Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN	
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
Sponsor Identification:	Dr. Reddy's Laboratories Limited
Phase:	Phase III
Sponsor Study Number:	CVD-04-CD-001
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Date of SAP:	**06JAN2021**
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2 Signatures

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1.0	09NOV2020	NA
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4 Abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
BP	Blood Pressure
COVID-19	Novel Corona Virus Disease 2019
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENT	Ear Nose Throat
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention-to-treat
mITT	Modified Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NEWS	National Early Warning Score
PPS	Per Protocol Set
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcriptase – Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHO-DG	World Health Organization Drug Global

5 Documents

This statistical analysis plan is based on the study protocol, version Final 5.0 dated 06 JAN 2021

6 Introduction

This statistical analysis plan (SAP) provides explicit guidance and describes the planned statistical and data handling methods to be followed during the final analyses and reporting of data collected in clinical trial CVD-04-CD-001. The intention of this document is to provide detailed information of the planned analysis of trial data related to safety and efficacy, and to describe applicable statistical procedures explicitly. Relevant statements are quoted directly from the protocol, within the applicable sections in this document (SAP). This SAP should read in conjunction with the study protocol version Final 5.0 dated 06 JAN 2021 and electronic case report form (eCRF) (version Final 3.0 dated 26-NOV-2020).

7 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

8 Study Design

8.1 Overview

8.1.1 Study Design

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.
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.

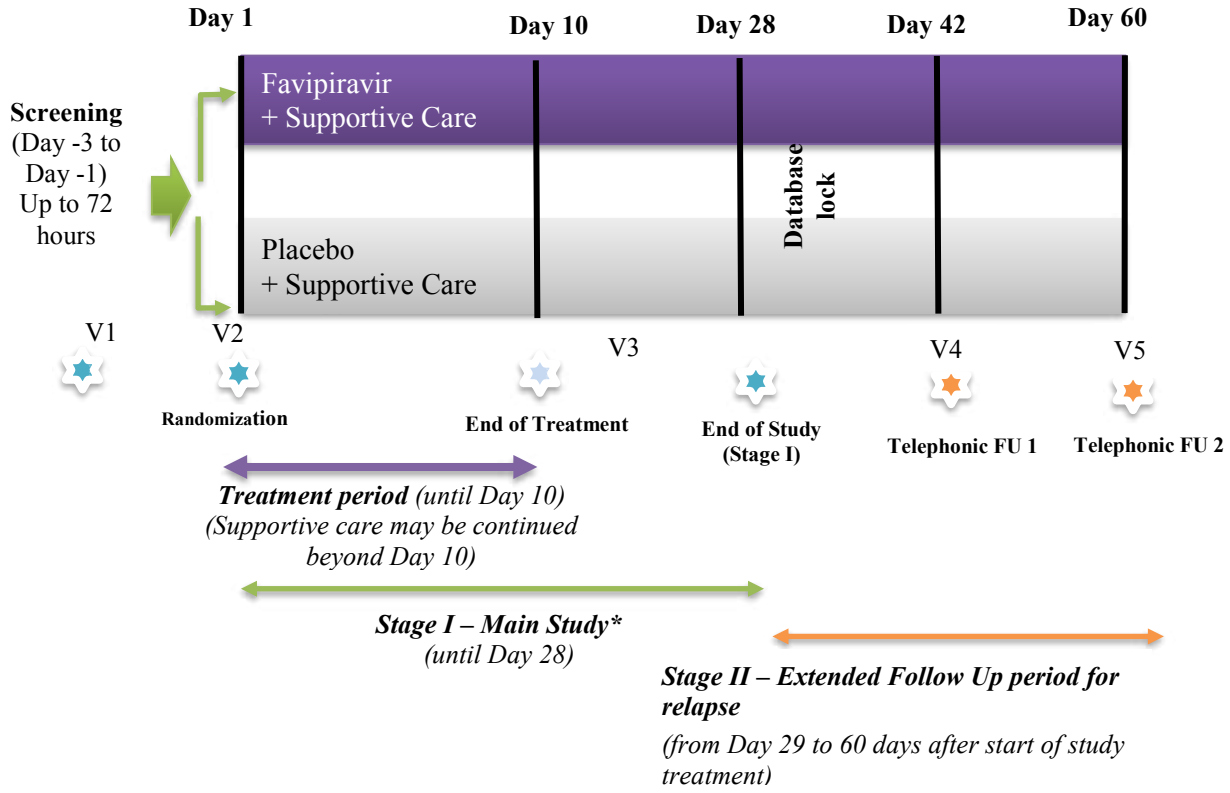
Stage I of the study will be completed when the 'Day 28' assessment is completed either as an in-patient assessment if the patient is still hospitalized, or as a telephonic follow up assessment if the patients are discharged earlier to Day 28.

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.

The below flowchart will describe about the 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 schedule of assessments will be as follows:

Table 1: Study Assessment Schedule

Assessments	STAGE I – Main Study[1]												Database 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	
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 **Error! Reference source not found.** 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 **Error! Reference source not found.** 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 **Error! Reference source not found.**).

Assessments	STAGE I – Main Study[1]												Database 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 supplementation) or SpO_2/ FiO_2 estimated on supplemental		●														

[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]												Database 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	
oxygen for confirmation of eligibility																
Randomization		●														
Dosing and compliance status[9] Morning			●		●											
Dosing and compliance status[9] Evening			●		●											
COVID-19 associated symptom severity assessment [10]	●	●		●												●[11]
RT-PCR (qualitative)[12]	●						●		●			●				●

[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

[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 time points, then the sample will be collected at discharge). No sample will be collected from patients at any time point 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.

Assessments	STAGE I – Main Study[1]												Database 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 Status by 10-point ordinal scale (SOLIDARITY SCALE)[13]	●	●		●												
Clinical Status by 8-point ordinal scale[14]	●	●		●												
NEWS-2 score[15]	●	●		●												
Clinical Laboratory Evaluations (Hematology, Serum Biochemistry, Urinalysis)	●					●		●	●	●	●	●				●
Chest X-ray	●	●				●		●	●	●		●				●
12-lead ECG	●	●				●		●	●	●	●	●				●
Vital signs[16]	●	●		●					●							●
Complete Physical	●															

[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).
[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.

Assessments	STAGE I – Main Study[1]												Database 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	
Examination[17]																
Partial Physical Examination[18]		●		●												●
Hospitalization period[19]	●	●	●	●												
Prior Medications	●															
Concomitant Medications		●	●	●						●	●	●		●	●	●
Pre-treatment Adverse Events	●	●														
Treatment Emergent Adverse events			●	●						●	●	●		●	●	●[20]
ICU admission status, supplemental oxygen and mechanical ventilation details [21]			●	●												●

[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.
[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

Assessments	STAGE I – Main Study[1]												Database 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 relapse[22]									●	●	●	●		●	●	

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

8.1.2 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 the Arabian Gulf region. 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.

8.2 Efficacy endpoints

Stage I

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.

Note: Part c) is applicable to patients in both a) and b)
i.e. Time to resolution of Hypoxia = either "a and c" OR "b and c" is met.

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 time points)

   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 samples on Days 5, 10 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned time points)

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 time points)
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 time points)

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 time points)
    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 time points)
    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 time points)

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).

Stage II

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:
        i. Admission to ICU
        ii. High flow nasal oxygen
        iii. Non-invasive mechanical ventilation
        iv. Invasive mechanical ventilation

        (AND)

b. Dying

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

8.3 Safety Endpoints

Safety endpoint will be as follows:

Stage I

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.

Stage II

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

9 General Statistical Considerations

9.1 Descriptive Statistics

The following descriptive statistics will be calculated for continuous data and for ordered categorical data (ordinal data):

Summary statistics are displayed with the following digits:

Description	Characteristic	Number of decimal places
Count	n	0
Count corresponding to the number of patients for a group	N	0
Mean	Mean	As in source + 1
Standard Deviation	SD	Mean+1
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Quartile 1	Q1	As in source+1

Description	Characteristic	Number of decimal places
Quartile 3	Q3	As in source+1
Inter Quartile Range	IQR	As in source+1
Percentage relative to N #	%	1

Number of decimal places can be more than one, if necessary. All table percentages should be rounded to one decimal place if not stated otherwise.

All data will be presented in the subject data listings.

If either table or listing does not include any observation, then the following placeholder will be used: "NO DATA CONTRIBUTED TO THIS TABLE / LISTING".

9.2 Analysis Population

Four analysis populations will be considered as defined below:

Analysis Population	Definition
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 analysis 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.

9.3 Definitions

In the following table, the definitions and calculation of derived variables are summarized

Variable / Term	Definition / Way of calculation
Age	Int ((informed consent date – Birth date +1)/365.25)
Baseline	The last valid value prior to the first dose of study treatment
Treatment Start Date	Date of dose administration on Day 1

Variable / Term	Definition / Way of calculation
Treatment End Date	Date of Last Study Medication Taken
Duration of exposure	Treatment end date- Date of randomization + 1
Treatment Emergent AE (TEAE)	An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first study drug administration or any AE that exist prior to first dose and its severity increased during the study.
Time to Resolution of Hypoxia	Date of first time the status trial score to become 4 or lower following baseline assessment when evaluated over a period of 24 hours – Date of randomization +1
Time to discharge	Date of discharge – date of randomization + 1
Time to ALL COVID-19 associated symptoms to become '0=absent' or 'mild =1' from Randomization	Earliest Date of ALL COVID-19 associated symptoms to become either '0=absent' or 'mild =1' in assessments over a period of 24 hours – date of randomization + 1
Time to achieve symptom improvement	Date of Change from baseline value for the particular symptom score to become less than or equal to '-1'and sustained at evaluations over a period of 24 hours – Date of randomization +1
Time to Negative	Date of first time to negative conversion in RT-PCR – Date of randomization + 1

9.4 Protocol Violation/Deviation

The relevant protocol violations/deviations have to be defined by a systematic data review prior to database closure. For this purpose, protocol violations that occurred during the study such as violations of inclusion/exclusion criteria or forbidden concomitant medications or subject non-compliance will be assessed as 'major' or 'minor' by depending on their potential to interfere with the objectives of the study. Listings will be prepared to show the eligibility of all patients. Comprehensive justification for the classification of a protocol violation/deviation as "major" will be given in the integrated clinical study report.

The list of protocol violations/deviations will be reviewed by the Sponsor and finalized before locking the database.

9.5 Data Handling

9.5.1 Imputation of Missing data

Efficacy: As the patients were in the hospital until discharge, missing data in the daily WHO clinical status scores were few. To facilitate the definition of the durable response as part of the primary efficacy endpoint which now requires five consecutive days of clinical status score at 4 or lower, a very limited and conservative imputation will be implemented to impute a missing clinical status score if adjacent to a valid score on both sides, the imputed score will be the higher (worse) of the two. For example, if Day 10 score is missing with Day 9 score of 5 and Day 11 score of 4, then the imputed Day 10 score will be 5.

Safety: To handle missing or partial AE and concomitant medication date, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the dose date, then impute the month and day of the dose date.
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the dose date.
    b. otherwise, assign "01"

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then do not impute the date and mark as ongoing for AE and Concomitant medication.
3. If month is known but the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of first study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant while the AE is defined by start date.
If the Adverse Event Relationship flag is missing, the relationship for adverse event will be imputed and will be considered as possibly related. If the Adverse Event Severity flag is missing, the severity will be imputed with the maximum severity will be considered as severity.

9.6 Sample Size Calculation

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 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.

9.7 Interim Analysis

Details of the interim analysis are provided in the appendix I "Interim Analysis".

9.8 Statistical Software

All statistical analyses will be performed with SAS®, Version 9.4 or later.

10 Statistical Analyses

10.1 Subject Disposition

Subject disposition will be tabulated with number and percentages of patient's screen failed, randomized, received one or more doses of study treatment, completed the study according to the protocol or discontinued the study prematurely. The patients who prematurely discontinued the study and the reasons for their discontinuation will be presented. The disposition table will be summarized using "Screened population" by treatment group.

10.2 Demographic Data and Baseline Characteristics

The demographic data and baseline characteristics will be summarized using descriptive statistics or by frequency and percentage for the applicable parameters using SAF Population by treatment group.

- Gender
- Age
- Race
- Height
- Weight
- Nationality
- BMI
- No. of days since first onset of symptoms associated with COVID-19 (at baseline)
- Clinical Status by 10-point ordinal scale
- Clinical Status by 8-point ordinal scale
- National Early Warning Score (NEWS Score)
- COVID-19 associated symptoms
- RT-PCR (Was RT-PCR test performed for SARS-CoV 2 ?)
- RT-PCR result
- Chest X-ray total RALE score

10.3 Medical History

All general medical history conditions and concomitant diseases will be coded using MedDRA version 23.0. General medical history conditions and concomitant diseases will be summarized by system organ class, preferred term and by treatment group using SAF population. The version of the utilized dictionary will be presented as part of the provided tables and listings. Listing of medical history will be provided.

10.4 Prior, concomitant and rescue medication

Prior, concomitant and rescue medications will be assessed at screening and at each subsequent study visit. Medications will be coded using WHODG B3 Mar 1, 2020.

Medication will be classified as prior, if the end date is known and is prior to the first use of the study medication. Medications that are ongoing or ended after the first use of the study medication will be classified as concomitant. All concomitant medication which are classified as rescue medication in eCRF will be considered as rescue medication. If the end date of the medication is unknown, it will also be considered as concomitant. Handling of missing date explained in section (Imputation of missing data section 9.5).

Prior, concomitant and rescue medications will be separately summarized by ATC class (the highest available level), preferred name, treatment group and by Stage I (both Prior and concomitant) and Stage II (Only for Concomitant medication) for the SAF population. Listings will be presented for prior and concomitant medications.

10.5 Treatment Exposure and Compliance

Treatment start date will be defined as date of first dose administration on Day 1. Treatment end date will be defined as date of Last Study Medication.

Treatment duration:
Duration of treatment exposure is derived as treatment end date – treatment start date + 1. The duration of treatment exposure will be summarized descriptively using SAF population by treatment group. Also, number of tablets administered, missed, additional tablets administered will be summarized; Data listing will be presented for dose administration.

Overall Treatment compliance: [{(A/B) * 100} + {(C/D)*100}]/2
Where,

A= Total actual number of tablets taken in the morning

B= Total Planned number of tablets to be taken in the morning

C= Total actual number of tablets taken in the evening

D= Total Planned number of tablets to be taken in the evening

The treatment compliance will be summarized descriptively using SAF population.

10.6 Efficacy Analysis

10.6.1 Primary Efficacy endpoint

Primary Efficacy endpoint will be as follows:

1. **Time to resolution of hypoxia**

The primary efficacy endpoint is "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), (as applicable) 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.

Note: Part c) is applicable to patients in both a) and b).
i.e. Time to resolution of Hypoxia = either "a and c" OR "b and c" is met.

Time to resolution of hypoxia will be compared between the treatment groups using the Cox proportional hazard model with age, gender, and baseline score on the 10-point ordinal scale of clinical status as covariates. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two-sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model.

As the patients were in the hospital until discharge, missing data in the daily WHO clinical status score were few. To facilitate the definition of the durable response, a very limited and conservative imputation will be implemented to impute a missing clinical status score if adjacent to a valid score on both sides, the imputed score will be the higher (worse) of the two, as discussed in Section 9.5.1.

Necessary steps will be taken to properly manage the situation of informative censoring for patients who did not reach the resolution of hypoxia endpoint. 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.

The above primary endpoint analysis will be done using ITT population

Also, the primary efficacy analysis will be repeated using PP population.

Sensitivity analysis for primary endpoint [1] [2]:

Three sensitivity analyses are planned.

1. The first is a more relaxed definition of time to resolution of hypoxia. In this analysis, the resolution of hypoxia is defined if subject's clinical status score ≤ 4 is maintained for two consecutive days. The timing of the resolution event will still be the first day when the score falls to 4 or lower. This sensitivity analysis will be done using ITT as described in the primary endpoint.

2. The second sensitivity analysis will be based on Kaplan-Meier estimates and log-rank test. Median time to event, along with standard error, percentage of patients achieved resolution of hypoxia, percentage of patients censored, and two-sided p-value obtained using log-rank test at 5% level of significance will be presented for observed case using ITT population.

3. The third sensitivity analysis will be a worst-rank analysis proposed by Lachin (1999). The two treatment groups will be compared by a Wilcoxon-Mann-Whitney test as implemented in SAS PROC NPAR1WAY. Tied ranks will be assigned the midrank. The ranks will be determined as follows:

   1) The lowest (best) ranks will be given to patients who meet the primary endpoint definition of treatment success, beginning with the earliest treatment success after beginning of treatment, and survive to Day 28.

   2) The next lowest ranks will be given to patients who do not meet the definition of success but are lost to follow-up or are missing endpoint data for Day 28, but survive to Day 28, beginning with the earliest day for which data are lost for the rest of the study.

   3) The next lowest ranks will be given to patients who are informative withdrawals – i.e., they withdraw for a reason related to probable treatment failure – but survive to Day 28, beginning with the withdrawals closest to Day 28 (i.e., the latest withdrawals).

   4) The next lowest ranks will be given to patients who are followed to Day 28 but do not meet the primary endpoint definition, beginning with patients with the lowest clinical status score on Day 28.

   5) The highest (worst) ranks will be given to patients who die, beginning with the deaths closest to Day 28. Thus, the highest rank will be assigned to the first death.

   This sensitivity analysis will be done using ITT population.

Listing will be provided for the 10-point ordinal scale of clinical status and oxygen saturation level.

10.6.2 Secondary Analysis:

All secondary analysis will be done using ITT population.

1. Time to discharge from hospital

   Time to discharge from hospital = Date of discharge – Date of randomization +1

Time to discharge in days will be summarized descriptively. Time to discharge will be compared between the treatment groups using the Cox proportional hazard model. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model; Also Median time, quartile, inter quartile range estimate will be presented.

Patients whose does not discharged up to Day 28 will be right censored as of day 28. Patients who discontinue the study for any reason – withdrawal because of an adverse event or worsening of symptoms, switch to rescue therapy, loss to follow-up, etc. – will be right censored at Day 28.

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).

Time to ALL COVID-19 associated symptoms to become '0=absent' or 'mild =1' from Randomization = Earliest Date of ALL COVID-19 associated symptoms became either '0=absent' or 'mild =1' in assessments over a period of 24 hours – Date of randomization + 1

Time to ALL COVID-19 associated symptoms to become '0=absent' or 'mild =1' from Randomization will be summarized descriptively. Time to ALL COVID-19 associated symptoms to become '0=absent' or 'mild =1' from Randomization will be compared between the treatment groups using the Cox proportional hazard model. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model; Also Median time, quartile, inter quartile range estimate will be presented.

Patients whose symptom score not improved to either '0=absent' or 'mild =1 by Day 28 will be right censored as of day 28. Patients who discontinue the study for any reason – withdrawal because of an adverse event or worsening of symptoms, switch to rescue therapy, loss to follow-up, etc. – will be right censored at Day 28.

Listing will be provided for COVID-19 associated symptoms.

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 time points)

Patients will be considered as improvement in ALL COVID-19 associated symptoms if ALL COVID-19 associated symptoms as either '0=absent' or 'mild =1'

Patients will be considered as improvement in ALL COVID-19 associated symptoms by Days 4, 7, 10 14, 21 and 28 will be summarized by number and percentage. Two sided Chi-square test/ Fisher-Exact (Fisher Exact test will be performed when the expected count for any cell is less than 5) test at 5% level of significance will be performed to test the difference of proportion between two treatments.

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.

Time to achieve symptom improvement will be considered to have been met at the earliest timepoint when the particular symptoms score has decreased by at least 1 grade over baseline.

Time to achieve symptom improvement = Date of Change from baseline value for the particular symptom score to become less than or equal to '-1' and sustained at evaluations over a period of 24 hours – Date of randomization +1

Time to achieve symptom improvement will be as follows:

Time to achieve symptom improvement will be summarized for each of the listed COVID-19 associated symptoms descriptively. Time to achieve symptom improvement of the listed COVID-19 associated symptom will be compared between the treatment groups using the Cox proportional hazard model with the baseline symptom score of each symptom as covariate and median time to achieve change from baseline as dependent variable. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model; Also Median time, quartile, inter quartile range estimate will be presented.

Patients whose each symptom score does not improved by at least 1 grade over baseline up to Day 28 will be right censored as of day 28. Patients who discontinue the study for any reason – withdrawal because of an adverse event or worsening of symptoms, switch to rescue therapy, loss to follow-up, etc. – will be right censored at Day 28.

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 the 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.

   Patients reporting a clinical relapse of COVID-19 will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact test at 5% level of significance will be performed to test the difference of proportion between two treatments with two-sided 95% level of significance.

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.

   Time to negative conversion will be compared between the treatment groups using the Cox proportional hazard model with cycle threshold value (RdRp Target) at baseline as covariate. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model; Also Median time, Quartile, Inter quartile range estimate will be presented and Kaplan-Meier plot will be plotted. Patients who don't turn to be SARS-CoV-2 negative by Day 28 will be right-censored as of day 28. Patients who discontinue the study for any reason – withdrawal because of an adverse event or worsening of symptoms, switch to rescue therapy, loss to follow-up, etc. – will be right censored at Day 28.

   Listing will be provided for RT-PCR.

7. Percentage of patients showing negative conversion of detectable SARS-CoV-2 viral RNA in the RT-PCR assays of respiratory samples on Days 5, 10 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints).

   Patients showing negative conversion (of detectable SARS-CoV-2 viral RNA) in the RT-PCR assays of respiratory samples on Days 5, 10 and 28 or discharge will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact (Fisher Exact test will be performed when the expected count for any cell is less than 5) test at 5% level of significance will be performed to test the difference of proportion between two treatments.

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 time points)

Time to Clinical status score improvement by 1 = Date of first time the status trial score improved by 1 following baseline assessment – Date of randomization +1

Time to Clinical status score improvement by 2 = Date of first time the status trial score improved by 2 following baseline assessment – Date of randomization +1

Changes in 10-point ordinal scale score from baseline until discharge will be summarized descriptively by visit and treatment group. The LSM, its 95% CI, and SE will be calculated by treatment group for each measurement point using the Mixed Model Repeated Measures (MMRM) with changes from baseline as an objective variable. Furthermore, differences in LSM between the treatment groups and its 95% CI will be calculated and compared between the treatment groups. Corresponding two-sided p-value at 5% level of significance will be presented.

Time to clinical status score improvement by 1 and by 2 points will be compared between the treatment groups using the Cox proportional hazard model with 10 point ordinal clinical status score at baseline as covariate. The hazard ratio and its corresponding two-sided 95% confidence interval (CI) and two sided *p*-value at 5% level of significance will be obtained from the above Cox proportional hazard model; Also, Median time, Inter quartile range estimate will be presented. Patients who doesn't have any Clinical status score of 4 or lower up to day 28 and patients who doesn't have improvement by 1 and 2 point in clinical status score from baseline up to day 28 will be right-censored as of day 28. Patients who discontinue the study for any reason – withdrawal because of an adverse event or worsening of symptoms, switch to rescue therapy, loss to follow-up, etc. – will be right censored at Day 28.

Proportion of patients showing clinical status score of 4 ('hospitalized, no oxygen required') or lower which 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 time points) will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact (Fisher Exact test will be performed when the expected count for any cell is less than 5) test at 5% level of significance will be performed to test the difference of proportion between two treatments.

Proportion of patients showing clinical status score improvement by 1 and by 2 points attained by Days 4, 7, 10, 14, 21 and 28 or discharge (if discharge happens earlier than one or more of the above-mentioned time points) will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact (Fisher Exact test will be performed when the expected count for any cell is less than 5) test at 5% level of significance will be performed to test the difference of proportion between two treatments.

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 time points)
    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 time points)
    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 time points)

Time (no. of days) from randomization to attain clinical status score of 4 or lower, Time (no. of days) from randomization to attain clinical status score of 3 or lower and Time (no. of days) from randomization to clinical status score improvement by 1 and by 2 points (from baseline) will be analysed descriptively by treatment group.

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), 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 time points) and 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 time points) will be summarized by number and percentage using treatment group.

Listing will be provided for 8-point ordinal scale.

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

Change from baseline will be calculated for Total RALE Score based on average score of both the examiners.

Change from baseline will be summarized descriptively by visit and treatment group. The LSM, its 95% CI, and SE will be calculated by treatment group for each measurement point using the Mixed Model Repeated Measures (MMRM) with changes from baseline as an objective variable. Furthermore, differences in LSM between the treatment groups and its 95% CI will be calculated and compared between the treatment groups. Corresponding two-sided p-value at 5% level of significance will be presented.

Also, proportion analysis of patients that 'improved' 'no change' and 'worsened' from baseline by Days 4, 7, 10, 14, 28 or discharge (if discharge happens earlier than one or more of the above-mentioned timepoints) will be presented.

Listing will be provided for chest X-ray.

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

Changes over time in the National Early Warning Score-2 will be summarized descriptively.

The LSM, its 95% CI, and SE will be calculated by treatment group for each measurement point using the MMRM with changes from baseline as an objective variable. Furthermore, differences in LSM between the treatment groups and its 95% CI will be calculated and compared between the treatment groups. Corresponding two-sided p-value at 5% level of significance will be presented.

Listing will be provided for National Early Warning Score-2.

12. Percentage of patients requiring, until Day 28 or discharge from hospital (if discharge happens earlier)
    a) Management in intensive care unit (ICU)
    b) High Flow Nasal Oxygen or Non-invasive mechanical ventilation
    c) Invasive mechanical ventilation

Percentage of patients requiring, until Day 28 of treatment of Management in intensive care unit (ICU), High Flow Nasal Oxygen supplementation or Non-invasive mechanical ventilation and Invasive mechanical ventilation will be summarized by number and percentage.

Listing will be provided for Hospitalization.

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

Definition of time to Management in intensive care unit, High Flow Nasal Oxygen supplementation and Non-Invasive Mechanical Ventilation and Invasive mechanical ventilation will be as follows:

Time to Management in intensive care unit = Start date of first admission to ICU of the COVID management hospital facility – Date of randomization +1

Time to High Flow Nasal Oxygen supplementation or Non-invasive Mechanical Ventilation = Start date of first administration of high flow nasal oxygen or non-invasive mechanical ventilation (earlier of the two, in case both have been administered) – Date of randomization +1

Time to Invasive mechanical ventilation= Start date of first time Invasive mechanical ventilation– Date of randomization +1

Time (no. of days) for Management in intensive care unit (ICU), High Flow Nasal Oxygen supplementation or non-invasive mechanical ventilation and Invasive mechanical ventilation will be analyzed descriptively. Log-rank test will be used to compare the median time for patients to start "Management in intensive care unit (ICU)", "High Flow Nasal Oxygen supplementation", "Non-invasive mechanical ventilation" and "Invasive mechanical ventilation" between the two treatment groups.

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)

Definition of time to Managed in intensive care unit, On Oxygen supplementation, On High Flow Nasal Oxygen Supplementation, On Non-invasive Mechanical Ventilation and On Invasive mechanical ventilation will be as follows:

Number of days Managed in intensive care unit = Stop date of ICU management – start date of ICU management + 1

Number of days On Oxygen supplementation= Stop date of Oxygen supplementation – start date of Oxygen supplementation + 1

Number of days On High Flow Nasal Oxygen = Stop date of High Flow Nasal Oxygen – start date of High Flow Nasal Oxygen + 1

Number of days On Non-Invasive mechanical ventilation= Stop date of Non-Invasive mechanical ventilation – Start date of Non-Invasive mechanical ventilation + 1

Number of days On Invasive mechanical ventilation= Stop date of Invasive mechanical ventilation – Start date of Invasive mechanical ventilation + 1

Duration (no. of days) for Managed in intensive care unit (ICU), on Oxygen supplementation On High Flow Nasal Oxygen Supplementation, On Non-invasive Mechanical Ventilation and on Invasive mechanical ventilation will be summarized descriptively. ANOVA will be used to compare the mean time(days): "Managed in intensive care unit (ICU), On Oxygen supplementation, On High Flow Nasal Oxygen Supplementation, On Non-invasive Mechanical Ventilation and On Invasive mechanical ventilation" between the two treatment groups.

Note: patients with multiple episodes of Managed in intensive care unit (ICU), On Oxygen supplementation, On High Flow Nasal Oxygen Supplementation, On Non-invasive Mechanical will be summed together and total duration (number of days) will be used for analysis.

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).

Patients dying due to any cause and COVID-19 associated complication will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact test at 5% level of significance will be performed to test the difference of proportion between two treatments with two-sided 95% level of significance.

Stage II

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.

Percentage of patients reporting a clinical relapse of COVID-19 when assessed from day of discharge to 59 days after the start of study treatment (Day 60) will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact test at 5% level of significance will be performed to test the difference of proportion between two treatments with two-sided 95% level of significance.

2. Proportion of patients
   a. with disease worsening and requires:
      v. Admission to ICU
      vi. High flow nasal oxygen
      vii. Non-invasive mechanical ventilation
      viii. Invasive mechanical ventilation
      (AND)
   b. dying
      until day 60 (regardless of whether patients are discharged from hospital before Day 28 or not)

Proportion of patients with disease worsening will be summarized by number and percentage. Two-sided Chi-square test/ Fisher-Exact test at 5% level of significance will be performed to test the difference of proportion between two treatments with two-sided 95% level of significance.

10.7 Safety Analysis

10.7.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 23.0), the coded terms will be used for summarizing the AE(s). Only treatment emergent adverse events (TEAE) will be summarized in tables, while all events will be listed. Adverse events will be analyzed using SAF population.

An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first study drug administration or any AE that exist prior to first dose and if it increased in severity during the study period. All AEs reported in stage II period- "Day of discharge to 59 days after date of first dose of study treatment' will be considered as TEAE. Handling of missing data and date are explained in section 9.5.1 (Imputation of missing data).

An overall summary table, which summarizes, the number and percentages of patients with treatment emergent adverse events at stage I & stage II , serious adverse events, adverse events leading to death, adverse events related to study drug, Study Drug Discontinued Permanently due to adverse event and adverse events by severity categories will be provided by treatment groups.

A separate treatment emergent adverse event table for stage II will be summarized for number and percentage of patients with treatment emergent adverse event (TEAE), serious TEAE, TEAE related to study drug and TEAE by severity categories will be provided by treatment groups.

Patients experiencing any treatment emerging adverse events will be summarized by Preferred Term (PT), SOC and treatment group. The number and percentage of patients with at least one TEAE, SAE, permanently discontinued study treatment (IP) due to AE, AE leading to Death, AE by relationship and TEAEs of severe intensity will be summarized by system organ class, preferred term and treatment group.

Furthermore, listings of SAEs and AEs that lead to study withdrawal will be provided.

AEs Tables by primary system organ class, preferred term and treatment group will be sorted in descending order of counts.

A patient experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a patient experiences multiple AEs within the same system organ class that patient will be counted only once in that system organ class. Maximum severity will be considered if a patient has multiple severity reported for same AE. In summaries by relationship, if a subject has the same AE on multiple occasions, the closest relationship to study drug, will be used for summary.

10.7.2 Laboratory assessments

Laboratory assessments will be measured at screening, 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 timepoints). Laboratory assessments will be summarized by treatment group and time point using SAF population.

The actual and change from baseline laboratory assessments parameters will be summarized descriptively by time point and treatment group.

The results falling out of normal ranges will be classified as High and Low and will be summarized by time point and treatment group. In addition, number and percentage of patients having 'Normal', 'Abnormal CS' and 'Abnormal NCS' results for laboratory parameters will be summarized by visits and treatment group.

Data listings will be presented for laboratory parameters.

10.7.3 Vital Signs

Vital signs will be measured at Screening, Day 1, Day 2 to Day 28 or discharge (if discharge happens earlier)
Vital signs will be analyzed using SAF population.

The vital signs parameters include:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (brpm)
- Body Temperature (°F)
- Blood Oxygen Saturation (SpO2) (%)

The actual and change from baseline vital signs parameters will be summarized descriptively by visits and treatment group.

Data listings will be presented for vital signs parameters.

10.7.4 ECG

ECG will be assessed at Screening, Day 1, Day 4, Day 7, Day 10, Day 14, Day 21 and Day 28 or discharge (if discharge happens earlier then one or more of the above-mentioned timepoints). The ECG parameters are as follows:

- PR Interval
- RR Interval
- QRS Duration
- QT Interval
- QT_cB Interval
- Heart Rate

The actual and change from baseline of quantitative ECG parameters will be summarized descriptively by visits and treatment group.

Quantitative ECG parameters will be analyzed descriptively and the proportion of patients in each class based on ECG interpretation (Normal, Abnormal CS, Abnormal NCS) will be summarized by frequencies and percentages using the SAF population by time point and treatment group.

Listing will be provided for the ECG.

10.7.5 Physical Examination

Complete Physical Examination will be assessed at screening. Partial Physical Examination will be assessed at Day 1, Day 2 to Day 28 or discharge (if discharge happens earlier). Complete Physical examination will include general appearance, skin, head, neck, ENT, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes. Partial Physical examination will include general appearance, ENT, heart and lungs nodes.

Physical Examination findings will be summarized by frequencies and percentages using the SAF population and treatment group.

Listing will be provided by subject for the Physical Examination.

10.7.6 Chest X ray

Chest X ray will be assessed at screening, Baseline, Day 4, Day 7, Day 10, Day 14 and Day 28/EOS.

The chest-X ray analysis has been described in the secondary endpoint section point number 9;

Listing will be provided by subject for the Chest-X ray.

10.7.7 Pregnancy Test

Listing will be provided for female subjects for the serum Pregnancy Test at each time point

10.7.8 IMP Administration

Listing will be provided for the IMP administration along with treatment compliance for each patient.

10.7.9 COVID-19 associated symptom severity assessment

COVID-19 associated symptom severity will be assessed at screening. Day 1, Day 2 to Day 28 or discharge (if discharge happens earlier).

COVID-19 associated symptom severity assessment parameters will be summarized by frequencies and percentages using the SAF population by study day and treatment group.

Listing will be provided for the COVID-19 associated symptom severity assessment.

10.7.10 Hospitalization

Listing of patients who require oxygen supplementation, ICU admission, Oxygen by HFNC or NIV and Invasive Mechanical Ventilation will be listed.

10.7.11 Subgroup Analysis:

Subgroup analysis will be performed for the "Time to resolution of hypoxia" by considering the severity category (moderate vs severe categories) as a subgroup using ITT population as an observed case analysis.

Subgroup analysis will be performed for the "Time to resolution of hypoxia" by considering the race category (White/ Caucasian vs Non-White / Non-Caucasian) as a subgroup using ITT population as an observed case analysis.

Subgroup analysis will be performed for the "Time to resolution of hypoxia" by considering the age category (Age group <50 years, Age group >=50 years) as a subgroup using ITT population as an observed case analysis.

Subgroup analysis will be performed for the "Time to resolution of hypoxia" by considering the gender category as a subgroup using ITT population as an observed case analysis.

11 Deviation from the Study Protocol

Not applicable

12 Database Lock and Unblinding

There will be two database lock for this study. One for stage I (Primary) and another one for Stage II (Secondary) analysis. The SAP will be finalized prior to primary database lock. After the data cleaning process is finalized according to the data management plan (DMP) and the assignment of patients to the analysis populations is agreed and signed by the Sponsor, the study database will be locked for primary and secondary separately.

13 References

1. *Lachin J. M. (1999). Worst-Rank Score Analysis with Informatively Missing Observations in Clinical Trials. Controlled Clinical Trials. 20:408–422.*

14 Appendices

Appendix I: Interim Analysis Plan

Appendix I: Interim Analysis Plan

A single unblinded interim analysis of the primary efficacy endpoint, that is, time to resolution of hypoxia, will be conducted. Resolution of hypoxia is defined as described in Section 10.6.1. This endpoint will be considered to have been met when the patient had attained a score of 4 or lower on the 10-point ordinal scale of clinical status used by the WHO in the SOLIDARITY trial, and either maintained the score of 4 or lower for five consecutive assessments over 5 days or was discharged after reaching the score of 4 or lower. In addition, the patient must also survive and not be readmitted to hospital due to COVID-19 related complications through Day 28 to be considered meeting the endpoint. To be performed when data for time to resolution of hypoxia become available for either the first 390 randomized subjects (50% of the target enrollment) or subjects enrolled by the end of year 2020, whichever is earlier, interim analysis will be conducted for three purposes: 1) Possible early stopping for demonstrated efficacy of the study treatment, 2) Possible early stopping for futility (lack of efficacy), and 3) Sample size reassessment. After reviewing the analysis, the DMC will make a recommendation concerning continuation of the study as planned, termination, or continuation with a larger sample size.

The interim analysis for efficacy will be performed like the primary efficacy analysis detailed in Section 10.6.1 of the Statistical Analysis Plan for the final analysis. Time to resolution of hypoxia will be compared between the treatment groups using the Cox proportional hazard model with age, gender, and baseline score on the 10-point ordinal scale of clinical status as covariates. A Lan-DeMets alpha spending function approach will be adopted in order to maintain the overall Type-I error or alpha at the desired two-sided 0.05 level (Lan & DeMets, 1983). The boundary for possible early stopping for demonstrated efficacy will be determined using a Type I error rate of 0.005 (one-sided); that is, the null hypothesis of zero treatment effect will be rejected if the observed effect is in the direction of treatment benefit and it is significant with one-sided $p < 0.005$. If the trial is not stopped after the interim analysis, the final primary efficacy analysis conducted upon study completion will be based on an adjusted Type I error rate of two-sided 0.04521 (i.e., the result will be considered statistically significant for a Z-statistic ≥ 2.0027).

Assuming the Z-statistic does not reach the boundary for early stopping for demonstrated efficacy, an analysis will be conducted for possible early stopping for futility. A DMC recommendation of early stopping for futility will be based on two factors. The first factor is the conditional power, i.e., the probability of finding a significant beneficial treatment effect with adjusted Type I error rate of two-sided 0.04521 at the end of the study, given the current data and appropriate assumptions about the true treatment effect. The second factor is the estimated effect size from the interim analysis. The DMC may recommend the study be stopped for reasons of futility if either 1) the conditional power is very low (for example, 20% or lower), assuming a hazard ratio equal to the estimated hazard ratio from the current data, or 2) the upper limit of a 95% confidence interval for the difference in median time to resolution of hypoxia is < 1 day. The conditional

power will be calculated as in Lachin (2005) and Chen, DeMets, & Lan (2004). Median times to resolution of hypoxia will be estimated by the Kaplan-Meier method.

If the interim analysis results do not suggest early stopping for efficacy or futility, the DMC will consider whether to recommend an increase in sample size, following the method given by Chen, DeMets, & Lan (2004). Conditional power will be calculated under the assumption that the true underlying hazard ratio is the same as the estimate from the current data. If this conditional power is less than 80%, the increase in sample size necessary to make the conditional power 70%, 75%, or 80% will be calculated. If the conditional power with the currently planned sample size is ≥ 50% and the sample size increment required for the desired power is less than approximately 1.5 times the original sample size, increasing sample size by this method will not affect the Type I error rate. In addition, simulations suggest the Type I error in this analysis will not be inflated for conditional power ≥ 20% and < 50%, as long as there is a stopping rule for very low conditional power (Lan & Trost, 1997). If the increase in sample size required to achieve a desired power is not feasible, a smaller increase may be made.

Two key secondary endpoints will also be analyzed in the interim analysis for considering by the DMC in their deliberations. These two endpoints are time to discharge from hospital and time to improvement from baseline of at least 2 points on the 10-point clinical status scale. Cox models and Kaplan-Meier analysis will be employed, as for the primary endpoint. Missing values will not be imputed.

Mortality and disease progression endpoints will be analyzed in the interim analysis. These analyses will be exploratory and will be based on the observed data only. The mortality endpoints will include patients dying from any cause and patients dying from a COVID-19 associated complication. Between-treatment comparisons will be performed for these mortality endpoints, as both binary and as time to event outcomes. For disease progression, patients requiring, until the earlier of Day 28 or discharge from hospital, management in intensive care unit, high flow nasal oxygen / non-invasive mechanical ventilation, and invasive mechanical ventilation will be separately tabulated. Time from randomization to each of these disease progression events will be compared between treatments. In addition, the duration of requiring (as measured by the number of days) management in intensive care unit, non-invasive mechanical ventilation, and invasive mechanical ventilation will be compared separately. Covariate-adjusted analyses will be performed if needed.

References:

Chen, Y. H., DeMets, D. L., & Lan, K. K. G. (2004). Increasing the sample size when the unblinded interim result is promising. Stat Med. 23(7): 1023-38.

Lachin J. M. (2005). A review of methods for futility stopping based on conditional power. Stat Med. 24: 2747-2764.

Lan K. K. G., DeMets D. L. (1983). Discrete sequential boundaries for clinical trials. Biometrika. 70: 659–663.

Lan, K. K. G., Trost D. C. (1997). Estimation of parameters and sample size re-estimation. Proceedings of the American Statistical Association, Biopharmaceutical Section: 48-51.