agreement related to the study will be reviewed and any discrepancies or omissions or any other issues will be resolved. The monitor or another CRO representative will be available between discussions or visit if the Investigator(s) or other staffs need information or advice.

After each remote monitoring contact or in person study visit, the monitor will prepare a monitoring report. A follow up letter will be prepared and sent to the Investigator for activities done and the resolution plan, if any. These activities will be as per the current version of the monitoring plan. A trial monitoring plan will be formulated and agreed upon between the Sponsor,

CRO, clinical manager, monitors (and sites, if applicable) before the first patient is enrolled into the trial.

The Principal Investigator or Sub-Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents as appropriate.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these remote monitoring or online discussion or in-person visits are addressed and documented.

12.2 Data Collection

The study eCRF is the primary data collection instrument for the study. Data will be collected using eCRFs that are specifically designed for this study. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the eCRFs must be completed for each patient enrolled according to the patient's source data and as this study is being conducted in a pandemic situation available documentation method will be utilized. All the eCRF entries should be made according to the instructions given in the Investigator's Remote Data Capture manual. Corrections to electronic forms will be automatically documented via the software's "audit trail".

If applicable, patients are to be identified by birth date and patient number. Data requested should be first recorded on the source document or any documentation facility as appropriate/agreed at investigational site and then on the eCRF; however considering the pandemic situation and in order not to hinder patient management, it may be agreed upon to utilize eCRF entries as source documents, for specific parameters. Data will be entered at the site by the appropriately designated and trained site personnel.

Each entered eCRF must be approved by the site Investigator, verified against the patient's source documents by the CRA/monitor and reviewed by Data Management prior to locking the database. Once all the eCRFs for a patient have been completed, approved, verified, reviewed and cleaned, the patient's eCRFs will be locked.

The Investigator e-signs according to the study data flow.

eCRF completion should be kept current to enable the monitor to review the patient's status throughout the course of the study. eCRF will be completed, reviewed and signed off or e-signed by the Investigator.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.3 Data Management

Data management will be handled by CRO. CRO shall ensure that clinical study data collected throughout the trial are complete, accurate and of the highest quality and shall be performed in accordance with applicable International Conference on Harmonization (ICH) guidelines and

regulations. All the source documents will be maintained at the study site for audit and monitoring purposes.

Data Management Plan (DMP) shall include all general and study-specific data management processes and will identify the applicable processes, the people responsible for performing it, all relevant SOPs to be used and what is expected as output/ documentation.

eCRFs shall be made available to the site. Clinical data discrepancies will be identified, and data queries shall be resolved depending on the type of query as described in the DMP. Types of data to be coded will include, AEs and medications. Adverse events will be coded using the MedDRA adverse experience coding dictionary. Medications will be coded using the WHO-DG.

Periodic reviews of the safety database and the clinical database will occur to ensure consistency between the databases. If there are any amendments to the protocol in future having an impact on the data points collected on the eCRFs, these would be considered for eCRF modifications as per the protocol requirements.

12.4 Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Signature List.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, progress notes, laboratory reports and pharmacy records, X-rays, and correspondence. As the Investigator is managing a pandemic situation, so as not to inconvenience site personnel and hinder patient management, it maybe be agreed upfront to utilize an e-Source platform and/or to utilize eCRF entries as source documents, for specific parameters as mentioned in the Monitoring plan.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

Essential documents include:

- Any Patient files as appropriate containing informed consents, and supporting copies of source documentation (if kept and as agreed)
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IEC/IRB and the Sponsor
- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

In accordance with the applicable regulatory requirement(s), the confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules.

12.5 Record Keeping

Records of patients' source documents, monitoring logs, inventory of investigational product, regulatory documents (e.g. protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in traceable appropriate study files at the site for 5 years from study completion.

Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for at least 5 years from study completion at the sites. Prior to transfer or destruction of these records Sponsor/CRO must be notified in writing and be given the opportunity to further store such records.

In the event that the Investigator withdraws from the study (*e.g.,* relocation, retirement), the records shall be transferred to a mutually agreed upon designee (*e.g.,* another Investigator, IRB). Notice of such transfer will be given in writing to the Sponsor.

12.6 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the center to perform audits or inspections, including source data verification. During this visit, they will be allowed access to CRFs, source documents and other study files. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at his or her center.

12.7 Training of Staff

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff) with support from CRO. He or she will ensure that appropriate training relevant to the study (including the current version of study protocol) is given to all of these staff members, and that any new information of relevance to the performance of this study is forwarded to the staff involved. There will be training and information on all study related processes through online remote trial initiation.

12.8 Changes to the Protocol

The study shall be conducted as described in this approved protocol. Any significant deviation must be documented in the eCRF. All revisions of the protocol will be discussed with the Sponsor or Sponsor' representatives. The study procedures will not be changed without the mutual agreement of Investigators, CRO and the Sponsor. Administrative changes also require the mutual agreement of Investigators, CRO and the Sponsor.

In the event a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Sponsor/CRO
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor/CRO. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be provided to or approved by IEC, and if applicable, also the regulatory authority, before implementation. In the event an Amendment substantially alters the study design or increases the potential risk to the patient:

1. The consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion;
2. The revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and
3. The new form must be used to obtain consent from new patients prior to enrollment.

The Sponsor or CRO will distribute amendments and new versions of the protocol to the Principal Investigator or designee, who in turn is responsible for the distribution of these documents to IRB/IEC.

12.9 Protocol Deviations and Violations: Condition Where the Study will be Terminated

After a patient is enrolled into the trial and is noticed to be noncompliant with inclusion and exclusion criteria, the same will be documented as a protocol violation(s). During the conduct of the trial process if deviation(s) are noticed from the norm mentioned in the protocol, the same will be documented as protocol deviation(s).

The severity of the protocol violation and protocol deviation will be graded as minor if the violation/deviation is not altering the integrity of the study plan or its safety and efficacy outcome, as major if the violation/deviation is altering the integrity of the study plan or its safety and efficacy outcome.

The Sponsor reserve the right to terminate the study at any time and bear the responsibility for informing applicable regulatory authorities. Whereas the Principal Investigator reserves the right to discontinue the study for safety reasons at any time and bears the responsibility to inform the IEC. The reason for this termination will be provided to the patients.

13 FINANCING AND INSURANCE

13.1 Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the Sponsor or CRO as agreed. This agreement will include the financial information agreed upon by the parties.

13.2 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14 ETHICAL CONSIDERATIONS

This study will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements and will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent must receive IRB/IEC approval/favorable opinion prior to initiation of the study. Freely given written informed consent must be obtained from every patient prior to clinical trial participation. The rights, safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society. Study personnel involved in conducting this trial should be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (*e.g.,* loss of medical licensure, debarment).

Systems with procedures will be implemented to assure the quality of every aspect of the study.

14.1 IRB/IEC Review and Communications

This protocol and any amendments will be submitted to Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) in agreement with local regulations, for formal approval of the study to be conducted. The opinion of the IRB/ IEC concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator will provide a list of IRB/IEC members and their affiliate to the Sponsor.

14.2 Informed Consent Process

The Principal Investigator(s) at each center will ensure that the patient/LAR is given full and adequate oral and written information about the nature, purpose, possible risk and benefits of the study. The procedures to be carried out and the possible potential hazards will be described to the patients/LAR in a language which the patient/LAR comprehends. The patient/LAR will be required to read and sign the consent form summarizing the discussion prior to enrolment in the study. A copy of the written informed consent form will be given to the patient/LAR, which describes the study procedures including the clinical/laboratory tests and the possible potential hazards in nontechnical terms in conformity with regulatory requirements. If the patient/LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to patient/LAR is read and explained to the patient/LAR in a language understood by him/her and if the patient/LAR has orally consented to his participation in the screening/study, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to and apparently understood by the patient/LAR and that the informed consent was freely given by the patient/LAR. The ICF will be signed and dated by the patient/LAR and the PI or designee.

The consent form will include a statement that the Sponsor or designated Sponsor' representatives) and regulatory authorities will have direct access to patient records. The Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients prior to the beginning of the study.

The ICF provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and they should receive IRB/IEC approval/favourable opinion prior to use. Any updates to the consent form and any updates to the written information will be provided to the patient during a patient's participation in the trial.

14.3 Statement of Patient Confidentiality Including Ownership of Data

The records of the patient's medical history, physical examination, laboratory results and any other information or data generated during the study will be made available to the Sponsor, CRO or their designees (auditors, monitors), ethics committee, and will be made available to applicable drug regulatory bodies of countries, formulary committees of hospitals, at the opinion of the Sponsor. A pre-condition for entry into this study will be patient's agreement to release all of the above-mentioned documentation and data for any lawful purpose. In such cases, the patients name will be removed from all documentation to ensure anonymity.

14.4 Termination of Study

The Sponsor and the Institutional Review Board/ Independent Ethics Committee reserve the right to terminate the study at any time. The reason for this termination will be provided to the patients. The Principal Investigator reserves the right to discontinue the study for safety reasons at any time.

15 PUBLICATION POLICY

The results of the study including all obtained data will be the property of the Sponsor.

However, the Investigator and CRO may seek permission to publish results of the study from the Sponsor. Unpublished data cannot be disclosed to any third party by the Investigators or CRO without written approval of the Sponsor. Any formal publication of data collected as a result of the study will be considered a joint publication by the Investigators and the appropriate Sponsor personnel. Authorship will be determined by mutual agreement.

All clinical trials should be registered in a public trials registry. It is the responsibility of the Sponsor or designee to register this trial in an acceptable registry such as www.clinicaltrials.gov. Results might also be published in a peer-reviewed journal and authorship issues should be discussed and agreed upon early in the process between the Principal Investigator, sub-Investigator and Sponsor.

16 SPECIAL CONSIDERATIONS

16.1 Procedures in Case of Medical Emergency

In a medical emergency requiring immediate attention, study staff will apply appropriate medical intervention, according to current standards of care. Regulatory authorities and IEC will be notified of the event(s) when applicable.

16.2 Investigator's Responsibilities

The Investigators responsibilities involves the following-

1. Monitor and record all AE(s), which includes SAE(s), regardless of the severity or relationship to IP.
2. Determine the seriousness, relationship, and severity of each event.
3. Determine the onset and resolution dates of each event.
4. Complete an SAE form for each SAE and e-mail it to the CRO/Sponsor within 24 hours of the study site staff becoming aware of the event.
5. Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the CRO/Sponsor within 24 hours of the study site staff becoming aware of the information and to IEC within 7 working days.
6. Ensure all AE and SAE reports are supported by documentation in the patient's medical records.
7. Notification of the Institutional Review Board/ Independent Ethics Committee must be sent to the Sponsor or designee in a timely manner.
8. During and following the patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the participant for any AEs.

17 REFERENCES

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18 APPENDICES

Appendix I: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry

Appendix II: Declaration of Helsinki

Appendix III: Investigator's Declaration

Appendix I COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2020
Clinical/Medical

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2020
Clinical/Medical

Contains Nonbinding Recommendations

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or the Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1370 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "Coronavirus Disease 2019 (COVID-19)," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and the FDA webpage titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an e-mail request to COVID19-productdevelopment@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1370 and complete title of the guidance in the request.

Questions

For questions about this document, contact Eithu Lwin, 301-796-0728, Eithu.Lwin@fda.hhs.gov.

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page

I. INTRODUCTION

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to assist sponsors in the clinical development of drugs[2] for the treatment or prevention of COVID-19. Preventative vaccines[3] and convalescent plasma[4] are not within the scope of this guidance.

This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service (PHS) Act. However, the recommendations described in the guidance are expected to assist the Agency more broadly in its continued efforts to assist sponsors in the clinical development of drugs for the treatment of COVID-19 beyond the termination of the

[1] This guidance has been prepared by the Office of New Drugs and the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] Clinical trials of preventative vaccines raise different and additional considerations, including those pertaining to subject selection, safety monitoring, and effectiveness evaluation. We encourage developers of preventative vaccines to contact the Office of Vaccines Research and Review in CBER.

[4] FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma.

COVID-19 public health emergency and reflect the Agency's current thinking on this issue. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

Given this public health emergency related to COVID-19 declared by HHS, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named SARS-CoV-2 and the disease it causes has been named Coronavirus Disease 2019 (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19, effective January 27, 2020, and mobilized the Operating Divisions of HHS.[5] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[6]

COVID-19 can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death. The incubation period for SARS-CoV-2 is thought to be as long as 14 days, with a median time of 4 to 5 days from exposure to symptom onset.[7] There are currently no FDA-approved drugs to treat COVID-19. Clinical management includes symptomatic and supportive care, such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) when indicated.

[5] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[6] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (March 13, 2020), available at https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[7] See the Centers for Disease Control and Prevention Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

This guidance describes FDA's current recommendations regarding phase 2 or phase 3 trials for drugs under development to treat or prevent COVID-19.[8] This guidance focuses on the population, trial design, efficacy endpoints, safety considerations, and statistical considerations for such clinical trials. This guidance does not provide general recommendations on early drug development in COVID-19, such as use of animal models. Drugs should have undergone sufficient development before their evaluation in phase 2 or phase 3. FDA is committed to supporting all scientifically sound approaches to attenuating the clinical impact of COVID-19. Sponsors engaged in the development of drugs for COVID-19 should also see the guidance for industry and investigators *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products* (May 2020).[9]

This guidance focuses on the development of drugs with direct antiviral activity or immunomodulatory activity. However, the recommendations in this guidance may be applicable to development plans for drugs for COVID-19 with other mechanisms of action. The mechanism of action of the drug may impact key study design elements (e.g., population, endpoints, safety assessments, duration of follow-up). Additionally, for some biological products (e.g., cellular and gene therapies and blood products) there may be additional considerations and we encourage you to reach out to the applicable review division as appropriate.

III. DISCUSSION

A. Population

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- A range of populations is appropriate for evaluation and may include outpatient, inpatient, or inpatient on mechanical ventilation populations.

- For treatment trials, sponsors should document diagnosis of COVID-19. Laboratory-confirmed disease is preferred.

- For treatment trials, FDA recommends that sponsors categorize the baseline severity of the enrolled population. The criteria used to describe baseline severity should incorporate objective measures. Examples of severity criteria are provided in the Appendix.

- For prevention trials, sponsors should conduct trials in communities with documentation of circulating SARS-CoV-2 infection.[10] Populations including the following may be considered:

[8] Phase 2 and phase 3 trials need to be registered at www.ClinicalTrials.gov as required by 42 CFR part 11.

[9] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[10] Subjects in prophylaxis trials may be either SARS-CoV-2 negative or have an unknown SARS-CoV-2 status.

105
106 – Pre-exposure prophylaxis trials in persons at high risk for SARS-CoV-2 exposure
107 with no symptoms (e.g., health care workers and first responders)
108
109 – Post-exposure prophylaxis trials in health care workers or household contacts with no
110 symptoms and with a documented exposure to a definite or clinically presumed case
111
112 • Given the expected fluctuation in regions in the frequency of SARS-CoV-2 infection,
113 sponsors should address the need to open new sites and potentially suspend existing sites.
114
115 • Clinical trials should include persons at high risk of complications such as the elderly,
116 persons with underlying cardiovascular or respiratory disease, diabetes, chronic kidney
117 disease, or other comorbidities, and immunocompromised persons (e.g., HIV-infected
118 patients, organ transplant recipients, or patients receiving cancer chemotherapy).[11]
119
120 • COVID-19 disproportionately affects adults, including older individuals. The geriatric
121 population should be appropriately represented in clinical trials.[12] Sponsors should
122 consider conducting trials in nursing homes or other elder care facilities.
123
124 • Racial and ethnic minority persons should be represented in clinical trials. Sponsors
125 should ensure that clinical trial sites include geographic locations with a higher
126 concentration of racial and ethnic minorities to recruit a diverse study population.[13]
127
128 • Patients with renal or hepatic impairment should be enrolled in clinical trials provided the
129 pharmacokinetics of the drug have been evaluated in these patients and appropriate
130 dosing regimens have been identified.
131
132 • The principles outlined in this document can be used to guide drug development for
133 children and pregnant and lactating individuals. There is a need to generate clinical trial
134 data to inform the use of drugs in these populations.
135

[11] See the Centers for Disease Control and Prevention Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html, and the web page Information for People who are at Higher Risk for Severe Illness, available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.

[12] See the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Design* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[13] Ibid.

- FDA encourages the enrollment of pregnant and lactating individuals in the phase 3 (efficacy) clinical trials if appropriate.[14]

- Children should not be categorically excluded from clinical trials of investigational COVID-19 products in which there is a prospect for direct benefit.[15]

  - Sponsors are encouraged to discuss pediatric drug development with FDA early in the course of clinical development, including the potential for extrapolation of adult efficacy data, appropriate pharmacokinetic trials in pediatric subjects to support dose selection, and the recommended size of the preapproval safety database in children. In addition, disease severity classification should reflect age-appropriate norms, as applicable. Decisions on the timing of initiating pediatric studies depend on several factors, including but not limited to the amount of available clinical and/or nonclinical safety data for the drug. For example, if dosing recommendations for a drug are the same for adults and adolescents[16] and there is sufficient prospect of benefit to justify the risks, then it may be appropriate to include adolescents in the initial phase 3 clinical trials.

  - Sponsors are encouraged to submit an initial pediatric study plan as soon as practicable.[17]

  - Under the Pediatric Research Equity Act, all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication or indications in pediatric populations unless this requirement is waived, deferred, or inapplicable.[18] FDA intends to work with sponsors to reach agreement on the initial pediatric study plan and any pediatric trial protocols as quickly as possible to avoid any unnecessary delays in the initiation of trials or submission of any marketing application.

[14] FDA has proposed relevant recommendations in the draft guidance to industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[15] See 21 CFR part 50, subpart D.

[16] For the purposes of this guidance, *adolescents* are defined as age 12 to younger than 18 years of age.

[17] See 505B(e) of the FD&C Act. Additionally, FDA has proposed relevant recommendations in the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[18] See 21 U.S.C 355c.

B. Trial Design

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- FDA strongly recommends that drugs to treat or prevent COVID-19 be evaluated in randomized, placebo-controlled, double-blind clinical trials using a superiority design.[19]

  – Background standard of care should be maintained in all treatment arms. Sponsors should address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19.

  – The standard of care is expected to change as additional information, such as from randomized controlled trials, emerges. Where treatments become standard of care for specific COVID-19 populations (e.g., severely ill hospitalized patients), trials in these populations should generally be designed as placebo-controlled superiority studies with an add-on design (i.e., the investigational agent or placebo added on to the standard of care agent). For agents with a similar mechanism of action as the standard of care (e.g., direct antiviral agent as the investigational agent when the new standard of care is also a direct antiviral agent), an active-comparator controlled study design may be considered if there is sufficient preclinical and initial clinical evidence of activity of the investigational agent. Sponsors should plan early discussion with the appropriate clinical division.

- Under certain circumstances it may be appropriate to conduct decentralized and/or platform clinical trials. Sponsors considering these approaches should discuss their plans with the Agency. FDA recognizes the potential of, and significant interest in, such approaches, and may provide additional recommendations as we gain more experience regarding their use in this context.

- Given the infection control concerns associated with COVID-19, sponsors should limit in-person data collection to those measurements intended to ensure safety and establish effectiveness or influence the benefit-risk assessment.

- The trial should be of sufficient duration to evaluate safety and effectiveness reliably (i.e., the duration should be adequate to capture the vast majority of COVID-19-related outcomes that are relevant for the population under study). For example, a 4-week duration would likely be sufficient to capture most important outcomes (e.g., mortality) in a trial of mechanically ventilated patients. Longer durations would potentially be appropriate for trials of patients who are less ill at baseline and for trials of preventive treatments. In some cases, longer follow-up should be considered to assess safety.

[19] FDA has proposed relevant recommendations in the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- When there is compelling preclinical or preliminary clinical evidence, it may be appropriate to move directly to conduct a trial of sufficient size and appropriate design to provide substantial evidence of effectiveness and adequate characterization of safety.

- In instances where there is some but limited information supporting the potential for efficacy,[20] approaches where an initial assessment of potential benefit can be made before enrolling a large number of subjects are appropriate. These approaches may include the following:

  – Conducting an initial small, controlled trial to assess for drug activity (proof-of-concept) that suggests the potential for clinical benefit.

  – Conducting a trial that incorporates prospectively planned criteria to stop the trial for futility (i.e., with the prospect of expanding from a proof-of-concept phase to a larger confirmatory trial). Such a trial might also incorporate additional prospectively planned adaptations (see additional comments on adaptive design proposals below).

- FDA encourages sponsors to use an independent data monitoring committee (DMC) to ensure subject safety and trial integrity.

  – Sponsors should submit the DMC charter as early as possible.

  – Sponsors should ensure there will be appropriate DMC monitoring to safeguard the welfare of subjects, accounting for important factors such as the expected enrollment rate, the expected lag time to analyze interim data for DMC meetings, and the frequency of DMC meetings.[21]

  – If enrollment is anticipated to be rapid, but additional safety data are needed before dosing a large number of subjects, an enrollment pause could be built into the trial. In this case, enrollment would be temporarily halted, and the DMC would assess the data and then recommend that the trial or dosing group either terminate or resume enrollment.

- FDA encourages sponsors to incorporate prospectively planned criteria to stop the trial for futility (lack of efficacy) or harm in any confirmatory trial. The stopping criteria should aim to ensure a high probability of halting the trial if the drug is harmful (e.g., associated with a higher risk of death), a reasonable probability of halting the trial if the

[20] See the guidance for industry and investigators *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products*, which describes the information and data recommended to support FDA's review for the initiation of clinical trials during the COVID-19 public health emergency.

[21] FDA has proposed relevant recommendations in the draft guidances for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006) and *Safety Assessment for IND Safety Reporting* (December 2015). When final, these guidances will represent the FDA's current thinking on these topics.

drug is ineffective, and a high probability of continuing the trial if the drug is effective. If accrual in such a trial is expected to be rapid, an enrollment pause may be considered to support stopping for futility.

- If a trial incorporates the possibility of early stopping for evidence of benefit or any adaptations to the sample size, dosing arms, or other design features, sponsors should prospectively plan the design in a manner to ensure control of the type I error rate and reliable treatment effect estimation.[22] An independent committee, such as a DMC, should be tasked with providing any recommendations for early termination or design adaptations based on unblinded interim data.

- FDA anticipates events that occur outside of an ongoing trial may provide important new information relevant to the ongoing trial (e.g., changes to the standard of care) and may motivate revisions to the trial design. Well-motivated changes based on information external to the trial can be acceptable and sponsors are encouraged to discuss these changes with the FDA.

C. Efficacy Endpoints

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- The drug development program should evaluate the effect of the investigational drug relative to placebo on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on the population studied, the clinical setting, and/or baseline disease severity (see Appendix).

- Examples of important clinical outcome measures in treatment trials include the following:

  – All-cause mortality

  – Respiratory failure (i.e., need for mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery)

  – Need for invasive mechanical ventilation

  – Need for intensive care unit (ICU) level care based on clear definitions and specific clinical criteria

  – Need for hospitalization based on clear definitions and specific clinical criteria

  – Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement)

[22] See the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (November 2019).

290 – Sustained clinical recovery (e.g., resolution of symptoms)
291
292 • The choice, time frame, and interpretation of endpoints may differ depending on the
293 population evaluated in the trial. For example,
294
295 – In a trial in severe and/or critical patients, examples of appropriate endpoints could be
296
297 ▪ All-cause mortality at an appropriate time point (e.g., at least 28 days)
298
299 ▪ Proportion of patients alive and free of respiratory failure at an appropriate time
300 point (e.g., at least 28 days)
301
302 ▪ Clinical status at an appropriate time point assessed using an ordinal scale[23] that
303 incorporates multiple clinical outcomes of interest (e.g., death, mechanical
304 ventilation) ordered by their clinical importance[24]
305
306 ▪ Time to sustained recovery assessed over an appropriate duration
307
308 – In an outpatient treatment trial, examples of appropriate endpoints could be
309
310 ▪ Proportion of patients hospitalized by an appropriate time point (e.g., at least 28
311 days)
312
313 ▪ Time to sustained clinical recovery assessed over an appropriate duration
314
315 • Sponsors should address potential relapses in their endpoint definitions to ensure
316 adequate assessment of the durability of response.
317
318 • In phase 2 treatment trials, a virologic measure may be acceptable as a primary endpoint
319 to support a phase 3 clinical endpoint study. However, virologic endpoints are not
320 appropriate as primary endpoints in a phase 3 trial because there is no established
321 predictive relationship between magnitude and timing of viral reductions and the extent
322 of clinical benefit of how a patient feels, functions, or survives. Additionally, the optimal
323 sample size, timing, methods for collection procedures, and assays for clinically relevant
324 virologic measurements have not been established. In phase 3 treatment trials, virologic
325 endpoints may be assessed as secondary endpoints. Collection of virologic data and
326 evaluation of antiviral resistance are important components of drug development for
327 COVID-19.
328
329 • For endpoints defined by events through or at a prespecified time point, the time point
330 should be defined as number of days after randomization. The time window should be

[23] An example can be found at WHO R&D Blueprint novel Coronavirus, available at https://apps.who.int/iris/handle/10665/330695.

[24] Ordinal data should be collected daily to inform analyses.

sufficiently long to ensure capture of important events related to patient status, treatment, and COVID-19 progression.

- In prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection (with or without symptoms) or SARS-CoV-2 infection with symptoms (i.e., COVID-19) through a prespecified time point.

  – Sponsors are encouraged to evaluate both laboratory-confirmed SARS-CoV-2 infections (with or without symptoms) and SARS-CoV-2 with symptoms (i.e., COVID-19) when possible.

  – Ascertaining whether COVID-19 is milder in persons receiving prophylaxis compared with persons not receiving prophylaxis is of interest. Sponsors should collect clinical outcome data (e.g., hospitalization) and data on symptoms to support such analyses.

D. Safety Considerations

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- It is important to include a broad population of subjects in adequate and well-controlled clinical trials to generate a safety database that will best inform the safe use of the drug.

- The size and composition of the safety database needed to support an indication for COVID-19 depends on factors such as the proposed population, the treatment effect, the drug's toxicity, and the extent of the prior clinical experience with the drug (and possibly with related drugs).

- Sponsors may provide a standardized toxicity grading scale for clinical trials in patients with severe COVID-19 or patients with serious comorbidities. Examples of toxicity grading scales include those published by the National Institutes of Health's Division of AIDS[25] and the National Cancer Institute (NCI).[26]

- Sponsors should address the potential for drug-drug interactions that could increase the risk for toxicities (caused by increased exposures of the drug or the drug that it interacts with) and propose mitigation strategies.

[25] See the National Institutes of Health's Division of AIDS Adverse Event Grading Tables, available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

[26] See the National Cancer Institute's Common Terminology Criteria for Adverse Events, available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- Safety assessments (e.g., vital signs, laboratory studies, electrocardiograms) should be performed on a schedule commensurate with severity of illness and the identified potential risk of the study drug.

- Sponsors should conduct safety reporting as outlined in FDA regulations[27] and relevant guidance.[28]

E. Statistical Considerations

Sponsors of drugs to treat or prevent COVID-19 should consider the following statistical considerations:

- The primary efficacy analysis should be conducted in an intention-to-treat population, defined as all randomized subjects.

- The primary efficacy analysis should be prespecified in the protocol.

- To the extent possible, sponsors should justify their assumptions in sample size calculations. The sample size should be large enough to provide a reliable answer to the safety and efficacy questions the trial is meant to address.

- Examples of analytic approaches for the primary efficacy analysis include:

  – Binary outcome analysis: each person is classified as having a successful or an unsuccessful outcome, with a difference in proportions used to compare treatment arms.

  – Ordinal outcome analysis: options include a proportional odds approach, a rank-based approach, and an approach to compare means with a score or weight assigned to each category. Any of these approaches should be supplemented by analyses communicating how treatment impacts different categories of the scale.

  – Time-to-event analysis: use of a proportional hazards model or log-rank test should be supplemented by a display of Kaplan-Meier curves in each treatment group.

- To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified prognostic baseline covariates (e.g., age, baseline severity, comorbidities) in the primary efficacy analysis and should propose methods of

[27] See 21 CFR 312.32.

[28] See the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012). In addition, FDA has proposed relevant recommendations in the draft guidance for industry *Safety Assessment for IND Safety Reporting*. When final, this guidance will represent the FDA's current thinking on this topic.

406 covariate adjustment. For example, for a binary endpoint, methods can be used to gain
407 precision in the evaluation of the difference in proportions.[29]
408
409 • If a treatment trial enrolls a mixture of patients with different baseline severity levels,
410 sponsors should conduct subgroup or interaction analyses by baseline severity to assess
411 for differential treatment effects.
412
413 • The trial should aim to minimize missing data. The protocol should distinguish between
414 discontinuation from the study drug and withdrawal from study assessments. Sponsors
415 should encourage subjects who discontinue therapy to remain in the study and to continue
416 follow-up for key outcomes. Virtual follow-up is acceptable if appropriate, and the aim
417 should be to record vital status for all subjects.
418
419 • For the primary analyses, death should not be considered a form of missing data or
420 censoring. Death should be incorporated into the endpoint as a highly unfavorable
421 possible outcome. For primary endpoints other than all-cause mortality, a treatment effect
422 could be driven by non-mortality components (e.g., hospitalization) despite increased
423 mortality on drug. Therefore, analyses of all-cause mortality will be important regardless
424 of the selected primary endpoint.
425

[29] Ge M, Durham LK, Meyer RD, Xie W, and Thomas N, 2011, Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, Drug Inf J, 45:481–493.

APPENDIX

EXAMPLES OF BASELINE SEVERITY CATEGORIZATION

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO_2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$
- No criteria for Critical Severity

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Evidence of critical illness, defined by at least one of the following:
  - Respiratory failure defined based on resource utilization requiring at least one of the following:
    - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
  - Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
  - Multi-organ dysfunction/failure

NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

Appendix II: Ethical Principles for Medical Research Involving Human Subjects

World Medical Association Declaration of Helsinki: Recommendation guiding Medical Doctors in Biomedical Research Involving Human Subjects.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic

value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of

information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsor, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAE. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24.Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any

possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the subject which aspects of their care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never adversely affect the subject-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsor, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsor, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of

interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual subject, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorized 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.

Appendix III: INVESTIGATOR'S DECLARATION

I, the undersigned declare that I have read and understood this protocol and hereby agree to conduct this study in accordance with the design and specific provision of this protocol. I will provide copies of this protocol and access to all information furnished by Sponsor/CRO to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study products and study procedures. I will let them know that this information is confidential and proprietary to the Sponsor and that it may not be further disclosed to third parties. I will maintain all information supplied by Sponsor/CRO in confidence and, when this information is submitted to an Independent/Institutional Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I further agree to conduct the study in accordance with all applicable requirements of local regulatory authority including national drug and data protection laws, Institutional Review Board /Ethic Committee regulations, International Council for Harmonization Guidelines for Good Clinical Practices, Declaration of Helsinki by World Medical Association and applicable standard operating procedures. I understand that the study may be terminated or enrolment suspended at any time by Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

_____ _____

Investigator's Signature Date

_____

Investigator's Name

Address: _____

_____

_____

_____