NOVOTECH
The Asia Pacific CRO

STATISTICAL ANALYSIS PLAN

A RANDOMIZED OPEN LABEL PHASE 2B/3 STUDY OF THE SAFETY AND EFFICACY OF NP-120 (IFENPRODIL) FOR THE TREATMENT OF HOSPITALIZED PATIENTS WITH CONFIRMED COVID-19 DISEASE (Pilot Phase)

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SAP APPROVAL

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List of Abbreviations

Abbreviation	Term
aPTT	Activated Partial Thromboplastin Time
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CSRs	Clinical Study Reports
CIs	Confidence Intervals
COVID-19	Coronavirus Disease Of 2019
CIF	Cumulative Incidence Function
DBP	Diastolic Blood Pressure
eCRF	Electronic Clinical Reporting Form
ECMO	Extracorporeal Membrane Oxygenation
FiO2	Fraction Of Inspired Oxygen
γ-GT/GGT	Gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
ID	Identifier
ICU	Intensive Care Unit
ITT	Intent-To-Treat
IL-12	Interleukin 12
IL-6	Interleukin 6
INR	International Normalised Ratio
IP	Investigational Product
KM	Kaplan-Meier
MP	Master Protocol
NEWS	National Early Warning Score
O2	Oxygen
SpO2	Oxygen Saturation
PaO2	Partial Pressure Of Oxygen
PP	Per Protocol
PCR	Polymerase Chain Reaction
PT	Prothrombin Time
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	Standard Of Care
SOPs	Standard Operating Procedures
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
TID	Ter In Die
TEAEs	Treatment Emergent Adverse Events
TNF-alpha	Tumor Necrosis Factor Alpha
IFNγ	Type II Interferon
VAS	Visual Analog Scale
WHO	World Health Organisation

Abbreviation	Term
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected from the AGN120-3 study (protocol version *2.0* dated *16 November 2020*). This SAP only covers the Phase2b part of the trial.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This is a Phase 2b/3, multicenter, open label, randomized, parallel group study to evaluate the efficacy of Ifenprodil in patients with coronavirus disease of 2019 (COVID-19) disease.

In the Phase 2b phase, patients will be randomized in a ratio of 1:1:1 to either a) 20 mg TID IP plus Standard of Care group, b) 40 mg TID IP plus Standard of Care or c) Standard of Care only group. Investigators will collectively enroll approximately 50 evaluable patients in each treatment group, for a total of 150 patients. Patients receive either oral Ifenprodil (20 or 40 mg ter in die (TID)) for up to 14 days in addition to Standard of Care, or Standard of Care only. The Standard of Care (SOC) for each patient will be captured in the electronic clinical reporting form (eCRF).

Randomization will be stratified by site, and age (<65 versus ≥65).

For Phase 2b, one interim statistical analysis will be performed on selected efficacy endpoints and for safety for each arm after the first 75 patients have completed up to 2 weeks of treatment (Day 15). This analysis is being done to allow safety assessment and some snapshots of efficacy assessments as the trial progresses.

The Phase 2b study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Data from the Phase 2b study will be used to down select and prioritize the secondary endpoints. The protocol would then be amended for Phase 3 study to include the additional required number of patients to be recruited for the study to meet statistical significance in its primary endpoint.

An additional placebo arm will be added in the Phase 3 portion of the study. The number of participants to be enrolled in Phase 3 pivotal stage will be determined based upon the outcome of pilot Phase2b stage of the study. Participants will be randomized to receive investigational product (IP) plus SOC, or Placebo plus SOC. Details will be outlined in a protocol amendment

Figure 1: Trial Design

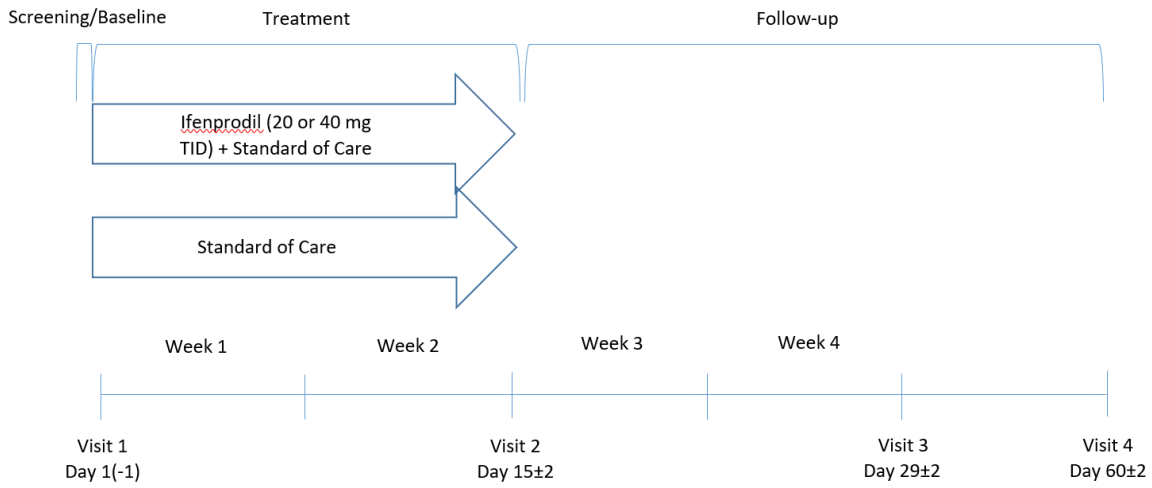

Table 1 Schedule of Events

Trial Activity	Screening/Baseline/ Enrolment visit	Daily until hospital discharge	End of treatment	Follow-up period	
Day	1	2-14	15	29	60
Allowed window for visit (±)	-1[a]		2	2	3
Visit	1		2[b]	3	4
Informed consent	●				
Inclusion/exclusion criteria including confirmation of COVID-19 diagnosis	●				
Confirmation SARS-CoV-2[h]	●	●	●	●	
Pregnancy test	●				
Demographics/Medical History	●				
Physical Exam	●				
Vital signs[c]	●	●	●	●	
Clinical support data collection[f]	●	●	●	●	
Safety Laboratory Testing[d]	●	●	●	●	
Cytokine Markers[k]	●	●	●		
Child-Pugh Score[i]	●	●			
PaO2 and PaO2/FiO2 ratio[j]	●	●	●	●	
ECG	●				
Cough Severity (VAS)[e]	●	●	●	●	
Extent of Dyspnea (Likert Scale)[e]	●	●	●	●	
Adverse Events documented	●	●	●	●	●
Concomitant Medications	●	●	●	●	
Randomization	●				
Administer IP	●	●			
Vital Status					●[g]

[a] Screening/baseline may occur up to 24 hours prior to randomization
[b] Treatment can be given up to 14 days post randomization, or until hospital discharge, whichever comes first. If patient is discharged prior to Day 14, the next visit should be Visit 2.
[c] Includes blood pressure (measured after the patient has been in a seated position (if possible) for ≥3 minutes of rest), pulse, respiratory rate, body temperature, and SpO2. Body weight and height will be measured at the screening visit only.
[d] Baseline, Days 3, 5, 8, 11 if hospitalized, Day 15, Day 29
[e] Baseline, Days 2, 4, 8, and 14 if hospitalized, Day 15 (if not done Day 14), Day 29
[f] Includes NEW Score, on Baseline, Days 3, 5, 8, 11 if hospitalized, Day 15, Day 29
[g] Vital status (is patient alive)
[h] Baseline, Days 5 (or discharge, whichever comes first) and 15. Day 29 for patients with viral RNA detected at Day 15. Qualitative (mandatory) and Quantitative (if available) testing done all days.
[i] Baseline, Days 3, 5, 8, 11 if hospitalized
[j] Minimum complete baseline, Days 3, 5, 8, 11, 15 and 29. If PaO2 not able to be taken, SpO2 should be obtained using a forehead sensor. Fingertip probes may be used if forehead sensors are not available. Remain consistent with the method of testing for the patient over the course of the study.
[k] Cytokine markers at Baseline, Day 5, Day 15 (if available per local lab): IFN-γ, GM-CSF, IL-6, IL-12, TNF-α

2.2 Objectives

2.2.1 Primary objectives

To investigate the clinical efficacy and safety of NP-120 (20 and 40 mg TID) compared to standard of care in patients hospitalized with COVID-19 disease.

- The choice of the primary outcome measure will be determined by a pilot study of the first 150 patients.
- Patient clinical status (on the WHO 7-point ordinal scale) at day 15 is the default primary endpoint

2.2.2 Secondary objectives

To investigate the clinical efficacy of NP-120 (20 and 40 mg TID) as compared to the control arm as assessed by:

- **Ordinal scale:**
  - Time to an improvement of one category from baseline on an ordinal scale.
  - Patient clinical status on an ordinal scale at days 3, 5, 8, 11, and 29.
  - Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 8, 11, 15 and 29 from baseline
- **National Early Warning Score (NEWS)**
  - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS
- **Oxygenation:**
  - Oxygenation free days in the first 28 days (to day 29)
  - Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients
- **Mechanical Ventilation:**
  - Ventilator free days in the first 28 days (to day 29)
  - Incidence and duration of new mechanical ventilation use during the trial
- **Hospitalization:**
  - Duration of hospitalization (days)
  - Time to discharge (days)
- **Mortality:**
  - 15-day mortality
  - 28-day mortality

2.2.3 Exploratory objective

To investigate the effects of NP-120 (20 and 40 mg TID) on lung function, health status, and SARS-CoV-2 RNA status in hospitalized patients with COVID-19 disease.

2.2.4 Safety objective

To study the safety of NP-120 (20 and 40 mg TID) in hospitalized patients with COVID-19 disease.

2.3 Endpoints

2.3.1 Primary endpoint

Patient clinical status (on the WHO 7-point ordinal scale) at day 15 in IP versus SOC control group patients:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
6. Hospitalized, on invasive mechanical ventilation or ECMO
7. Death

2.3.2 Secondary endpoints

- Status on an ordinal scale assessed daily while hospitalized and on days 15 and 28 in IP versus control group patients
- NEWS assessed days 3, 5, 8 ,11 while hospitalized and on days 15 and 29 in IP versus control group patients
- Rate of mechanical ventilation in IP versus control group patients
- Duration of mechanical ventilation (if applicable) in IP versus control group patients
- Duration of supplemental oxygen in IP versus control group patients
- Time to return to SpO2 > 94% on room air
- Duration in ICU (if applicable) in IP versus control group patients
- Rate of Mortality in IP versus control group patients
- Duration of hospitalization in IP versus control group patients
- Time to discharge in IP versus control group patients
- Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients

2.3.3 Exploratory efficacy endpoints

- Changes in the extent of dyspnea from baseline, using a Likert scale, at Days 2, 4, 8, and 14 in IP versus control group
  [Likert scale: The patient grades his/her current breathing compared to when he/she first started the study (from -3 to 3). "0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse]. For the first questionnaire (at baseline), the patient compares their current shortness of breath to their shortness of breath when they are well.
- Rate of change to patient's experience of cough (Visual analog scale [VAS]) at Days 2, 4, 8, and 14 in IP versus control group
  VAS: The patient draws a vertical line on an axial graph (from 0 to 100) to show the degree of how he/she feels about coughing. The number "100" equals the worst coughing the patient has ever felt and the number "0" equals the best he/she has felt since baseline.
- Changes in D-dimer in IP versus control group
- Qualitative PCR for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)
- Quantitative PCR (if available) for SARS-CoV-2 at baseline, days 5 (while hospitalized, and days 15 and 29 (if able to return to clinic or still hospitalized)

2.4 Safety Endpoints:

- Type, frequency, severity, and relationship of AEs to investigational product (IP)
- Number of patients who discontinue IP due to any AE
- Frequency of clinically significant changes in vital signs and/or laboratory findings

2.5 Sample Size

For the pilot phase, a sample of 150 patients (50 in Arm A, Arm B and SOC) will be recruited. To account for drop out of 10%, a total of 168 patients will be enrolled.

For the pivotal phase, A sample of 462 patients (231 in the SOC group and 231 in the active treatment group) achieves 90% power to detect a change in the log odds ratio of 0.5596 when the significance level (alpha) is 0.05 using a two-sided test. A log odds ratio of 0.5596 corresponds to an odds ratio of 1.75 comparing treatment to SOC. The sample size was estimated using the *Tests for Two Ordered Categorical Variables* module in PASS 14. To account for drop out of 10%, a total of 514 patients will be enrolled.

The sample size assumes that the distribution of patients on day 15 will be as shown in Table 2, which is scenario 4 in the WHO master protocol (2020) for enrolled patients with moderate to severe disease under an odds ratio of 1.75.

Table 2 Distribution of Patients Across Outcome Categories at Day 15: SOC (WHO MP Scenario 4) and Treatment (Assuming OR of 1.75)

	Percent of Patients	
Outcome	**SOC**	**Treatment**
7. Death	2	1.0
6. Hospitalized & on mechanical ventilation or ECMO	1	0.6
5. Hospitalized & on non-invasive ventilation or high flow O2	2	1.2
4. Hospitalized & requires supplemental O2	5	3.03
3. Hospitalized not requiring supplemental O2	17	11.45
2. Not hospitalized but limitations on activities	36	31.90
1. Not hospitalized & no limitations on activities	37	50.70

2.6 Randomization

Static randomization using block size of 3 will be employed with stratification by site and age (<65 versus ≥65). Patients who withdraw from the study or are lost to follow-up after signing the informed consent form and randomization will not be replaced.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative (Novotech) Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP).

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings and will be listed and sorted by treatment arm, participant number and visit, where applicable. All descriptive summaries will be presented by treatment group and scheduled visit/time point (where applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD and median values and other derived values will be displayed to one more decimal than the source data for the specific variable.

  95% Confidence Intervals (CIs), mean differences (among treatments and from baseline) and adjusted means values will be displayed to one more decimal than the source data for a specific variable. P-values will be displayed to 3 decimal places.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the aforementioned rules.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

  95% Confidence Intervals (CIs), difference in proportions, odds ratio's and other categorical parameters will be displayed to one decimal place for percentages. Proportions will be displayed to 3 decimal places. P-values will be displayed to 3 decimal places.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.

- Result display convention: Results will be center aligned in all summary tables and listings. Participant identifiers visit and parameter labels may be left-aligned if required.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  Date only: YYYY-MM-DD

  Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

- Specific items in relation to multiple comparisons, missing values, coding of medical, AE and medications and inferential statistics are covered in each of the specialized sections.

3.2 General Key Definitions

The following definitions will be used:

- Date of the First Study Treatment Administration: The date of the first study treatment administration is defined as the earliest date on which a study treatment was administered.
- Date of the Last Study Treatment Administration: The date of the last study treatment administration is defined as the latest known date on which a study treatment was administered.
- Baseline: The Baseline value is value taken on Day 1. If Day 1 value is missing, Baseline is defined as the last available valid, non-missing observation for each patient prior to first study treatment administration on Day 1. Repeat and unscheduled assessments will be included in the derivation of the Baseline values only if Baseline visit value is missing.
- Change from Baseline: The absolute change from Baseline value is defined as the difference between the result collected/derived at a post-baseline visit and the Baseline value.

  The change from Baseline value at each post-baseline visit will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at post-baseline visit – Baseline Value

  The change from Baseline value will only be calculated if the specific post-baseline visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise. In the data listings, the change values will be set to '-' (not applicable) for pre-baseline assessments.

  The rate of change from baseline is defined as: Change from Baseline value/Baseline Value

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study treatment administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study treatment administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

3.3 Handling of Missing Data

All data will be analysed as collected and missing values will not be imputed or replaced unless stated otherwise.

3.4 Treatment Groups

- Arm A: Ifenprodil (20 mg TID)
- Arm B: Ifenprodil (40 mg TID)
- SOC: Standard of Care

4. ANALYSIS POPULATIONS *(ANALYSIS SETS)*

In this study three analysis populations are defined: The Intent-to-Treat (ITT), Per Protocol (PP) and the Safety population.

4.1 Population Descriptions

4.1.1 ITT

The ITT population consists of all enrolled patients assigned to receive treatment regardless of whether they took study drug or stopped active treatment to receive only SOC. Patients will be classified according to the treatment group to which they were randomized.

4.1.2 PP

The PP population consists of all ITT patients who are not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions. Protocol violations that would exclude patients from the PP population will be defined and documented in the SAP prior to unblinding.

4.1.3 Safety

The Safety population consists of all patients who received at least one dose of study drug. This population will be used for all assessments of safety and tolerability. Patients will be summarized according to actual dose of study drug taken.

5. PARTICIPANT DISPOSITION

Participant disposition and analysis population analysis will be based on the all patient population. Participant disposition and analysis populations will be summarized descriptively as described in 3.1.

The following participant enrolment and disposition information will be reported:

Summary of Enrolment:

- Number of Patients Enrolled
- Number of Patients Re-screened
- Number of Screen Failures
- Reasons for Screen Failure (percentage denominator based on number of screen failures):
    - Failed I/E criteria

Summary of Disposition:

- Number of Patients Completed
- Number of Patients Withdrawn/Not Completed
- Reason for Withdrawal/Non-Completion (percentage denominator based on number of withdrawn patients)

Counts and percentages will be reported for summary of enrolment, for all enrolled patients who gave consent. For the summary of disposition counts and percentages will be provided for the ITT population for treatment groups defined in section 3.4.

Listings will be provided for summary of enrolment along with the date the participant provided informed consent, date received study drug/treatment received and sorted by patient ID . For summary of disposition, listing will be provided by treatment arm (section 3.4) sorted by patient ID for the Safety population, along with the date of randomization, date and time of first study drug administration, date of treatment termination/last visit.

6. PROTOCOL DEVIATIONS

All protocol deviations and important protocol deviations leading to exclusion from PPS will be categorized as per protocol deviation management plan version 1.0, 14 July 2020.

Listing of protocol deviation including information on whether the protocol deviation lead to exclusion from PPS will be provided by treatment arm (section 3.4) sorted by patient ID for the Safety population. Age and sex of the patient, date and time of first study drug administration, date of treatment termination/last visit, and whether the patient completed the study will also be included in the listing.

7. ANALYSIS POPULATIONS

The following analysis set information will be reported:

- Patients included in ITT
- Patients included in PPS
- Patients included in Safety

Counts and percentages for these patients under this population set will be provided using the Safety population for treatment groups defined in section 3.4

Listing of patients in analysis sets will be provided by treatment arm (section 3.4) sorted by patient ID for the ITT population, along with date and time of study drug administration, date of treatment termination/last visit, and whether the patient completed the study.

8. DEMOGRAPHICS AND MEDICAL HISTORY

8.1 Demography and Baseline Characteristics

The demographics variables to be reported are listed below:

- Age (years)
- Age classification (< 65 and ≥ 65)
- Gender
- Women of child-bearing potential
- Contraception used – Female
- Contraception used – Male
- Ethnicity
- Race
- Height (cm) at Baseline
- Weight (kg) at Baseline
- BMI (kg/m^2) at Baseline
- BMI<18.5 (Underweight), 18.5 ≤ BMI < 25 (Normal), 25≤ BMI < 30 (Overweight) and BMI>30 (Obese).

These variables will be summarized using descriptive statistics in accordance to section 3.1 under ITT and PPS population for treatment groups defined in section 3.4. Demographics variables and site will also be listed by treatment arm (section 3.4) under ITT population sorted by patient ID.

8.2 Site and Age

Counts and percentages of patients classified by age (< 65 and ≥ 65) at each site will be summarized using ITT population by treatment groups defined in section 3.4. Denominator for site will be based on number of patients in ITT population for each treatment group and denominator for age classification will be based on number of patients within each site for each treatment group.

8.3 Medical /Surgical history

Medical history conditions, medical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23. Patients with any medical history, any ongoing medical history, any medical history resulting in concomitant medication, any medical history resulting in concomitant procedure will be summarized by counts and percentages by treatment arm. Patients with any medical history (SOC and PT) will be summarized using counts and percentages for the Safety population by treatment groups defined in section 3.4. Medical history will be ordered by the highest frequency in the overall column by SOC and PT.

Medical history listings will be provided by treatment arm (grouping provided in section 3.4) sorted by patient ID for the Safety population, along with ongoing status of medical history and age/sex/baseline weight of the patient.

9. PRIOR AND CONCOMITANT MEDICATIONS & THERAPIES

Prior and concomitant medications and therapies will be coded using Anatomical Therapeutic Chemical (ATC) classification system version March 2020 which is controlled by the World Health Organization Drug Dictionary (WHO-DD). Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, with ATC Level 2, ATC Level 4 presented as the primary interest for the analysis.

Concomitant medications and therapies are additional medications or therapies taken on or after the first dose of study treatment up and including the follow up period. Medications or therapies taken before first dose of study drug and stopped before the first dose of study drug will be classified as prior medication/therapy. If missing dates prevent a clear determination as to whether the medication or therapy is concomitant, the medication will be regarded as concomitant.

The number and percentage of patients using at least one prior or concomitant medication/therapy will be displayed together with the number and percentage of patients using at least one medication/therapy within each therapeutic class and preferred term. These will be summarized under Safety population for treatment groups defined in section 3.4 and repeated for concomitant medication/therapy used for different purposes: adverse events, medical history or other.

Listing of full details of prior and concomitant medications/therapy (classification, medication taken, indication (adverse events, medical history or other), corresponding AE or medical history number, dosage, unit and route, start and stop dates/ongoing status will be provided by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

10. TREATMENT EXPOSURE AND COMPLIANCE

SOC medications and therapies will be coded in the same manner as prior and concomitant medication/therapy with ATC Level 2, ATC Level 4 presented as the primary interest for the analysis. Summary of counts and percentages will be provided for all sites and for each site for the ITT, PPS and Safety population, with denominator being the available patients at each site.

- The Treatment Exposure (duration in days) is defined as:

  Date of Last Study Drug Administration - Date of First Study Drug Administration + 1.

- The COVID-19 Treatment Exposure (duration) from randomization during the study is defined as:

  Date and Last treatment - Date of Randomization + 1

- The overall COVID-19 Treatment Exposure (duration) during the study is defined as:

Date and Last treatment - Date of First COVID19 medication/treatment + 1Both of these COVID-19 treatment exposure durations will be categorized into ≤ 15 days, > 15 days but ≤ 29 days, and > 29 days

- The Treatment Compliance is defined as:

  For arm A: Total dosage taken / (3×{Number of days in hospital up to 14 days}×20 mg=840mg)
  For arm B: Total dosage taken / (3×{Number of days in hospital up to 14 days}×40 mg=1680mg)
  No treatment compliance is calculated for SOC as this differs between sites and regimen.

  Treatment compliance with respect to counts and percentage of patients with <80% and ≥ 80% compliance will be reported.

- The Number of Days in Hospital (duration in days) is defined as:

  Maximum of {Date and Time of First Hospital Discharge - Date and Time of First Hospital Admission + 1 or 14 days}.

Treatment exposure in duration and compliance will be summarized using descriptive statistics in accordance to section 3.1 under ITT, PPS and Safety for treatment groups defined in section 3.4. These information will be listed by Arm A and B sorted by patient ID and visit for the ITT and Safety population, along with the age, sex, baseline weight of the patient as well as the dates and times of study drug administration at each visit, whether the patient is in PPS, route and method of administration (after food, crushed) and whether drug administration was interrupted or missed and reasons for dose/study drug not administered.

For SOC, the listing will cover treatment exposure and will be sorted by patient ID and visit for the ITT and Safety population, along with the age, sex, baseline weight of the patient as well as site, ATC Level 2, ATC Level 4 classification of SOC medication/therapy, dosage, unit and route, start and stop dates/ongoing status.

11. EFFICACY AND EXPLORATORY ANALYSES

All efficacy and exploratory analyses will be conducted for ITT and PPS. Listings for all efficacy and exploratory endpoints will be provided at each scheduled timepoints for the ITT population, with an additional flag indicating the inclusion in PPS. All of these will be provided for each treatment arm, sorted by patient ID, along with the age, sex and baseline weight of the patient.

11.1 Primary Efficacy Analysis

For patients who died, their WHO7 responses of 7 (death) will be carried forward to all applicable visits. For example, a patient who died on Day 9, will be recorded as having WHO7 response of 7 on Day 11, 15 and 29.

The SOC and treatment arms under WHO7 ordinal scale will be compared with respect to the primary endpoint using proportional odds models (ordinal logistic regression) adjusted for site and age. Treatment will be compared to SOC by testing whether the common odds ratio differs from 1.0 at day 15 using two-sided tests at 2.5% level of significance under the ITT population set, followed by PP population set. All modeling assumptions will be verified.

The relevant SAS code for proportional odds model takes the following form, where Treatment represents SOC, Arm A, Arm B and Response represents the WHO7 ordinal scale categories.

```
proc logistic data=dataset;
class Treatment Response Site/ param=ref ref=first;
model Response = Treatment Age Site;
run;
```

The odds ratio under the fitted proportional odds model will be reported for Arm A and B vs SOC, along with the Wald 95% CI and corresponding Chi-squared p-value. Score test p-value testing the assumption of proportional odds will also be reported. To adjust for multiple comparison, p-values must be < 0.025 to be considered statistically significant. P-values < 0.05 may still be considered as potentially promising for the next study phase.

In addition, counts and percentages of patients in each of the WHO-7 category will also be reported for each treatment arm.

Separate 95% CIs (Newcombe) and p-values (Chi-Squared test without continuity correction) will be computed across each of the ordinal scale between SOC and treatment arms A and B. To adjust for multiple comparison, p-values must be $< \frac{1}{280}$ or (0.05/14) to be considered statistically significant. The reason for adopting the most stringent rule for multiple adjustment is because this pilot phase of the study is essentially exploratory in nature, and care must be taken to minimize the event of a premature conclusion being made purely due to chance.

The above analyses will be done for ITT and PPS.

11.2 Secondary Efficacy Analysis: General Population Considerations

All secondary efficacy analyses will be performed for ITT and PPS.

11.3 Secondary Efficacy Analysis: Time to Event General Considerations

Time to event endpoints will not be evaluated if any subjects experienced an event prior to randomization in any of the treatment arms.

Time-to-event endpoints without competing risk will be analysed for each dosing group using the Kaplan-Meier (KM) method. Medians (with corresponding 95% confidence intervals) and quartiles (25th and 75th percentiles), minimum, and maximum survival times will be presented. In addition, the number of patients with an event and the number of censored patients will also be reported. The corresponding Kaplan-Meier survival plot will also be presented along with number at risk statistics at the appropriate time points. Adjusted hazard ratio, 95% CIs and p-values between active treatment groups to SOC under Cox proportional hazard model with age, site and treatment groups as covariates will be reported.

Time-to-event endpoints with competing risk will be analysed for each dosing group using the Cumulative Incidence Function-CIF (KM) graphical display. Adjusted hazard ratio, 95% CIs and p-values between active treatment groups to SOC under Fine-Gray sub-distribution hazard model with age, site and treatment groups as covariates will be reported. Competing risk is identified by the presence of death outcome, which prevent the observation of the current outcome of interest.

11.4 Secondary Efficacy Analysis: WHO-7 Ordinal Scale

11.4.1 Time to first improvement of one category from baseline on WHO-7

The time to first improvement of one category on WHO-7 scale from baseline (Days) is defined as:

Date of First Improvement on Ordinal Scale – Date of Baseline Assessment + 1.

If the patient did not experience an improvement, the patient will be censored at the last known date the patient is known to not have experienced an improvement:

Final Date of Confirmation of No Improvement - Date of Baseline Assessment + 1.

11.4.2 WHO-7 Ordinal scale by timepoint

Descriptive statistics treating WHO-7 scale as continuous data in accordance to section 3.1 will be reported for each treatment arm and overall at Baseline, Day 3, 5, 8, 11, 15 and 29. Change from baseline descriptive statistics will also be given for these timepoints for each treatment arm and overall. P-values and 95% CI comparing the differences between SOC and treatment arms A and B will also be provided for change from baseline analysis using a mixed model with baseline, treatment arm, age, day, site, interaction between day and treatment arm as fixed effects and patients as random effects with random intercepts using unstructured covariance structure. In the event of non-convergence, a simplified covariance structure may be chosen.

```
Proc Mixed data = adeff;
class site trt subjid day;
model chg_bl = baseline site trt age day trt*day/ddfm=kr;
random int/sub= subjid type= un;
LSMEANS Trt*day / AT MEANS CL DIFF SLICE = day;
run;
```

11.5 Secondary Efficacy Analysis: NEWS

11.5.1 Time to the earlier of discharge or NEWS of ≤ 2 maintained for 24 hours

The time to earlier of discharge or NEWS of ≤ 2 maintained for 24 hours (Days) is defined as:

Date of First earlier of discharge or NEWS of ≤ 2 maintained for 24 hours – Date of Baseline Assessment + 1.

If the patient did not experience discharge or NEWS of ≤ 2 maintained for 24 hours, the patient will be censored at the last known date the patient is known to not have experienced either of these events:

Final Date of Confirmation of no discharge nor NEWS of ≤ 2 maintained for 24 hours - Date of Baseline Assessment + 1.

If a patient died before discharge or NEWS of ≤ 2 maintained for 24 hours, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.5.2 NEWS by timepoint

Descriptive statistics treating NEWS scale as continuous data in accordance to section 3.1 will be reported for each treatment arm and overall at Baseline, Day 3, 5, 8, 11, 15 and 29. Change from baseline descriptive statistics will also be given for these timepoints for each treatment arm and overall. P-values and 95% CI comparing the differences between SOC and treatment arms A and B will also be provided for change from baseline analysis using a mixed model with treatment arm, age, day, site, interaction between day and treatment arm as fixed effects and patients as random effects with random intercepts.

11.6 Secondary Efficacy Analysis: Respiratory Support

For the part of the analysis, respiratory support is defined as:

- Any respiratory support (any of Oxygenation only, Mechanical Ventilation (Invasive and non invasive), ECMO
- Oxygenation only
- Invasive Mechanical Ventilation
- Non Invasive Mechanical Ventilation
- ECMO

11.6.1 Rate of Respiratory Support: Oxygenation only, Mechanical Ventilation (Invasive and non invasive), ECMO

Counts and percentages of patients for respiratory support at least once will be reported for each treatment arm. If patients were eligible for respiratory support but did not receive one due to lack of resources, an additional analysis on counts and percentages of patients required to receive respiratory support will be reported for each treatment arm. Separate 95% CIs (Newcombe) and p-values (Chi-Squared test without continuity correction) will be computed between SOC and treatment arms A and B for patients with at least one respiratory support.

11.6.2 Duration of Respiratory Support: Oxygenation only, Mechanical Ventilation (Invasive and non invasive), ECMO

Counts and percentages of patients with the following categories (based on total number of hours of respiratory support) will be reported for each type of respiratory support and for each treatment arm. The duration calculation is only applicable to patient with respiratory support. For patients with ongoing respiratory support with no end date and time at data cut off, the date of data cut off will be used to calculate the end date for the ongoing at time of data cut off category.

The duration is defined as:

Date and time at end of respiratory support-Date and time at end of respiratory support.

- < 6 hours
- ≥ 6 hours but < 12 hours
- ≥ 12 hours but < 24 hours
- ≥ 24 hours but < 72 hours
- ≥ 72 hours but < 120 hours
- > 120 hours
- Ongoing at time of data cut off (≥ 6 hours) [The hour can be amended based on real data]
- Ongoing at time of data cut off (≥ 12 hours) [The hour can be amended based on real data]
- Ongoing at time of data cut off ((≥ XX hours) etc…
- Prolonged respiratory support (consecutive respiratory support for 21 days with at least ≥ 6 hours per day)

Separate 95% CIs (Newcombe) and p-values (Chi-Squared test without continuity correction) will be computed between SOC and treatment arms A and B for prolonged respiratory support.

11.6.3 Time to Respiratory Support: Oxygenation only, Mechanical Ventilation (Invasive and non invasive), ECMO

The time to respiratory support (Day) is defined as:

Date of first respiratory support – Date of Baseline Assessment + 1.

If the patient did not require respiratory support, the patient will be censored at the last known date the patient is known to not require respiratory support:

Final Date of Confirmation of no respiratory support needed - Date of Baseline Assessment + 1.

If a patient died before obtaining respirator support, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.6.4 Time from first Oxygenation Support to first termination of Oxygenation Support:

This calculation is only applicable for those with oxygenation support.

The time to from first oxygenation support to first termination of oxygenation support is defined as:

Date of first termination of oxygenation support – Date of first oxygenation support + 1.

If the patient was still on oxygenation support, the patient will be censored at the last known date the patient is known to still on oxygenation support:

Final date of confirmation of still on oxygenation support - Date of first oxygenation support + 1.

If a patient died before terminating oxygenation support, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.7 Secondary Efficacy Analysis: Oxygenation

11.7.1 PaO2 and PaO2/FiO2

Continuous data descriptive statistics (3.1) for PaO2 and PaO2/FiO2, change from baseline, percentage of change from baseline in accordance to 3.2 will be reported for each treatment arm at all scheduled visits. T-test assuming unequal variance p-values and 95% CI comparing the differences between SOC and treatment arms A and B will also be provided for percentage change from baseline analysis.

11.7.2 Time to first return to SpO2 > 94% on room air

The time first return to SpO2 on room air (Day) is defined as:

Date of first return to SpO2>94% on room air – Date of Baseline Assessment + 1.

If the patient did not experience a return of SpO2>94% on room air the patient will be censored at the last known date the patient is known to not have achieved this criterion:

Final Date of Confirmation of no return to SpO2>94% on room air - Date of Baseline Assessment + 1.

If a patient died before achieving a return of SpO2>94% on room air, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.7.3 Time to first return to PaO2 of 80-100 mmHg.

The time first return to PaO2 of 80-100 mmHg is defined as:

Date of first return to PaO2 of 80-100 mmHg – Date of Baseline Assessment + 1.

If the patient did not experience a return to PaO2 of 80-100 mmHg the patient will be censored at the last known date the patient is known to not have achieved this criterion:

Final Date of Confirmation of no return to PaO2 of 80-100 mmHg - Date of Baseline Assessment + 1.

If a patient died before achieving a return to PaO2 of 80-100 mmHg, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.7.4 Time to first return to PaO2/FiO2 of > 400 mmHg.

The time first return to PaO2/FiO2 of > 400 mmHg is defined as:

Date of first return to PaO2/FiO2 of > 400 mmHg – Date of Baseline Assessment + 1.

If the patient did not experience a return to PaO2/FiO2 of > 400 mmHg the patient will be censored at the last known date the patient is known to not have achieved this criterion:

Final Date of Confirmation of no return to PaO2/FiO2 of > 400 mmHg - Date of Baseline Assessment + 1.

If a patient died before achieving a return to PaO2/FiO2 of > 400 mmHg, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.8 Secondary Efficacy Analysis: Hospitalization and ICU

11.8.1 Duration of Hospitalization and ICU

Counts and percentages of patients with the following durations for hospitalization and ICU will be reported separately for each treatment arm. The duration calculation is only applicable to patient with the respective hospital or ICU stay. For patients with ongoing hospital or ICU stay with no end date at data cut off, the date of data cut off will be used to calculate the end date for the ongoing at time of data cut off category.

The duration for hospital/ICU stay (Day) is defined as:

Date at hospital discharge-Date of hospital admission+1.
Date at ICU discharge-Date of ICU admission+1.

- < 1 Day
- ≥ 1 Day but < 3 Days
- ≥ 3 Days but < 7 Days
- ≥ 7 Days but < 10 Days
- ≥ 7 Days but < 14 Days
- ≥ 10 Days but < 14 Days
- ≥ 14 Days but < 21 Days
- > 21 Days
- Ongoing at time of data cut off (≥ 1 Day) [The day can be amended based on real data]
- Ongoing at time of data cut off (≥ 3 Days) [The day can be amended based on real data]
- Ongoing at time of data cut off ((≥ XX Days) etc…

11.8.2 Time to Hospitalization and ICU discharge

The time to discharge is defined as:

Date of discharge from hospital – Date of Baseline Assessment + 1. (For hospitalization)
Date of discharge from ICU – Date of Baseline Assessment + 1. (For ICU)

If the patient did not discharge from hospital or ICU patient will be censored at the last known date the patient is known to be still in hospital/ICU according to the following:

Final Date of Confirmation the patient is still in hospital - Date of Baseline Assessment + 1. (For hospitalization)

Final Date of Confirmation the patient is still in ICU - Date of Baseline Assessment + 1. (For ICU)

If a patient died discharge, the patient will be censored as a competing risk based on the following:

Date of Death - Date of Baseline Assessment + 1.

11.9 Secondary Efficacy Analysis: Mortality

Counts and percentages of patients who died by Day 15 and Day 28 and overall will be reported separately for each treatment arm. Separate 95% CIs (Newcombe) and p-values (Chi-Squared test without continuity correction) will be computed between SOC and treatment arms A and B.

Time to death (Day) will be reported using KM method as described on 11.3. Time to death will be calculated as follows:

Date of Death - Date of Baseline Assessment + 1.

If the patient did not die the patient will be censored at the last known date the patient is known to be still alive:

Final Date of Confirmation the patient is still alive - Date of Baseline Assessment + 1.

11.10 Exploratory Analysis: Dyspnea

The Likert scale categories (0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse) will be reported using counts and percentages at all scheduled timepoints for all treatment arms and overall.

11.11 Exploratory Analysis: Cough VAS and D-dimer

Percentage of change from baseline (defined in 3.2), change from baseline and actual values of Cough VAS and D-dimer at all scheduled timepoints will be summarized using continuous descriptive statistics (defined in 3.1) for all treatment arms and overall. T-test assuming unequal variance p-values and 95% CI comparing the differences between SOC and treatment arms A and B will also be provided for the percentage of change analysis.

11.12 Exploratory Analysis: Qualitative and Quantitative PCR SARS-Cov-2

Counts and percentages for type of sample (nasal, nasopharyngeal, oropharyngeal, blood and other) for qualitative and quantitative PCR SARS-Cov-2 will be provided for all treatment arms and overall at all scheduled time points.

Continuous data involving log 10 transformed quantitative viral RNA load results and change from baseline will be reported in accordance to 3.1 for all treatment arms and overall at all scheduled time points.

11.13 Cytokine Marker Results

The following Cytoking marker will be taken at the time points specified in the study procedure schedule (section Table 1):

- IFNγ
- GM-CSF
- IL-6
- IL-12
- TNF-alpha

Summary statistics for cytokine markers in accordance to section 3.1 will be presented for baseline and for each scheduled pre and post-baseline visit (which also includes change from baseline, clinical significance) where applicable. These summary tables will be done for ITT and PPS populations for treatment groups defined in section 3.4.

All information related to cytokine marker (cytokine marker type, result, reasons not done, date and time of sample collection) will be presented in the by-participant data listings by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

12. SAFETY

All Safety endpoints will be analysed using the Safety analysis set.

12.1 Dose Limiting Toxicity

The occurrence of any of the following toxicities from the initial dose of Ifenprodil administration (in combination with Standard of Care (SOC)) which results in:

a. The necessity to delay ifenprodil administration in the participant, OR
b. To reduce the dose of ifenprodil administered, either for the participant, or for subsequent participants,

will be considered a DLT, if judged by the investigator to have a reasonable possibility of being related to the ifenprodil administration.

Severity is graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 equivalents of mild, moderate or severe:

1. Grade 3 or higher toxicity, except elevations in gamma-glutamyltransferase (GGT)
2. Grade ≥ 3 AST/ALT elevation
3. Grade ≥ 2 AST/ALT elevation with Grade ≥ 2 bilirubin elevation

Dose Limiting Toxicity will be identified in AE listings.

12.2 Adverse Events

All AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21. Chest X-ray resulting in AEs will also be reported. Treatment Emergent Adverse Events (TEAEs) are all events which start or worsen after the first dose of study drug up to and including the follow up period. If missing dates or time prevent a clear determination as to whether the AE is treatment emergent, the adverse event will be regarded TEAE. If a patient experienced the same adverse event multiple times, this will only be counted once for the purpose of counting the number of patients experiencing that adverse event. For the SOC arm, all AEs are considered TEAEs.

An overall summary of TEAEs for counts and percentages by treatment groups defined in section 3.4 will be provided for the following items:

- Any TEAE
- Any Serious TEAE
- Any type of serious TEAE (Result in Death, Immediately Life-Threatening, Inpatient hospitalization or prolongation of existing hospitalization, Persistent or Significant Disability or Incapacity, Congenital abnormality or birth effect, Important Medical event may require medical intervention to prevent events above)
- Any TEAE grade (intensity) experienced (Mild [Grade 1] Moderate [Grade 2] Severe [Grade 3] Life-Threatening [Grade 4] Fatal [Grade 5])
- Worst TEAE grade (intensity) experienced (Mild [Grade 1] Moderate [Grade 2] Severe [Grade 3] Life-Threatening [Grade 4] Fatal [Grade 5])
- Action taken (None, Medication Given, Procedure/Intervention Needed, Other)
- Action taken for Ifenprodil (Dose discontinuation, Drug interrupted, Unknown, None, Not Applicable)
- Action taken for SOC (Dose discontinuation, Drug interrupted, Unknown, None, Not Applicable)
- Outcome of TEAE (Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Not recovered, Death, Unknown, Patient discontinued from study)

- Relationship to Ifenprodil/SOC (Reasonable Possibility, No Reasonable Possibility, Not Applicable)

The following table summaries (counts, percentages and number of events) will be presented by System Organ Class and Preferred Term by treatment arm (defined in section 3.4):

- Summary of TEAEs
- Summary of Serious TEAEs.
- Summary of TEAEs (grade 1 or 2).
- Summary of TEAE (grade of 3 or more)
- Summary of Ifenprodil related TEAEs (applicable to Arm A and B only)
- Summary of SOC related TEAEs (applicable to all treatment arms)
- Summary of Ifenprodil related Serious TEAEs (applicable to Arm A and B only)
- Summary of SOC related Serious TEAEs (applicable to all treatment arms)
- Summary of TEAEs Leading to Study Discontinuation.
- Summary of TEAEs Leading to Death.

All AEs will be listed and will include the start and stop date of AEs, AE number, verbatim term, Preferred Term, System Organ Class, treatment, SAE/Type, TEAE, actions taken for AE, actions taken with SOC/Ifenprodil, causality to SOC/Ifenprodil and outcome. Separate listings will be created for SAEs. These listings will be presented by treatment arm (grouping provided in section 3.4) sorted by patient ID and AE start date for the Safety population, along with age, sex and baseline weight of the patient.

12.3 Safety Laboratory Assessments

The following laboratory measurements will be taken at the time points specified in the study procedure schedule (Table 1):

1) Hematology: Hemoglobin, hematocrit, white blood cell counts, including differential, platelet count, red blood cell count, myoglobin

2) Biochemical tests: Glucose, blood urea nitrogen (BUN), serum creatinine, sodium, potassium, chloride, bicarbonate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (γ-GT/GGT), total bilirubin, calcium, phosphorus, albumin, total protein, uric acid

3) Coagulation: activated partial thromboplastin time (aPTT) prothrombin time (PT), international normalised ratio (INR), D-dimer.

4) Urinalysis: Specific gravity, hydrogen ion concentration (pH), protein, glucose, bilirubin, ketone, urobilinogen, blood, leukocytes, casts, bacteria.

In some instances, continuous variables are expressed as a range (i.e. < 10). In such cases, as long as the limit of quantification is at least 1, values may be converted to the range boundary (upper or lower limit as applicable) by subtracting or adding the smallest whole number of the limit of quantification. As an example, a value of <10 may be converted to 9. A value of > 100 may be converted to 101. Such substitutions will be clearly documented in the footnotes of relevant outputs.

For the hematology, blood coagulation, chemistry, continuous and discrete (low, normal, high) data summary statistics (as described in section 3.1) will be presented for values and change from baseline value/shift from baseline at each visit. For urinalysis, discrete data summary statistics on categorical results (as described in section 3.1) will be presented for values at each visit. For pH the result will be

classified into <5, 5 to 8 and >8. For Specific Gravity, the result will be classified into ≤ 1.015, 1.061 to 1.021, 1.021 to 1.025, 1.026 to 1.030 and > 1.030. For Urobilinogen, the result will be classified into ≤ 1 mg/dL, 1 mg/dL to < 2 mg/dL and > 2 mg/dL. These summary tables will be done for Safety population for treatment groups defined in section 3.4

The listings of laboratory parameters (hematology, chemistry and urinalysis) will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each pre and post baseline (scheduled and unscheduled) visit will be presented, along with reasons for laboratory assessments not done. These listings will be presented by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with age, sex and baseline weight of the patient.

12.4 Vital Signs

The following vital signs measurements will be taken at the time points specified in the study procedure schedule (section Table 1):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse Rate (beats/min)
- Respiratory rate (breaths/min)
- Body Temperature (ºC)
- Oxygen Saturation SpO2 (%)
- Level of Consciousness (Alert, Arousable only to voice, Arousable only to pain, Unresponsive)
- Presence of clinically significant result

Summary statistics for vital sign parameters in accordance to section 3.1 will be presented for baseline and for each scheduled pre and post-baseline visit (which also includes change from baseline, clinical significance) where applicable. These summary tables will be done for Safety population for treatment groups defined in section 3.4.

The listing of vital sign parameters will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each pre and post baseline (scheduled and unscheduled) visit will be presented along with whether the result was clinically significant (AE/MH numbers if applicable) and reasons not done. This listing will be presented by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

12.5 12-Lead Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the study procedure schedule (section Table 1):

- Ventricular HR (beats/min)
- PR interval (msec)
- QRS interval (msec)
- ST segment (msec)
- QTcF interval (msec)
- Presence of clinically significant result (normal, abnormal not clinically significant, abnormal and clinically significant)

Summary statistics for 12-Lead ECG parameters in accordance to section 3.1 will be presented for baseline and for each scheduled pre and post-baseline visit (which also includes change from baseline). These summary tables will be done for Safety population for treatment groups defined in section 3.4

The listing of 12-Lead ECG parameters will include all the information collected (including an overall assessment of presence of clinically significant result). In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each pre and post baseline (scheduled and unscheduled) visit will be presented along with whether the result was clinically significant (AE/MH numbers if applicable) and reasons not done. This listing will be presented by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

12.6 Physical Examinations

By-participant data listings will be created for all physical examination parameters and all time points by treatment arm (grouping provided in section 3.4) along descriptions of abnormality, associated AE/MH numbers where applicable, and reasons not done, sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

12.7 Pregnancy Test Results

All information related to pregnancy testing (whether urine and serum based, result, reasons not done, date and time of sample collection) will be presented in the by-participant data listings by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

12.8 Child Pugh Score

Summary statistics for total Child Pugh score in accordance to section 3.1 will be presented for baseline and for each scheduled pre and post-baseline visit (which also includes change from baseline, clinical significance) where applicable. These summary tables will be done for Safety population for treatment groups defined in section 3.4

All information related to child Pugh score (component of child Pugh score, total child Pugh score, result, reasons not done, date and time of sample collection) will be presented in the by-participant data listings by treatment arm (grouping provided in section 3.4) sorted by patient ID and visit for the Safety population, along with the age and sex and baseline weight of the patient.

13. CHANGES TO THE PLANNED ANALYSIS

14. AN AD-HOC ANALYSIS BASED ON ALL PATIENTS WHO RECEIVED REMDESIVIR AS PART OF THEIR SOC IN ALL TREATMENT ARMS MAY BE PERFORMED AS DESCRIBED IN 14.3.

INTERIM AND FINAL ANALYSIS

14.1 Interim Analyses

The DSMB will review safety data after every 25 patients are entered into the trial up to 100 patients, and then at every 50 patients. Ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews. Based on the recommendations of the WHO R&D Blueprint Clinical Trials Expert Group and given the severity of illness in COVID-19, there are no pre-specified study stopping rules for safety.

For Phase 2b, an interim analysis will also be performed when 75 patients completed Day 15 assessments for primary endpoint. For this interim analysis with first 75 patients with Day 15 efficacy data, in addition to standard DSMB outputs, the following descriptive statistics efficacy analysis will also be presented:

1. WHO-7 efficacy with Day 15 assessment
2. Status on an ordinal scale assessed daily while hospitalized and on days 15
3. NEWS assessed days 3, 5, 8 ,11 while hospitalized and on days 15 in IP versus control group patients
4. Effect on the rate of change of partial pressure of oxygen (PaO2) and PaO2/FiO2 ratio taken at baseline and measured once daily up to 2 weeks of treatment in IP versus control group patients
5. Rate of mechanical ventilation in IP versus control group patients (Patients who received Invasive/non-invasive Mechanical Ventilation by Day 15)

For item 5, if a patient did not experience mechanical ventilation by Day 15, he/she will be marked as a negative response even if the patient did experience mechanical ventilation past Day 15. This is different to the final analysis described above.

A preliminary full analysis report of 150 patients with up to Day 29 data entered may also be presented.

14.2 Final Analysis (End of Study)

The final analysis will be conducted after all participants have completed the study, the clinical database has been locked, the analysis populations have been approved.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

14.3 Ad-hoc Analysis (End of Study)

An ad-hoc analysis may be reran for all outputs for all patients who received Remdesivir as part of their SOC in all treatment arms.

15. SOFTWARE

- SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

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16. TABLES, LISTINGS AND FIGURES

Please refer to mock shell template. A separate DSMB tables listings and figures mock shell is also available.

17. REFERENCES

1) Clinical Study Protocol Version *2.0* dated *16 November 2020*.
2) Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998; 17: 873–890