Statistical Analysis Plan (SAP)

Protocol Title:	A randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care in adult subjects with COVID-19.
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1.0 Approvals

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2.0 Change History

Version/Date	Change Log
0.05	Created as new
0.1	Updates following Sponsor Comments on draft v0.05
0.15	Updated to remove line referring to block size
0.2	Updated following Sponsor Comments on draft V0.1
0.25	Updated following Sponsor comments on draft v0.2
0.3	Updated per Sponsor and DMC committee members comments; Updated to new template
0.4	Updated per FDA comments on SAP version 0.25 and Sponsor comments on SAP version 0.3
1.0	Stable version
1.1	Significant changes due to sponsor discussions and Protocol Amendment V5.0. All changes were implemented without access to unblinded data from the ongoing trial. 1. The primary endpoint has been changed from proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15 to all-cause mortality up to Day 60. The previous primary endpoint is now considered a key secondary endpoint. Major changes throughout the document to reflect the new primary endpoint for the study. 2. Sample Size has been reduced from 600 to maximum 300 patients. Section 8.0 and Section 8.1 have been updated to reflect the reduced sample size. Power calculations have been updated to incorporate the new primary endpoint. 3. The hierarchy of key secondary endpoints has been adjusted (refer to Section 9.2.1) leading to re-ordering of sections and text within the document for consistency. 4. Section 12.5.2 has changed to reflect the new primary endpoint and the primary analysis to be performed for this endpoint. 5. Hypothesis in Section 12.5.1 has been updated to reflect the new primary endpoint. 6. Removal of sensitivity analysis for key secondary endpoints. Last observation carried forward and adjusted multiple imputation model have been removed as the remaining sensitivity analysis is sufficient to test the underpinning assumptions of the primary analysis for the key secondary endpoints. 7. Reference to an Interim Analysis, planned to occur when 300 subjects reach Day 15 have been removed from multiple sections. The planned Interim Analysis for futility and sample size re-estimation will no longer occur. 8. Added an additional sensitivity analysis for the key secondary endpoint time to sustained discharge, which will perform the analysis using the multiple imputed datasets. Refer to Section 10.12 and 10.19.1 for further details.

9. Updated Section 10.19.1 as follows:
   - Include specific information on how to handle day of death/day of discharge in the multiple imputation.
   - In Step 1 of the imputation process remove the line "And number of discarded datasets between imputations" as this is not relevant as we are performing a single imputation in this step.
   - In Step 2, clarify that the imputation model can only provide possible imputed values based on what is recorded in the data at the timepoint; that imputed values may be inconsistent with other data; rules for rounding the number of imputations; and the option in SAS PROC MI to use for likelihood if maximum likelihood parameters can not be estimated
   - Added in Step 3 Time to Sustained hospital discharge analysis using the multiple imputed dataset.
   - Adjusted in Step 3, the order of endpoints to align with new hierarchy
   - Added in Step 4, detail on the transformation required for log-rank results
10. Updated Section 10.1 definition of baseline for efficacy to include detail on how to handle multiple assessments at the baseline visit (Visit 2- Day 1).
11. Updated Section 10.4 to state that only subjects who are initially dispensed C21 will be assigned C21 as actual treatment. Individual dose administration is not recorded in the database/kit file, only tablets dispensed at the initial dispensing visit are recorded.
12. Updated Section 10.9 to remove the line "If a scheduled visit and an EWD visit occur in the same window, the scheduled visit will be used in the analysis." as this contradicted other rules for visit windowing outlined in this Section. Updated to state that is multiple records exist on the same trial day for Ordinal Scale, the record at the scheduled visit will be recorded for use in the analysis. Updated to state if visit Day 29 occurs on relative day greater than 29, it will be set to be Day 29 in the analysis.
13. Updated Section 10.10 to explicitly state that recorded values of 1 on the 8-point ordinal scale will not be changed to be a value of 2 on the adjusted 8-point ordinal scale.
14. Updated Section 10.13 to define oxygen free days relative to the adjusted 8-point ordinal scale and not the original 8-point ordinal scale.
15. Updated Section 10.18 to include information on how to assign SpO_2 if only one value is available at a visit.
16. Updated Section 12 to state that pooling of stratum may occur and will be defined in a blinded manner prior to database lock.
17. Updated Section 12.3.1 for the total cumulative dose derivation and to add derivation for percentage of doses taken at the hospital.
18. Updated Section 12.6.4 to state that the average of multiple readings at a visit will be used as the analysis value for select vital signs parameters.

	19. Changes to Appendix 1 and definitions of Estimands to reflect the new primary endpoint. 20. Moved Section on Logistic Regression and definitions for this analysis to an Appendix to enable the document to flow better. 21. Minor updates throughout document with no impact on analysis (for example changing the abbreviation of IMP to be Investigational Medicinal Product; ensuring subgroup risk factors for severe COVID-19 is consistently labelled across all sections).
1.2	Updates based on Sponsor comments on Version 1.1: 1. Updated Section 6.1 to align with Protocol v5.0 2. The PK samples will be collected on a subgroup of approximately 10 subjects. Updates throughout the document to reflect a smaller PK sample group. Updated Section 9.5.5 to add details on exclusion from the PK population. Updated 12.7, to remove Q1 and Q3 as due to low number of subjects available for PK analysis, these summary statistics will not be informative. Updated 12.7.2 to add details on the calculation of select PK Parameters. 3. Updated Section 8.1 to align Sample Size derivation with Protocol v5.0. 4. Updated Section 9.5.3 to state that subjects with no follow-up data at Day 60 will be excluded from the Per Protocol analysis set. 5. Updated Section 10.10: - To clarify collected values of 1, 3 and 4 will not be changed even if evidence of supplemental oxygen usage in the data. - To specify that the question " Was COVID-19 related supplemental oxygen for at home use prescribed?" on the hospitalization CRF page will only be considered in the determination of whether a subject was on oxygen or not on the day of discharge if the scheduled ordinal scale value is missing or a value of 2. 6. Added Section in Conventions and Derivations for All-Cause Mortality. 7. Changed the sensitivity analysis for time to sustained hospital discharge such that, the consideration of non-COVID-19 related re-hospitalizations and multiple imputation will be the same sensitivity analysis as re-hospitalization will be a rare event. Updates to Section 10.13, 10.19.1 and 15.5.3.6. 8. Added clarification to Section 10.14, that subjects with missing data will have their data multiply imputed as per Section 10.19.1. 9. Updated the sensitivity analysis for duration of hospitalization to be similar to time to sustained discharge. Updates to Section 10.15, 10.19.1 and 12.5.4. 10. Updated Section 10.18 to provide details on how to assign values of FiO_2 when the value is missing in the data and how to handle the $Sp0_2/FiO_2$ ratio

	calculation when multiple oxygen supplementation usage is given at the same visit. 11. Section 10.19.2 added to discuss multiple imputation for sensitivity analysis for the primary endpoint. 12. Section 10.19.3 updated to describe general approach for tipping point analysis for all key secondary endpoints. 13. Updated Section 10.19.4 to remove the worst case approach for the key secondary endpoint "number of oxygen free days" as this endpoint will have the same worst case analysis approach as other endpoints. 14. Updated Section 12.3.1 to include a rule for cumulative dose derivation for subjects who discontinue treatment and have no returned capsules amount collected and the first dose was in the evening. Updates to this section to use cumulative dose and not 56 in the derivation of % doses taken in hospital. 15. Updated Section 12.5.1 to define notation $S_1(t)$. 16. Per FDA recommendation add Race and Ethnicity as subgroups for the supplementary analyses of the primary and key secondary endpoints (updates to Sections 12.5.2.4 and 12.5.3.7). Updated Section 12.5.3.7 to refer to Section 12.5.2.4 and not repeat text. 17. Updated Section 12.5.3.2 to remove "if a sufficient number meet the endpoint" as due to current blinded data status a significant number of subjects are discharged and hence, this line will no longer be relevant. 18. The Key Secondary Objective in Appendix 1 for key secondary estimands updated to be "To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19" and not "Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19" to align with Protocol version 5.0. 19. Update the endpoints of subjects free of respiratory failure to define free of respiratory failure as a score of ≤5 and not <6 for consistency with how other endpoints are expressed.
1.3	Minor updates due to Sponsor review of Version 1.2
1.4	- Update Section 12.5.4 to clarify presentation of all-cause mortality at Day 8, Day 15, Day 22 and Day 29. - Minor updates on format and grammar throughout document - Clarification added in Section 12.7 that the coefficient of variation is for the geometric mean - Minor edits to Sections 12.1 (removal of line "together with a breakdown of the reason for exclusion from each analysis set"); Section 12.2 (clarification of the Region variable to be presented in output); Section 12.3.2 (update of typo) and Section 12.6.1 (update of typo) to ensure alignment with the tables, listings and figures shells.

1.5	1. Updated Section 6.1 for differences between Protocol V5 and the SAP 2. Section 9.5.3: Update of the Per Protocol Population definition to potentially exclude patients who discontinue treatment. 3. Section 10.10: Updated to state that all concomitant oxygen usage will be considered on oxygen for the purposes of the adjusted 8-point ordinal scale regardless of the reason for use. 4. Section 10.12 updated for definition of time to sustained discharge: a. Update definition to be based on actual discharge date b. Clarification added on the sensitivity analysis using Multiple Imputation 5. Section 10.14 updated for definition of number of respiratory failure free days: a. Clarification on how to handle subjects who die b. Clarification on how to count the days of respiratory failure free between Day 29 and Day 60 6. Section 10.16 updated for duration of ICU stay: a. Clarifying that deaths will always be considered in ICU even if they were not in the ICU at time of death. b. Clarifying that if the ICU start date is prior to treatment start, treatment start date should be used in the analysis for the start date of the of the ICU stay to align the derivation with other duration calculations. 7. Section 10.19.1: a. Subjects who die will be removed from the imputation at Step 2 in the process i.e subjects who die will not have data imputed. b. Updated to add details for MCMC and non-convergence handling c. Updates to add detail on combining results from Cox regression d. Update to clarify calculation of imputations 8. Section 10.19.3: a. Update details on tipping point for Respiratory failure free at Day 15 and number of oxygen free days b. Added tipping point for All Cause Mortality c. Clarified tipping point will only be performed if the main analysis has a significant p-value. 9. Section 12: a. Text added to stated the pooled region will be used. Region and pooled region are used interchangeably throughout the document. b. Added text that factors will be removed form models if appropriate. 10. Section 12.5.2.4: a. Added text on the handling of small subgroups i.e. only presenting subgroup strata with >10% subjects. 11. Section 12.5.5: a. Text updated to clarify the model and statistics presented for log transformed data. 12. Section 12.8: Data considerations added to discuss how to handle data that may not have a full SDV review. 13. Appendix 4: Added an appendix to refer to the Blinded Data review specifications 14. Appendix 5: Added to summarize all derivations for efficacy endpoints
1.6	1. Update per protocol population to specify that subjects who withdraw from treatment due to subject decision prior to Day 11 will be excluded 2. Updated Section 10.19.1 to be clear that the transformed estimates from Ge et al are combined using Rubin's rule

	3. Updated Section 10.19.1 and 12.5.3.6 to specify for the sensitivity analysis for the time to sustained discharge, median will be presented as the average value of the median within each imputed dataset. 4. Updated Section 12.8 to remove discussion on non-sdv'd data as this is no longer relevant to the study.
2.0	1. Removed section on data considerations as no longer a consideration for the study 2. Update version number to version 2.0

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Vicore Pharma Protocol VP-C21-008.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Trial Objectives
- Trial Design
- Trial Estimands
- Analysis Sets
- Conventions and Definitions
- Applicable Trial Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the trial protocol and case report forms (CRF). This version of the plan has been developed using the protocol version 5.0 dated 13-Apr-2022 and CRF version 3. 0 dated 30-Mar-2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The trial is a randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care (SoC) in adult subjects with COVID-19.

This SAP describes the statistical methods used for the final analysis. A final version of the SAP will be issued for sponsor approval prior to database lock, at which point the blinded team members will become unblinded to the actual randomized assignment.

6.1 Changes from Protocol

- The protocol text uses “Major” and not “Important” to describe significant protocol violations. The SAP has been updated to use “Important” to align with CRO terminology. For the purposes of this trial major protocol deviations and important protocol deviations are interchangeable and have the same meaning as in the trial protocol.
- The protocol defines time to sustained discharge as “The first occurrence of a score ≤ 2 whereafter the score stays ≤2 for the remainder of the 60 days trial period”, in the SAP this has been updated to state the time to date of discharge after which subjects are not re-hospitalized for COVID-19 reasons. These definitions are functionally equivalent. Due to how the ordinal scale is handled for other secondary endpoints (the day after discharge is the first value set to be ≤2) it is necessary to update the SAP definition to ensure that the initial day of discharge is used in the analysis for time to sustained discharge.
- Section 9.2 of the Protocol defines the Per Protocol population as: “All subjects in the ITT set without major protocol deviations deemed to have an impact on efficacy readouts. In addition, subjects who prematurely discontinued IMP during the treatment period but continued with data collection in the trial will also be excluded from the PP. Subjects withdrawn from the trial unrelated to trial participation due to extraordinary circumstances (for example subjects lost-to follow up due to unstable geopolitical situation) may also be excluded from the PP set (further specified in the SAP). Subjects will be included in the analyses according to the intervention they were randomized to.”. For the SAP this will be update to exclude subjects with any important protocol deviations impacting efficacy or subjects who discontinue treatment due to subject decision or subjects not treated.

- Section 9.3.3 of the protocol states "Other endpoints assessing proportion of subjects will be compared using similar logistic regression models as for the primary endpoint with the treatment effect expressed as a difference in proportions." however the primary analysis of the primary endpoint does not use a logistic regression model, this SAP clarifies that this is the sensitivity analysis of the primary endpoint.
- Section 9.3.3 of the protocol has the following line "Other endpoints assessing time to event will be compared using the stratified log-rank test similar to time to sustained discharge with similar imputations for missing data". For the endpoint time to sustained discharge, as the primary analysis no missing data is imputed. Further there are no other secondary endpoints that are assessing time to event, due to this, this line in the protocol was not repeated in the SAP.
- Section 9.3.3 of the protocol states "Endpoints assessing duration of event will be compared between treatments using the Wilcoxon rank sum test, with similar imputations for missing data.", however apart from the endpoint "Duration of hospitalizations, including all re-hospitalizations, up to Day 60, no imputation for missing data for duration endpoints is performed.

7.0 Trial Objectives

7.1 Primary Objective

To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19.

7.2 Secondary Objectives

- Evaluate the safety profile of C21 versus placebo as add on to SoC in subjects with COVID-19.
- Characterize the PK profile of C21 in subjects with COVID-19. A subgroup of approximately 10 patients will be used to assess PK.
- Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19.

7.3 Exploratory Objective

- To explore the effect of C21 versus placebo as add on to SoC on inflammation.
- To explore the effect of C21 versus placebo as add on to SoC on lung injury.

8.0 Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter trial to evaluate the efficacy and safety of C21 versus placebo as add-on to the SoC in adult subjects with COVID-19.

The trial will enroll a maximum of 300 randomized subjects, up to 150 per arm (oral C21 100 mg twice a day (b.i.d.) or placebo for 14 days) according to a 1:1 randomization. Randomization occurs at visit 2 (Day 1) and will be stratified by:

- Disease severity (based on the 8-point ordinal scale score at Day 1 with a score of 5 or 6).
- Region (North America, South and Central America, Europe, Asia, Africa).

Approximately 350 subjects will be screened to achieve a maximum of 300 enrolled and randomly assigned subjects to investigational medicinal product (IMP) treatment.

Subjects hospitalized due to ongoing COVID-19 and who have a score of 5 or 6 on the 8-point ordinal scale will be enrolled. The trial consists of 3 consecutive periods (Table 1): a screening period of up to 48 hours, a 2-week IMP treatment period and a follow-up period of up to 7 weeks. Daily visits are required until discharge. Discharged subjects should return to the clinic for the Day 15 visit. Days 8, 22, 29 and 60 visits will be conducted as phone or video visits for all discharged subjects. The trial duration for an individual subject will not exceed 9 weeks. End of trial is defined as the last subject's last follow-up visit.

An independent data monitoring committee (DMC) will actively monitor data from the trial and will review unblinded safety data from the trial after data collection for 15 days on the first 150 randomized subjects. In addition, the DMC members may call for an ad hoc safety review meeting at any time during the trial.

All subjects will undergo a series of efficacy, safety, and laboratory assessments. Laboratory samples will not be collected at Days 3, 5, 8 and 11 if the subject is discharged from hospital prior to the visit. The primary endpoint is all-cause mortality up to Day 60. The key secondary endpoints are time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure at Day 15 and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15. Type 1 errors will be controlled using a fixed sequential testing hierarchy.

Table 1: Schedule of Activities (SoA)

	Screening	IMP Treatment Period				In-patient Stay[1]	Follow-up Period[2]			Unscheduled[3]
Visit	**V1**	**V2**	**V3-15[1,4]**	**V16[4]**	**EWD[5]**	**V17-29**	**V30**	**V31**	**V32**	**UV**
Day (Visit window)	Up to 48h prior to V2	Day 1	Days 2-14	Day 15 (+1 day)		Days 16-28	Day 22 (±1 days)	Day 29 (±1 days)	Day 60 (±3 days)	
Eligibility/General										
Informed consent	x									
Eligibility criteria	x	x[6]								
Demographics	x									
Medical history	x									
IMP and Concomitant Therapy										
Randomization		x								
IMP administration[7]		x	x							(x)
Check of fasting criteria		x	x							(x)
IMP accountability			x[8]	x	x					
Previous and concomitant therapy	x	x	x	x	x	x	x	x		(x)
Trial Assessments and Procedures										
8-point ordinal scale	x	x	x	x	x	x	x	x	x	(x)
Supplemental O_2	x	x	x	x	x	x	x	x		(x)
Oxygen saturation	x	x	x	x	x	x				(x)
Hospitalization	x	x	x	x	x	x	x	x	x	(x)
Physical examination	x			x	x					(x)
Body weight and height	x									
Vital signs	x	x	x	x	x	x				(x)
12-lead ECG[9]	x									(x)
Adverse events	x	x	x	x	x	x	x	x	x[10]	x
Biochemistry[11]	x	x[12]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Haematology[11]	x	x[12]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Urinanalysis[11]	x	x[12]		x	x					(x)
Pregnancy testing[13]	x			x	x					(x)
Oropharyngeal swab		x								
Pharmacokinetics[14]		x								
Blood sample for future exploratory analysis		x[12]		x	x					

1. Daily visits until discharge. Visits will be re-initiated in case of a COVID-19 related hospital re-admission.
2. Follow-up visits by phone or video.
3. Assessments marked with () will be performed per investigator judgment at e.g., COVID-19 related hospital re-admission after Day 29.
4. Days 8 and 15 visits must be performed for all subjects. If a subject is discharged before Day 8, the Day 8 visit will be done by phone or video. Site assessments e.g., oxygen saturation, vital signs and blood sampling will not be performed.
5. An early withdrawal (EWD) visit should be performed for subjects withdrawn from the trial prior to Day 15 (Visit 16).
6. Re-evaluation of eligibility including evaluation of electrocardiogram (ECG) and laboratory results from screening.
7. IMP is administered b.i.d. from Days 1 to 14.
8. IMP accountability will be performed at hospital discharge.
9. A historical 12-lead ECG is acceptable. The ECG should be ≤2 days old at the time of screening (Visit 1).
10. SAEs only.
11. Blood samples taken at screening will be analyzed locally. Samples taken at Days 1 to 15, or at the EWD visit will be analyzed at a central laboratory. Days 3, 5, 8 and 11 samples will only be collected if the subject is hospitalized.
12. Blood sampling and urinalysis must be performed prior to IMP dosing.
13. Applicable in women of childbearing potential. If positive, the urine dipstick will be followed up by a blood test.
14. Pharmacokinetic (PK) samples will be collected in a subgroup of approximately 10 subjects.

8.1 Sample Size Considerations

The sample size is based on the all-cause mortality up to Day 60. For the placebo (SOC) group, the proportion of subjects dead at Day 60 is estimated to 10% (Marconi et al., 2021).

With 150 evaluable subjects per trial group, there will be an 80% power to detect a difference between C21 and placebo if the proportion of subjects dead at Day 60 in the C21 group is 2.5% (corresponding to a Hazard Ratio of 0.24). In this calculation a 5% withdrawal rate has been assumed. For the actual detection limit (corresponding to 50% power), if 15 subjects die in the placebo group, significance will be seen if at most 6 subjects die in the C21 group.

This assumes using a 2-sided test at a 5% significance level. Analysis will be by intention-to-treat; thus, all randomized subjects should be accounted for in the statistical evaluation.

8.2 Randomization

Subjects will be randomly assigned in a 1:1 ratio to C21 or placebo treatment. Subject randomization will use a randomly permuted block design and stratified by severity of disease (5 or 6) measured by the 8-point ordinal scale score on trial Day 1 and region.

Registration and randomization will take place using a centralized Interactive Web Response System (IXRS) contracted through Almac. At registration, the IXRS will assign a unique subject identification number that will be used on all of that subject's eCRFs and serious adverse event (SAE) report forms.

This is a double-blinded trial, only a few number of the trial team members are not blinded for conduct of the trial or ensuring subject safety purposes. The unblinded team members will include CRO DMC team members (statistician, programmers and project manager), CRO clinical supply program manager, CRO clinical system designer, CRO clinical system developer and CRO safety personnel. Details are provided in the Data Blinding and Documentation Plan.

9.0 Trial Endpoints

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is all-cause mortality up to Day 60.

9.2 Secondary Endpoints

9.2.1 Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- Time to sustained hospital discharge up to Day 60.
- Supplemental oxygen free days up to Day 29.
- Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15.
- Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15.

9.2.2 Other Secondary Efficacy Endpoints

- Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29.
- Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, extra corporeal membrane oxygenation (ECMO) or supplemental oxygen use at Days 8, 15, 22, 29 and 60.
- Proportion of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60.

- Duration of hospitalization, including re-hospitalization, up to Day 60.
- Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60.
- Duration of intensive care unit stay, including re-admission, up to Day 60.
- Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60.
- Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60, and respiratory failure free days up to Day 60.
- All-cause mortality up to Days 8, 15, 22 and 29.
- Change from baseline in peripheral capillary oxygen saturation (SpO_2) / fraction of inspired oxygen (FiO_2) at Day 15.

9.2.3 Secondary Safety Endpoints

- Adverse events (AE)s.
- Serious AEs (SAE)s.
- Changes in safety laboratory assessments.
- Withdrawals due to AEs.
- PK Parameters (on a subset of approximately 10 subjects).

9.3 Exploratory Endpoints

- Change from baseline in CRP (C-reactive protein) at Day 15.
- Change from baseline in lactate dehydrogenase (LDH) at Day 15.

9.4 Estimand Attributes

Appendix 1: Estimand Attributes presents the primary and key secondary trial endpoints and corresponding estimands as specified in the protocol, Section 3. Sensitivity analysis of the primary and key secondary estimands are described in Sections 12.5.2.3 and 12.5.3.6 respectively. Supplementary analysis is described in Section 12.5.2.4 and 12.5.3.7 for the primary and key secondary respectively. The analysis for other secondary and exploratory endpoints will be detailed in Section 12.5.4 and Section 12.5.5 respectively.

9.5 Population Sets

For the purposes of the final analysis, the following analysis sets are defined:

9.5.1 All-Screened-Subjects

The all-screened-subjects analysis set will include all subjects that signed informed consent for the study.

9.5.2 Intention-To-Treat Analysis Set

The Intention-to-treat analysis set (ITT) comprises all randomized subjects. Subjects will be included in the analyses according to the intervention they were randomized to.

9.5.3 Per Protocol Analysis Set

The per protocol analysis set (PP) comprises all subjects in the ITT without important protocol deviations deemed to have an impact on efficacy endpoints. In addition, subjects who prematurely discontinued IMP prior to Day 11 during the treatment period due to "Withdrawal by Subject" or similar will be excluded. Subjects who were randomized and not treated will also be excluded from the PP population.

Prior to database lock and unblinding of the trial, a blinded data review of the important protocol deviations will be performed to identify the important deviations impacting on the efficacy endpoints. Additionally a review of all subjects who discontinue treatment will be performed to assess if they should be excluded from the PP. Subjects excluded together with the reason for exclusion will be documented in a blinded manner prior to database lock. Subjects will be included in the analyses according to the intervention they were randomized to.

9.5.4 Safety Analysis Set

The safety analysis set (SS) is defined as all subjects who are exposed to at least one dose (even partially) of the IMP. Subjects will be analyzed according to the intervention received.

9.5.5 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKS) is defined as subjects who were randomized to C21, exposed to IMP and with at least one post-IMP blood sample with quantifiable C21 concentration collected. Participants may be excluded from the PK analysis population if they have important protocol deviations that are judged to significantly impact the PK analyses. PK sample is limited among a pre-selected number of trial sites in a subgroup of approximately 10 subjects including those randomized to Placebo. Only samples from subjects randomized to C21 will be analyzed and included.

10.0 Conventions and Derivations

10.1 Baseline and Change from Baseline

For Efficacy assessments baseline is defined as the last non-missing assessment obtained prior to randomization. If more than one assessment could be baseline, the record associated with the visit, Visit 2 – Day 1 in the eCRF will be selected as the baseline record for efficacy. For safety assessments it is defined as the last assessment prior to the administration of first dose of IMP. If time of assessment is not collected and the assessment is collected on the same date as the first dose of IMP, the assessment will be assumed to be per protocol i.e. prior to first dose administration.

Change from baseline at any post-baseline time point will be defined as:

$$Change\ from\ baseline = value\ at\ post\ baseline\ time\ point - value\ at\ baseline$$

10.2 Trial Day

Trial Day 1 is defined as the date of first dose of IMP. For subjects whose treatment assignment is randomly assigned but not dosed, Trial Day 1 is defined as the date of randomization assignment. For dates prior to Trial Day 1, the Trial Day is calculated as:

$$Trial\ Day\ =\ (Date\ of\ Interest/Assessment\ -\ Date\ of\ Trial\ Day\ 1)$$

For dates on or post Trial Day 1,

$$Trial\ Day\ =\ (Date\ of\ Interest/Assessment\ -\ Date\ of\ Trial\ Day\ 1)+1$$

10.3 Dates of First and Last Dose of IMP

The date of first dose of IMP will be the earliest date of IMP documented on the Exposure – Dose Administration CRF page. If no date of first dose of IMP is available and the subject was not treated, date of first dose of IMP will be missing and the date of randomization will be used in any calculations requiring treatment start date.

Date of last dose of IMP for hospitalized subjects at Day 14 will be set to the last dose of IMP recorded on the Exposure – Dose Administration CRF page. For discharged subjects prior to the completion of the treatment period, the date of last dose of IMP will be set to the date of treatment completion/discontinuation as recorded on the End of Treatment CRF page. If date of last dose of IMP is not available and subject is lost to follow-up based on End of Treatment CRF page, date of last scheduled visit or date of last telephone contact where a dose is recorded, will be used as the date of last dose of IMP.

10.4 Actual Treatment

Subjects who are initially dispensed C21 will be assigned actual treatment of C21 100 mg b.i.d. This includes subjects who were randomized to placebo.

10.5 Prior and Concomitant Therapy

Prior therapies are defined as those with a start date prior to the first dose of IMP.

Therapies which start prior to the first dose of IMP and are ongoing at the time of first dose of IMP will be summarized as both prior and concomitant therapies.

Concomitant therapies are defined as those started prior to but continuing after randomization or with a start date on or after randomization. For therapies that start prior to but ended on randomization date they will be considered prior therapies only.

10.6 Adverse Events

1) Adverse Event Leading to Discontinuation of Trial

An AE will be classified as an AE leading to discontinuation of the trial if the answer to the question "Did the adverse event cause the subject to be discontinued from the study?" is Yes on the AE CRF page.

2) Adverse Event leading to IMP Withdrawal

An AE will be classified as an AE leading to IMP withdrawal if the answer to the question "Action Taken with Study Treatment" on the AE CRF page is "Drug Withdrawn".

3) IMP-related adverse events

An AE will be classified as related to IMP if the relationship to study treatment is indicated as Related on the AE CRF page. Additionally, if the relationship is missing, then the AE will be deemed IMP-related.

4) Treatment-emergent adverse events (TEAE)

Treatment-emergent adverse event is defined as an event that starts on or after the date of first dose of IMP or worsens after first dose of IMP.

5) Duration of AEs

Duration of AEs will be calculated as AE end date – AE start date + 1. AE duration will only be calculated when complete dates for the start and stop date are provided.

10.7 Imputation of Missing Dates

There will be no imputation of partial and missing dates. Duration of events will not be calculated if start or stop date is partial and listings will display the collected date and not the imputed date. The following rules will be implemented to determine the assignment of AEs as TEAE and therapies as prior and concomitant for the analysis.

In general, in such cases an AE will be considered treatment-emergent, unless there is evidence in the (partial) dates available that it was not treatment-emergent. In particular, in case of missing start dates of AEs, these will be considered treatment-emergent, unless the stop date of the AE is prior to the first dose of IMP. In the case of partially missing start dates, the AE will be considered treatment-emergent, unless the information from the partial dates clearly shows that the AE was not treatment-emergent i.e. the year/month is prior to treatment start date.

For therapies if start date is missing and the end date is prior to the first dose of IMP, the therapy will be considered prior. If start date is missing or partial and the end date is missing or after first dose of IMP, the therapy will be considered both prior and concomitant unless there is evidence in the partial dates that clearly classifies the therapy as prior or concomitant (i.e. start year/month is after the first date of IMP). If end date is partial or missing and start date is after first dose of IMP the therapy will be considered concomitant.

10.8 8-point Ordinal Scale

The clinical status of COVID-19 is scored at each visit according to the 8-point ordinal scale. For hospitalized subjects this will be assessed by the investigator once daily until Day 29. For discharged subjects the 8-point ordinal scale will be assessed at Day 8, Day 15, Day 22, Day 29 and Day 60. Discharged subjects will be assessed for daily supplemental oxygen use since the previous visit. If there was supplemental oxygen use on the days between visits, the subject will be considered to be on oxygen on those days and an 8-point ordinal scale score of 2. For further details on the assessment of supplemental oxygen use for discharged subjects please refer to Section 10.10.

If a subject is discharged, the 8-point ordinal scale will be updated at discharge as an unscheduled visit. If there is a change in clinical status between Day 29 and Day 60 the 8-point ordinal scale score should also be updated. A subject re-hospitalized for a non-COVID-19 related reason should be considered non hospitalized while scoring the clinical status of COVID-19 on the 8-point ordinal scale.

The 8-point ordinal scale is defined in Table 2. In the efficacy analysis for some key secondary endpoints subjects will be considered a responder at a time point if they have achieved a score of ≤ 2 on the 8-point ordinal scale and have no supplemental oxygen use. For the purpose of the analysis an adjusted version of the 8-point ordinal scale will be used which will re-map subjects with a score of 2 and no at home oxygen use at a time point to have a value of 1 on the adjusted 8-point ordinal scale. Subjects with a clinical status of 2 on the 8-point ordinal scale and no oxygen use will be treated as the best case clinical status in all analysis and equivalent to a status of 1 in the analysis. Refer to Table 3 and Section 10.10 for details on determining the oxygen status of a subject at a time point.

Table 2: 8-point Ordinal Scale

1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Table 3: Adjusted 8-point Ordinal Scale for Multiple Imputation

1	Not hospitalized, no limitations on activities; limitation on activities and no home oxygen required
2	Not hospitalized, requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

10.9 Visit Windowing

Subjects are expected to attend daily visits until hospital discharge. Visits will be re-initiated in case of a COVID-19 related hospital re-admission. Subjects who do not discharge will have daily assessments up to Day 29. Subjects who do discharge will have visits Day 8, 15, 22, 29, 60. All subjects will have a follow-up visit at Day 60.

No visit windowing will occur for the 8-point ordinal scale. Daily values for the 8-point ordinal scale will be assigned based on the trial day the assessment occurs i.e. the value recorded on trial day X will be assigned as the value of the ordinal scale at Day X in the analysis. For discharged subjects, information on the oxygen use at home between visits will be entered on the concomitant medication page and the daily 8-point ordinal scale value for discharged subjects will be derived. If a subject has oxygen use on a trial day as per Section 10.10, they will be assigned a value of 2 on the adjusted 8-point ordinal scale (refer to Table 3 in Section 10.8) on the trial days between the oxygen start and end day. If Day 29 occurs on trial day greater than 29, for the analysis purposes a value of Day 29 will be assigned. For Day 60 the value collected at the Day 60 visit will be used in the analysis, even if this did not occur on trial Day 60. All endpoints for the 8-point ordinal scale will summarize Day 8, 15, 22, 29 and were applicable Day 60 time points. If a subject has multiple non-missing ordinal scale assessments on a trial day the assessment that occurred on the scheduled visit per the eCRF will be used in the analysis.

For hospitalized subjects, vital signs, supplemental oxygen use and oxygen saturation will be collected daily. Therefore, no visit windows will be assigned and results in the analysis will be summarized for each trial day up to Day 29. Trial day calculation is defined in Section 10.2. If the trial day an assessment occurs on does not align with the visit trial day in the CRF, the trial day will take precedence in terms of analysis. Laboratory assessments (including CRP and LDH) will be conducted while in hospital but not daily. Analysis visit windows as defined in Table 4 will be used for laboratory assessments. If a subject has multiple assessments in a window, the visit closest to the target day will be selected. For visits that are equally close to the target day, the assessment latest in time will be selected.

An early withdrawal visit (EWD) will be conducted for subjects who discontinue the trial prior to Day 15. This visit will be mapped to analysis visits per Table 4 and to a daily time point based on the trial day the assessment occurs. If a scheduled visit and EWD occur on the same day, the scheduled visit will be used in the analysis for the 8-point ordinal scale.

Table 4: Visit Windowing for Laboratory Assessments and CRP/LDH

Visit	Target Trial Day	Lower Limit	Upper Limit
Baseline	1		1 (pre-baseline)
Day 3	3	1 (post-baseline)	3
Day 5	5	4	6
Day 8	8	7	9
Day 11	11	10	12
Day 15	15	13	16

10.10 Supplemental Oxygen Use

Hospitalized subjects will be assessed on a daily basis for their oxygen use. If a subject is discharged, they may be prescribed supplemental oxygen for at-home use. On each visit following discharge a subject will be assessed if they have used oxygen since the last visit and which days and if they have used supplemental oxygen this will be recorded on the concomitant medication page of the CRF. Subjects who have used supplemental oxygen since the previous visit will also be assessed if they are still on oxygen at the visit.

If a subject has a scheduled ordinal scale score of 1, 3, or 4 (i.e. free of supplemental oxygen use) and there is evidence of supplemental oxygen usage, the value on the adjusted ordinal scale will not be changed and the investigator's judgement will be considered the most accurate assessment of clinical status. The collected ordinal scale value will be used as the value in the analysis and the subject will be considered free of supplement oxygen usage on the trial day of interest.

For discharged subjects, the daily oxygen use will be derived. If a subject has oxygen use on a trial day they will be assigned a value of 2 on the adjusted 8-point ordinal scale on the trial days between the oxygen start and end day. A discharged subject will be considered to be using supplemental oxygen on a trial day if:

1. The subject has a record at the time point for supplemental oxygen use on the Oxygen supplementation during oxygen saturation measurement page of the CRF.
2. The subject has "Yes" at a time point to the question "Was subject still on COVID-19 related supplemental oxygen at the time of visit" on the Visit page of the CRF for discharged subjects at Day 8, Day 22, Day 29 and Day 60 and on the End of Treatment page for Day 15.
3. If a subject has a missing ordinal scale score on the day of discharge or a value of 2 on the ordinal scale and on the Hospitalization CRF page the question "Was COVID-19 related supplemental oxygen for at home use prescribed?" is Yes then a subject will be considered on supplemental oxygen at discharge and the visit that corresponds with discharge.
4. Subject has a record on the concomitant medication page for post-baseline supplemental oxygen use (preferred term entered as Oxygen and the therapy is concomitant per Section 10.5)

Otherwise the subject will be considered oxygen free at a time point. If the subject has an ordinal scale score of 2 at these time points and is not on supplemental oxygen they will be assigned an adjusted ordinal scale score of 1.

10.11 All-Cause Mortality

All-cause mortality is defined as time to day of death from any cause during the study. Time to all-cause mortality will be defined as:

$$Time\ to\ all\ cause\ mortality\ (days) = Date\ of\ Death\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

where the date of death will correspond to the date of death recorded in the CRF. Subjects without the event will be censored at day of withdrawal/Day 60 follow-up date in this analysis. If a subject is indicated to have died in the data, but date of death is missing, the last available date for the subject in the database will be used as the day of death.

10.12 Time to Sustained Hospital Discharge

Time to sustained hospital discharge is defined as the time to the date of discharge from initial hospitalization or re-hospitalization due to COVID-19 after which the subject is not re-hospitalized for COVID-19 related reasons.

If a subject dies, they will be censored at Day 60, if a subject withdraws (for reasons other than death) from the trial prior to observing the event (i.e. while still hospitalized) they will be censored at the time of withdrawal. If a subject has an event and subsequently withdraws (for reasons other than death), they will be treated as having the event in the analysis. Subjects who complete the trial without the event i.e. are still hospitalized at Day 60, will be censored at Day 60 in the analysis.

The calculation will be as follows:

$$Time\ to\ sustained\ discharge\ (Days) = Date\ of Event\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

where date of event for subjects who discharge will be the date of discharge from hospital (after which the subject is not re-hospitalized for COVID-19 reasons) as recorded on the Hospitalization CRF page. If a subject is re-hospitalized for COVID-19 reasons, the date of event will be the end date of this re-hospitalization (if no subsequent re-hospitalization for COVID-19 reasons).

Additionally, a sensitivity analysis will be performed where all re-hospitalizations are considered as COVID-19 related regardless of the investigator indicated cause. In the sensitivity analysis, date of event for subjects with missing data and no discharge record on the hospitalization form will be the relative day a value of ≤2 is achieved after which a subject has only imputed values of ≤2 for all subsequent visits. If subjects with imputed data have a recorded value of discharge on the hospitalization page and imputed data is ≤2 from this date of discharge, the recorded date of discharge will be used as event date in the calculation. If subjects with imputed data have a recorded value of discharge on the hospitalization page and any imputed data is >2 from this date of discharge, time to sustained discharge will be the relative day a value of ≤2 is achieved after which a subject has an imputed value of ≤2 for all subsequent visits. If a subject with imputed data never observes the event they will be censored at Day 60.

10.13 Number of Oxygen Free Days

Subjects will be considered oxygen free on a trial day if they do not have supplemental oxygen usage on that day. Supplemental oxygen usage is defined in Section 10.10 and subjects will be assessed for supplemental oxygen usage on each post treatment day up to trial Day 29 (i.e. from trial Day 2 to Day 29).

The number of oxygen free days for a subject will be the sum of the number of oxygen free days in hospital and number of oxygen free days at home if applicable. These days do not need to be consecutive. Missing data will be imputed as per Section 10.19.1.

10.14 Number of Respiratory Failure Free Days

The number of days a subject is free of respiratory failure will be the number of days a subject has a score of ≤5 on the ordinal scale post-baseline.

If a subject dies, they will be considered in respiratory failure from the date of death up to Day 60.

For hospitalized subjects this will be the number of days a subject has a score of ≤5 on the 8-point ordinal scale CRF page. Up to Day 29, the adjusted 8-point ordinal scale will be used, for days between Day 29 and Day 60 the following rules will apply:

- If the clinical status on both days is ≥ 6 the subject will be assumed to be in respiratory failure for all days between Day 29 and Day 60.
- If the clinical status on both days is ≤5 and there is no observed data (for example unscheduled visits) indicating a worsening of status the subject will be assumed to be respiratory failure free for all days between Day 29 and Day 60. If there is a worsening of a status such that the ordinal scale has a value of ≥6, the subject will not be considered respiratory failure free from the duration of this status (if duration of status is known).
- If the clinical status at Day 29 is ≥ 6 and Day 60 is ≤5 and the date of the change of status is known, the subject will be counted as respiratory failure free from the date the status improved. If the date of change in status is unknown (for example data is imputed), only Day 60 will be counted as respiratory failure free.
- If the clinical status at Day 29 is ≤5 and Day 60 is ≥6 and the date of the change of status is known, the subject will be counted as respiratory failure free until the date the status worsen. If the date of change in status is unknown (for example data is imputed), only Day 60 will be counted as in respiratory failure.

For discharge subjects, if a subject does not have a change in status up to Day 60 following discharge i.e. they are not re-hospitalized due to a COVID-19 related illness, the number of respiratory failure free days after discharge will be calculated as

$$Respiratory\ Failure\ free\ (days) = Day\ 60\ visit - Date\ of\ Discharge + 1$$

If a subject is re-hospitalized due to a COVID-19 related illness and the ordinal scale on re-admission is ≥ 6 the number of respiratory failure free days after discharge and prior to re-hospitalized will be calculated as

$$Respiratory\ Failure\ free\ (days) = Date\ of\ re - hospitalization - Date\ of\ Discharge$$

The number of respiratory failure free days will be the sum of the days the subjects met the criteria i.e. the number of days a subject has a score of ≤5 on the 8-point ordinal scale while hospitalized and the numbers of days a subject meets the criteria while discharged. These days do not need to be consecutive.

Subjects with missing data will have their data multiply imputed as per Section 10.19.1.

10.15 Duration of Hospitalization

The duration of hospitalization will be calculated as

$$Duration\ (days) = End\ date\ of\ hospitaliztion - Start\ date\ of\ hospitalization + 1$$

The duration of multiple hospitalizations, including re-hospitalizations due to COVID-19 in the period will be summed together to derive the overall duration of hospitalization. For subjects who were hospitalized on the date of first dose of IMP, the date of first dose of IMP will be used as the start date. If a subject is still hospitalized at the end of the 60-day period the date of trial completion will be used.

For subjects who die they will be considered hospitalized from date of death through Day 60. For subjects who discontinue the trial prior to discharge from hospital, the number of days of hospitalization will be set to 60 days (it will be assume they did not discharge from hospital). If a subject discontinues the trial following discharge for reasons other than death and there is no further hospitalization data available then for the purpose of the analysis the subject will be considered to be not re-admitted in the period and no additional imputed days will be added to the number of days recorded on the available assessments.

An additional sensitivity analysis will be performed where missing data will be imputed as per Section 10.19.1, such that subjects who are early withdrawals will have data imputed following withdrawal and

where all re-hospitalizations are considered as COVID-19 related regardless of the investigator indicated cause.

10.16 Duration of ICU Stay

The duration of ICU stay will be calculated as

$$Duration\ (days) = End\ date\ of ICU\ stay - Start\ date\ of\ ICU\ stay + 1$$

The duration of multiple ICU stays in the period will be summed together to derive the overall duration of ICU stay. If a subject dies or discontinues prior to the end of the ICU stay or the subject died and had no ICU stay, the subject will be considered in the ICU from the date of death/discontinuation through Day 60. For subjects who discontinue the trial in hospital but not in ICU or discontinue following discharge they will not have any imputed additional days added to the number of days recorded on the available assessments. If the start date of the ICU stay is prior to treatment start, the treatment start date will be used as the ICU start date in the above derivation. For subjects with no ICU stay a value of 0 days will be used in the analysis. Note that ICU stays associated with re-admission for non-COVID reasons should not contribute to the duration.

10.17 Duration of Invasive Ventilation or ECMO

The duration of invasive ventilation or ECMO use will be calculated as

$$Duration\ (days) = End\ date\ of\ use - Start\ date\ of\ use + 1$$

The duration of multiple invasive ventilation or ECMO use will be summed in the period to derive the overall duration. For subjects who die they will be considered on invasive ventilation or ECMO from date of death through Day 60. Subjects who discontinue the trial prior to discharge from hospital with last ordinal scale assessment of 7 will be considered on invasive ventilation or ECMO from date of discontinuation through Day 60. Subjects who discontinue the trial in hospital with last known status on the 8-point ordinal scale of ≤6 or subjects who discontinue following discharge will be considered not on invasive ventilation or ECMO through Day 60 and will have no additional days added to the number of days recorded on the available assessments. For subjects with no invasive ventilation/ECMO use a value of 0 days will be used in the analysis.

10.18 Data handling for SpO_2 and FiO_2

SpO_2 will be collected on the Oxygen saturation form daily for hospitalized subjects. SpO_2 will be collected twice at a visit and the average of the two assessments will be used as the value in the analysis. If only one assessment is available at a visit this will be the value used in the analysis. Discharged subjects will not have site assessments performed. Day 15 will be the only time point examined for this endpoint.

Subjects on low flow oxygen, high flow device or mechanical ventilation will use the value of FiO_2 as entered on the eCRF by the investigator. Subjects on room air will have a value of 21% for FiO_2 assigned. Subjects on ECMO will not have FiO_2 collected. In this case in the calculation of the SpO_2/FiO_2 ratio the last observation for this ratio prior to the subject moving to ECMO ventilation will be used. If the value of FiO_2 is missing, but information on the type of device and oxygen flow is collected, Appendix 3 will be used to assign a value of FiO_2 to use in the calculation of the SpO_2/FiO_2 ratio.

At a visit a subject may have a SpO_2 reading on an oxygen device and another reading at the same visit on room air. In this case the ratio SpO_2/FiO_2 will be calculated using the on room air value only for SpO_2 and a value of 21% for FiO_2.

10.19 Missing Data

In general, missing safety data will not be imputed. However, safety assessments in the form of <x (i.e. below the lower limit of quantification) or >x (i.e. above the upper limit of quantification) will be imputed as x in the calculation of summary statistics but displayed as <x or >x in the listings. Missing FiO_2 values will be imputed as per Appendix 3.

In all efficacy analysis subjects who die will always be treated as the worst case following the date of death. For endpoints where multiple imputation will not be implemented, subjects who discontinue the trial early will be assessed in the analysis based on their last known status as discussed in Sections 10.15, 10.16 and 10.17. Other missing data will be imputed using multiple imputation as outlined below.

10.19.1 Multiple Imputation

Missing ordinal scale data at scheduled time points will be imputed using multiple imputation. Multiple imputation relies on the assumption of data being missing at random (MAR) i.e. the missingness can be explained by the observed data and missing data does not depend on unobserved data after accounting for observed factors. Subjects will only have missing data imputed for post-baseline scheduled visits (Day 2 to Day 29, Day 60).

The following steps will be used to impute the missing data. Prior to the missing data imputation all observed 8-point ordinal scale data will be re-mapped per Table 3 to ensure discharged subjects with supplemental oxygen use are treated as clinically worse than discharged subjects with no oxygen use. This will also ensure information on at home oxygen use is explicitly contained in the ordinal scale score. The value of the adjusted 8-point ordinal scale to use in the analysis for all days following discharge will be assigned as per Section 10.10. On the day of discharge, the following rules will be used to assign a value of the adjusted ordinal scale:

- If a subject has a scheduled visit with an ordinal scale value other than 2, this value will be used in the analysis for the day of discharge.
- If a subject has a missing assessment or a value of 2 is recorded as the scheduled assessment, a subject will be assigned a value of 1 or 2 on the adjusted 8-point ordinal scale on the day of discharge as outlined in Section 10.10.

If a subject has an ordinal scale value of 8 at any visit or the subject has a date of death, records on or following date of death will be handled as follows in the analysis:

- All days following day of death will be set to 8.
- For the day of death, if the subject has a non-missing value on the ordinal scale that is not a value of 8 this will be the value used in the analysis.
- If a subject has a missing value on the day of death the value of 8 will be used.

Subjects who die will be removed from the Imputation in step 2. Only subjects who have not died will have their data imputed. Following the imputation, data for subjects who died will be included in all imputed datasets as observed.

A random seed of 2188 will be used for all imputation in this analysis.

1. Prior to the imputation, missing data pattern for ordinal scale data will be explored. If the pattern of missing data is non-monotone (for example intermediate missing data due to missing follow-up visits), intermittent missing ordinal scores will be imputed under a missing at random (MAR) model for missing data using a Markov chain Monte Carlo (MCMC) method of imputation to ensure data follows a monotone missing data pattern i.e. if data is missing at Day X it will be missing for all subsequent time points. The 8-point ordinal scale will be imputed using PROC MI with the MCMC impute=MONOTONE specification and specifying the variables in order of scheduled visits (Day 2 up to Day 29, Day 60), in order to partially impute intermediate missing values only.

   A minimum value of 1 and maximum value of 7 will be specified to ensure values are not outside the range of possible ordinal scale scores. Values will be rounded to the nearest whole number and 1,000 burning iterations will be used. Graphical tools will be used to check for any signs of non-convergence and if non-convergence is an issue, the number of burn-in iterations should be increased.

If the model does not converge as values within the minimum/maximum range can not be imputed, the minimum and maximum criteria will be removed. Subjects which have values outside the minimum and maximum will be reviewed and the following process will be followed to obtain convergence:

- For values below the minimum and above the maximum the largest absolute deviation from the minimum/maximum will be determined. The subject with the largest absolute deviation for the non-monotone data will have the data point assigned using last observation carried forward (LOCF)
- The MCMC will be re-run (with minimum/maximum specified). If setting the minimum/maximum results in convergence these results will be used in Step 2 of the MI process. Otherwise the process will be repeated until setting minimum/maximum results in convergence or no further subjects with unrealistic data can have non-monotone data imputed with LOCF.
- If after these steps are applied and there is no convergence, the MCMC will not be used and LOCF will be used for all subjects to impute their non-monotone data.

This step will only be performed if missing data does not follow a monotone missing data pattern. This step assumes data is multivariate normally distributed which will not be the case for ordinal data. However, as the number of non-monotone data is expected to be small, the overall impact of this partial imputation step on the analysis at the time point of interest will be small. Subjects who died will be included in this step. Further it is accepted that values of 1 and 2 may be imputed for non-monotone data prior to the observed date of discharge. No adjustments will be made for this as these values are theoretically possible.

2. Missing 8 point ordinal scale data at time point X will be imputed for subjects who did not die using a logistic regression model with the factors of
    a. Treatment group
    b. Actual baseline ordinal scale score
    c. Region (Pooled)
    d. Age (will not be included in the CLASS statement in the PROC MI)
    e. Post-baseline daily values of adjusted 8-point ordinal scale up to time point X

Values will be restricted to a minimum value of 1 and a maximum value of 7, as values of 8 will not be present in the data per the previous rules outlined. It is noted that at a time point only values of the ordinal scale recorded at the time point will be possible imputed values. Imputed values may be inconsistent with other data, for example it is possible that an imputed value will be 3 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care) even if supplemental oxygen is documented on the concomitant medication page.

The number of imputations will depend on the percentage of missing data to be imputed and will range from a minimum of 20 to a maximum of 50. The number of imputations will increase from the minimum of 20 to the maximum of 50 according to the formula:

$$Number\ of\ imputations = 20 + 1.5 * (m)$$

where m is the proportion of missing data, expressed as a percentage. The smallest integer that is greater than or equal to the number will be used (note this will be based on missing data present following step 1 and will not included subjects who died in the calculation)

By default SAS PROC MI, uses the option "LIKELIHOOD=NOAUGMENT" for the computation of maximum likelihood estimates. If the maximum likelihood parameter estimates do not exist or any warning results from this option, the option "LIKELIHOOD=AUGMENT" will be used to get the maximum likelihood estimates.

3. Imputed values from each of the imputed datasets in step 2, data for subjects who died and non-missing data will be used to calculate the responder status for a subject at a time point for the following endpoints:

Sensitivity Analysis for Time to Sustained Hospital Discharge

For each of the imputed datasets, the time to sustained hospital discharge will be derived. If a subject has an observed or imputed score of ≤2 on the ordinal scale where for all subsequent visits the observed or imputed score stays at or below 2 the earliest occurrence will be considered the time to sustained hospital discharge. Note for subjects with no missing data, the time to sustained discharge will be per the rules in Section 10.12. If a subject was re-hospitalized for a non-COVID-19 related reason, the subject will not be considered discharged during this re-hospitalization period for this analysis. For all subjects who do not have the event or who die, they will be censored at Day 60. The calculation will be as follows:

$$Time\ to\ sustained\ discharge\ (Days) = Date\ of Event\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

For subjects where the event occurs on an imputed visit, the value of time to sustained discharge will be set to the trial day of the imputed visit (i.e. if the event first occurs for Day 29 and is an imputed value, the time to sustained discharge will be set to 29). For each of the datasets the analysis (stratified log-rank) as per Section 12.5.3.2 will be implemented.

Number of Days Oxygen Free

A subject will be considered as oxygen free at a time point if the observed and imputed value of the adjusted 8-point ordinal scale is 1, 3 or 4. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.3 will be implemented.

Proportion of subjects free of respiratory failure at Day 8, 15, 22, 29, 60

A subject will be considered a responder at a time point if the value of the 8-point ordinal scale is ≤5. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.4 will be implemented.

Subjects discharged and free of supplemental oxygen at Day 8, 15, 22 and 29

A subject will be considered a responder at a time point if the value of the adjusted 8-point ordinal scale, observed and imputed, is 1. For each of the datasets imputed in step 2, the analysis as specified in Section 12.5.3.5 will be implemented.

Number of Days Free of Respiratory failure

A subject will be considered free of respiratory failure at a time point if the value of the 8-point ordinal scale is ≤5. For details on this derivation refer to Section 10.13. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.3 will be implemented.

Other Non-Key Secondary Endpoints

For the endpoints of proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, a subject will be considered on invasive mechanical ventilation or ECMO if the imputed value at the time point is ≥ 7.

For the endpoint of proportion of subjects on non-invasive, invasive mechanical ventilation, ECMO or supplemental oxygen use at Days 8, 15, 22, 29 and 60, subjects will be considered on non-invasive, invasive mechanical ventilation, ECMO or supplemental use if they have an imputed or observed score of ≥ 5 at the time point.

For sensitivity analysis for the endpoint of duration of hospitalization, the duration of multiple hospitalizations, including re-hospitalizations due to COVID-19 and non-COVID-19 related reasons in the period will be summed together to derive the overall duration of hospitalization. For subjects with no missing data, duration of hospitalization will be calculated as per Section 10.15. For subjects with missing data following observed discharge date, no additional days will be added for

duration if the imputed values are ≤2 following this date, otherwise if subjects have a value of >2 following last observed discharge, the number of days where the imputed values are >2 will be added to the observed duration. For subjects with missing data with no observed discharge date, if the imputed values are ≤2, then the subject will have the duration of hospitalization calculated as relative day of last value >2 – start date of hospitalization +1. If the subject has multiple values > 2 following the first imputed discharge, the number of days where the imputed value is >2 will be added to the duration. Note that Day 59 should be used in the calculation if imputed Day 29 is >2 and imputed Day 60 ≤ 2. If imputed Day 29≤2 and Day 60>2 only Day 60 will be counted as in hospital.. If a subject does not have the event across the imputed and observed data duration will be calculated as Day 60/study completion – date of initial hospitalization +1.

4. Results from the analysis (log-rank, logistic regression as per Appendix 2, statistics from the analysis for number of days oxygen free as per Section 12.5.3.3 and ANOVA) will be combined using Rubin's rule (Rubin, 1987). Estimates will be combined using PROC MIANALYZE in SAS. Rubin's rule assumes the estimates are asymptotically normally distributed.

   Analysis of Proportions using Logistic Regression (Appendix 2)

   Estimates from the logistic regression are transformed using the method outlined in Appendix 2. The standardized weighted differences, standard errors and the 95% CI based on the delta method (Ge et al, 2011) are approximately normal, no adjustment is required.

   Analysis using Log-Rank

   Estimates from log-rank are based on a chi-square distributed statistic and prior to combining the estimates via Rubin's rule, the estimates will need to be normalized using a Wilson-Hilferty transformation (Moscovici and Ratitch, 2017).

   Analysis using Cox Regression

   For results from Cox regression, the estimates obtained from PROC PHREG are log hazard ratios, and after combining via Rubin's rule, the results will be exponentiated to obtained the hazard ratios and associated confidence intervals (Moscovici and Ratitch, 2017).

   ANOVA

   Estimates from ANOVA are approximately normal and no transformation is required.

10.19.2 Multiple Imputation as a Sensitivity Analysis for the Primary Endpoint

As a sensitivity analysis for the primary endpoint, all-cause mortality at Day 60, missing data for Day 60 will be imputed using a logistic regression model and the proportions of deaths at Day 60 analyzed per Appendix 2. The steps for this multiple imputation will follow Section 10.19.1 with the following exceptions:

- Deaths in the data will be included in the imputation model.
- For Step 1, imputation of non-monotone data using MCMC, the maximum value allowed will be 8
- At the imputation step only missing data for Day 60 will be imputed using the following model:
  - Treatment group
  - Actual baseline ordinal scale score
  - Region (Pooled)
  - Age
  - Last known post-baseline ordinal scale value (for subjects with complete data collection up to Day 60, this will be the value collected at Day 29 analysis visit)

10.19.3 Tipping Point Analysis

To assess the robustness of the efficacy analysis, an additional sensitivity analysis using a tipping point will be performed. Tipping point analysis will be performed for the key secondary endpoints of oxygen supplemental free days up to Day 29, proportion of subjects free of respiratory failure at Day 15, and subjects discharged and free of supplemental oxygen usage at Day 15. A series of analyses will be performed with different values of a shift applied until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that changes the conclusions of the analysis from significant to non-significant will represent the tipping point. The results of the tipping point will be summarized showing the treatment difference, 95% CI and p-values for each level of δ. The analysis will not be performed if the primary efficacy analysis for the endpoints results in a non-significant result.

All-Cause Mortality

For the endpoint all-cause mortality, missing data will be imputed using Section 10.19.2. For each imputed dataset generated, a subject with missing data at Day 60 will be assigned as a death/survival based on the value of the adjusted 8-point ordinal scale. Prior to step 3 (performing the logistic regression analysis on the imputed datasets), a shift will be applied to the number of subjects classified as survivors across the imputed datasets. Among the subjects with missing data in the active arm, the number of survivors in this group will be reduced incrementally across each dataset (i.e. changing the subject from survival status to death status), starting at 1 to a maximum value of the number of subjects with missing data (for example if 10 subjects have a missing data at Day 60 in the active arm, each dataset will have the number of responders reduced from 1 up to 10 in the active arm at Day 60) or until it is not possible to reduce the number of survivors any more in an imputed dataset (i.e all subjects at Day 60 with missing data are set to Death status).

For each incrementally shift in the number of responders across missing data in the active arm, step 3 and step 4 will be performed as in Section 10.19.2. If no tipping point is found by just applying a shift to the number of responders in the active arm, the procedure will be repeated with the number of survivors across subjects with missing data at Day 60 in the placebo arm increased.

The choice of the subject to change from a survivor to death will be done at random. Using the random seed of 150822, each subject with missing data will be assigned a numeric value. The subject's values will be changed incrementally based on the numeric order generated by this process.

Respiratory Failure Free at Day 15/ Discharged and Free of Supplemental Oxygen Usage at Day 15

For these endpoints, a similar approach as all-cause mortality will be applied. For each imputed dataset as generated per Section 10.19.1 a subject will be assigned as a responder/non-responder depending on the value of the adjusted ordinal scale. For each imputed dataset, a shift will be applied to the number of responders across the imputed datasets. Among the subjects with missing data in the active arm, the number of responders in this group will be reduced incrementally across each dataset, starting at 1 to a maximum value of the number of subjects with missing data at Day 15 or until it is not possible to reduce the number of responders any more in an imputed dataset (i.e all subjects at Day 15 with missing data are set to be non-responder). If a shift is not found by just applying to the active arm, a shift will be applied to the Placebo arm (increasing the number of responders). The choice of which subject to change from responder to non-responder will be assigned following the approach for all-cause mortality.

Number of Supplemental Free Days up to Day 29

For the endpoint oxygen supplemental free days up to Day 29, the imputation as described in Section 10.19.1 will be performed and for each imputed dataset the number of days oxygen free will be tabulated. Then for subjects in the active arm with missing data up to Day 29, the number of days oxygen free will be reduced incrementally starting at 1 up to the number of days the subject had a missing value. For each reduction, the analysis as described in step 3 and step 4 in Section 10.19.1 will be performed. If no tipping point is found by just applying a shift to the number of days in the active arm, the procedure will be repeated with the number of days across subjects with missing data in the placebo arm increased.

10.19.4 Worst Case Imputation

In order to assess the robustness of the primary efficacy analysis for selected key secondary endpoints, the worst case analysis will be used which will assign missing data in the active arm using the average of the observed values in the placebo arm at a visit. Likewise for missing values in the placebo arm, the average of the observed values in the active arm at a visit will be used. This analysis will only be considered meaningful if the results of the primary analysis for the key secondary endpoints are significant for C21.

The adjusted ordinal scale value will be used in this analysis and the average will be rounded to the nearest whole number prior to analysis. For the key secondary endpoint of oxygen supplemental free days, death will be given a value of -1, subjects with no post treatment data a value of 0 in the analysis.

11.0 Interim Analyses

No formal interim analysis will be performed in the study. The DMC will review the safety results after the first 150 randomized subjects have completed study up to Day 15.

12.0 Statistical Methods

All statistical analyses will use SAS® version 9.4 or higher. Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% which will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, Standard Deviation (SD), median, Q1, Q3, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, median, Q1, and Q3 to a further decimal place and the SD to two additional decimal places. The maximum number of decimal places will be 4, unless otherwise noted. P-values will be presented to 3 decimal places, with values less than 0.001 presented as <0.001.

In general, all data summaries will be presented by treatment group and overall. Efficacy outputs will not have an overall column. If not stated otherwise, p-values from statistical tests will be two-sided and CIs will be calculated using a 95% CI.

Stratification will be done based on baseline disease severity, that is the score on the ordinal scale at baseline (5 or 6), and region (North America, South and Central America, Europe, Asia, Africa). The actual stratification will be used as factors in the statistical analysis, subjects included in wrong stratum at randomization will be moved to their correct strata belonging in the analyses. Small stratum may be pooled in the analysis. Any pooling of stratum will be agreed prior to unblinding of the database. Region will be pooled as Europe vs the rest of the world (North America, South and Central America, Asia, Africa). For all models where region is a factor (including in the imputation), pooled region will be used. In the text of this document, region will mean pooled region. Factors may be removed from models if the factor is causing an issue with convergence. For subgroup analysis, factors that are aligned with the strata division will be deleted from the model.

Missing data will be handled as described in Section 10.19. The ITT is used to analyze endpoints related to the efficacy objectives, the PP will be used for sensitivity analyses related to efficacy objectives and the SS is used to analyze the endpoints and assessments related to safety. PK analyses will be presented using the PKS.

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in hierarchical order as below:

1. All-cause mortality up to Day 60
2. Time to sustained hospital discharge up to Day 60
3. Supplemental oxygen free days up to Day 29
4. Proportion of subjects free of respiratory failure at Day 15

5. Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15

This means that statistically significant results for the comparison in the higher rank are required to initiate the testing of the next comparison in the lower rank. All analysis will be performed in the above order, however if a statistical comparison is non-significant then all subsequent statistical analysis will be exploratory in nature and no formal conclusions will be drawn. In other words, if the test for endpoint 3 in the above order is non-significant, then endpoints 4 and 5 will be exploratory in nature.

Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.

All data collected during this trial regarding subject characteristics, efficacy and safety will be listed, unless otherwise specified. Screen failures will be excluded from all listings and tables if not otherwise noted. Listings will not show imputed data but will present data as reported.

12.1 Subject Disposition

The number of subjects screened, and the number and percentage of screen failure subjects, together with the reason for screen failure will be presented.

The number and percentage of subjects randomized, not treated and treated in the trial will be presented, with the number and percentage of subjects who prematurely withdrew from the treatment, withdrew from treatment but completed the trial, prematurely withdrew from the trial and a breakdown of the corresponding reasons for treatment and trial withdrawal.

Tabulations of the number and percentage of subjects included in each analysis set. A tabulation of subjects still in the trial at each post-baseline time point will be provided.

Subjects disposition will be listed for all randomized subjects.

12.2 Demographic and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the ITT, SS, and PP. Additionally, a summary of demographic characteristics by actual baseline severity strata will be presented for the ITT.

Descriptive statistics will be provided for

- Sex (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Country
- Actual Region (North America, South and Central America, Europe, Asia, Africa) [Randomized region will be presented if any difference between actual region and randomized]
- Age (years) at informed consent (as collected on the Demographics CRF page),
- Age group (< 65 years, ≥ 65 years)
- Baseline body weight, height, and BMI. BMI will be derived as Weight (in kg)/Height (in m)^2
- Actual Baseline Disease Severity strata (ordinal score 5 or 6 at baseline based on actual value and not randomized)
- Randomized Baseline Disease Severity strata (ordinal score 5 or 6 at baseline based on value used in randomization)

- Presence of Risk factors for Severe COVID-19 (subjects with any medical history preferred terms selected as a risk factor as defined by the investigator on the Medical history page of the CRF will be counted as Yes otherwise subjects will be counted as No)
- Number of Risk Factors (count of unique medical history preferred terms selected as risk factor for severe COVID-19 by the investigator)
- SARS-CoV-2 Variant

A listing for demographics will be provided for ITT.

Medical history conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later. The number and percentage of subjects with each medical history term will be summarized by the MedDRA system organ class (SOC) and preferred term (PT) using the ITT. A listing for medical history presented for the ITT. Additionally medical history indicated by the investigator on the CRF as a risk factor for severe COVID-19 will be summarized by SOC and PT in the ITT.

COVID-19 diagnosis and history will also be summarized for ITT with descriptive statistics presented for the following:

- History of previous COVID-19 infections (Yes, No)
- Time since onset of current COVID-19 signs and symptoms calculated as:

$$Time\ since\ onset\ (days) = Start\ date\ of\ treatment - date\ of\ onset$$

- Time since current COVID-19 diagnosis

$$Time\ since\ diagnosis\ (days) = Start\ date\ of\ treatment - date\ of\ diagnosis$$

- Duration of current hospitalization calculated as:

$$Duration\ (days) = Start\ date\ of\ treatment - Start\ date\ of\ hospitalization$$

  The start date of hospitalization is the start date for records indicated as Initial hospitalization on the COVID-19 Hospitalizations CRF page. Additionally the following categories for duration of current hospitalization in days will be presented :0, 1, 2, 3, 4, 5 days.

- Type of Oxygen Supplementation for current infection at baseline (Low flow oxygen device, High flow oxygen device, non-invasive mechanical ventilation). All types of oxygen supplementation will be presented even if not specifically specified in this list.

Information on COVID-19 diagnosis and history will also be listed for the ITT.

12.3 Treatments

12.3.1 Extent of Trial Drug Exposure

For the IMP, summary statistics will be provided for SS for duration of exposure, total number of dose administrated and total cumulative dose in the treatment period. The number and percentage of subjects who experience at least one overdose on any day during the treatment period will be provided. Any dose of C21 exceeding a total daily dose of 200 mg (i.e., 4 capsules of IMP) is considered an overdose.

The total cumulative dose will be calculated as:

$$Cumulative\ dose\ (mg) = 50x\ (Number\ of\ Capsules\ dispensed\ [56] - Capsules\ returned)$$

The total number of doses administered will be the difference between the number of capsules dispensed [56] and number of capsules returned. If returned amount is missing and the subject is indicated to have completed treatment, they will be treated as taking all capsules. If the subject discontinues treatment and

returned amount is missing, they will be treated as taking capsules as planned up to the day of discontinuation derived as:

$$Cumulative\ dose\ (mg) = 50 * (4 * (duration\ of\ exposure))$$

where duration of exposure for this calculation will be set to a minimum of duration of exposure and 14 days.

If first dose for subject that discontinues treatment and has no returned amount is in the evening (p.m.) the calculation will be as follows:

$$Cumulative\ dose\ (mg) = 50 * (2 + 4 * (duration\ of\ treatment - 1))$$

For these subjects with first dose in the p.m., if duration of exposure is >14 indicating the subject took the full treatment course, the cumulative dose will be assumed to be 56.

The duration of exposure will be derived as:

$$Duration = (Last\ dose\ of\ IMP - First\ dose\ of\ IMP) + 1$$

Duration of exposure will be summarized overall, by subjects whose first dose was in the morning and by subjects whose first dose was an evening dose. Duration of exposure will also be summarized by duration categories, the number of subjects exposed for 1-6 days, 7-13 days and 14+ days.

Overall compliance will be calculated as follows:

$$Treatment\ Compliance\ (\%) = 100 * \frac{Total\ Number\ of\ Doses\ adminstered}{Expected\ Number\ of\ Capusles}$$

For subjects who completed treatment, expected number of capsules will be 56. For subjects who discontinue treatment:

$$Expected\ Number\ of\ Capsules = 4 * Duration\ of\ exposure$$

Compliance will be summarized using the following categories: <80%, 80-90%, >90%.

The percentage of doses taken in hospital will be presented and derived as follows:

$$\%\ of\ Doses\ taken\ = 100 * \frac{56 - Number\ of\ Capsules\ dispensed\ on\ discharge}{Cumulative\ dose\ (total\ capsules\ taken)}$$

For subjects who do not discharge during the treatment period or who discontinue the study prior to discharge from hospital during the treatment period, the % doses taken will be 100%.

The number of doses missed and reason dose missed will be summarized for subjects (this information will only be collected during the hospitalized period). Trial drug exposure will be listed. Drug accountability will also be listed.

12.3.2 Prior and Concomitant Therapies

Therapies received prior and concomitantly with IMP, categorized by medication group and subgroup according to the World Health Organization Drug Dictionary (WHODRUG) Global version March 2021 B3 or later will be summarized using ITT.

Prior and concomitant therapies (see Section 10.5) will be summarized separately using Anatomical Therapeutic Chemical (ATC) levels 2 and 4. The number and percentage of subjects using any therapy will be displayed together with the number and percentage of subjects using at least one therapy within each medication group and subgroup.

A summary of vaccinations will be provided for the ITT. Vaccinations will be collected on the concomitant medication page and will be identified via code review by medics.

12.4 Important Protocol Deviations

Per PRA/ICON processes, protocol deviations data will be entered into the PRA/ICON system of record (PSO), in accordance with the Protocol Deviation Guidance Document. Important protocol deviations are defined in the protocol deviation guidance document. The last approved version of protocol deviation guidance will be finalized before the database lock. The trial team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable subjects throughout the trial, adjusting the deviation criteria as seems appropriate.

Protocol deviation data will be reviewed prior to database lock and important deviations with an impact on efficacy leading to the elimination of subjects from the PP will be identified. The PP must be finalized at the blinded data review meeting (or earlier), prior to database lock.

The number of subjects with Important protocol deviations will be summarized in the ITT by category of violation and by treatment group including subset of Important protocol deviations leading to exclusion from the PP. Site level protocol deviations will be summarized as individual subject level protocol deviations for subjects at the impacted site. All protocol deviations will also be listed using the ITT.

12.5 Efficacy Analysis

12.5.1 Hypothesis Testing Strategy

The objective of the primary efficacy analysis will be to evaluate the efficacy of C21 versus placebo as add on to SoC in subjects with COVID-19 by comparing the all-cause mortality at Day 60. The aim of the efficacy analysis is to demonstrate superiority of C21 over placebo.

The null and alternative hypotheses used to evaluate the efficacy for the primary endpoint are to evaluate the difference in time to all-cause mortality up to study follow-up Day 60 between C21 ($S_1(t)$, survival distribution for C21 over time t) and placebo ($S_2(t)$, survival distribution for placebo over time t).

Null hypothesis i.e. no difference in survival up to Day 60 between the two groups:

$$H_0: S_1(t) = S_2(t)$$

Alternative hypothesis i.e. difference in survival up to Day 60 between the two groups :

$$H_1: S_1(t) \neq S_2(t)$$

The overall 2-sided significance level of 5% will be applied to the primary endpoint and the 2-sided p-value obtained from a log-rank test presented in the outputs.

Analysis of the key secondary endpoints will be performed using a hierarchical testing procedure as defined in Section 12.0. All tests for the key and non-key secondary endpoints will be at the 2-sided significance level of 5% and testing the null hypotheses that there is no difference between C21 and placebo, against the alternative hypothesis that C21 is better than placebo. Efficacy of C21 in comparison to Placebo with respect to the key secondary endpoints will be demonstrated only if efficacy is demonstrated in the primary endpoint otherwise these endpoints will be exploratory only.

12.5.2 Primary Estimand

The estimand of interest is all-cause mortality up to Day 60 defined as the time to day of death from any cause assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or important protocol deviations according to the treatment policy, with subjects with no confirmed death before or at Day 60 being censored at day of withdrawal/Day 60 follow-up (refer to Appendix 1).

Intercurrent events will be handled according to the treatment policy strategy. Treatment policy strategy is defined as the strategy that considers "The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs" (See ICH E9 R1 addendum). All scheduled scores of clinical status will be considered for the analysis, even if collected after the occurrence of intercurrent events of (1) discontinuing IMP, (2) returning to initial treatment and/or (3) initiating a new treatment.

12.5.2.1 Imputation Methods

Missing data will not be imputed for the primary estimand.

12.5.2.2 Primary Analysis

All-cause mortality at Day 60 will be defined as time to day of death from any cause within Day 1 to Day 60 follow-up (refer to Section 10.11). All-cause mortality will be estimated using the Kaplan-Meier methodology where subjects in this analysis without the event will be censored at Day 60 follow-up. Withdrawn subjects without the event will be censored at day of discontinuation (this assumes the censoring is non-informative).

Treatment groups will be compared using a stratified log-rank test adjusting for treatment, actual baseline disease severity and region. The p-value from the stratified log-rank will be presented. The size of the treatment effect will be estimated as a hazard ratio, obtained using a Cox proportional hazards regression model, and the Cox regression model will include a factor for randomized treatment, baseline disease severity and region. The estimated Hazard Ratio comparing C21 to Placebo will be presented together with the corresponding 95% CI (based on Wald test). A Kaplan-Meier plot of time to all-cause mortality will also be produced.

12.5.2.3 Sensitivity Analyses

1. Subjects with any important protocol deviations (as defined in Section 12.4) that impact efficacy, who prematurely discontinue IMP will be excluded from the analysis. In the primary analysis, subjects with important protocol deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect. Additionally, subjects withdrawn from treatment due to patient decision may be excluded. For subjects in the PP, the analysis approach as described in Section 12.5.2.2 for primary analysis will be followed.

2. The proportion of deaths before or at Day 60 between treatment groups will be compared using a logistic regression model adjusting for randomized treatment, actual baseline disease severity and region as per Appendix 2 on the ITT. Subjects with no confirmed death or missing data due to premature withdrawal will have missing data imputed as per Section 10.19.2. The number of deaths at Day 60, the adjusted proportions as calculated from Ge et al., 2011, and the associated statistics (treatment difference (C21-Placebo), SE and CI) will also be presented.

3. Sensitivity to IMP discontinuation: No analysis will be performed to assess the impact of IMP discontinuation. Subjects who prematurely discontinue due to subject decision up to Day 11 will be excluded from the PP set since this is equivalent to less than 80% compliance.

12.5.2.4 Supplementary Analyses

Additional analyses examining the consistency of the intervention effect in the following subgroups using the ITT will be performed. A forest plot and repeat of the analysis as per Section 12.5.2 in the following subgroups will be presented:

- Age group: <65 vs ≥65 years
- Sex: female vs male
- Actual baseline disease severity (8-point ordinal scale 5 or 6 at Day 1)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (Europe, Rest of the World)
- Presence of risk factors for severe COVID-19 (Yes, No)

The subgroup categories may be redefined prior to unblinding the study due to the following reasons:

- If the number of subjects is too small (less than 10% of the ITT population) within a subgroup then only the categories with >10% of subjects will be presented in the output.
- If other subgroups appear to be of interest (for example the medications used as SOC) they will be included in the summary.

12.5.3 Key Secondary Estimands and Multiplicity

The key secondary endpoints will be tested in a hierarchical order following the test of the primary endpoint (see Section 12.0).

Other secondary endpoints will be tested independently without adjustment for multiple tests.

ITT will be used for all key secondary endpoint. Subjects will be included in analyses as randomized. The key secondary endpoints are the time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure at Day 15, and the proportion of subjects discharged and free of supplemental oxygen at Day 15.

12.5.3.1 Missing data

Imputation of data due to intercurrent events (treatment discontinuation due to lack of efficacy, occurrence of important protocol deviation, rescue therapy) will not be performed. Subjects who die will have their missing data set as non-responders in the relevant analysis for all time points of interest following the date of death.

Subjects who discontinue the trial for reasons other than death will have their data multiply imputed as per Section 10.19.1. It is anticipated that missing data will be due to discharged subjects not returning for subsequent scheduled visits, or a worsening of clinical status such that the subject can no longer participate in the trial, or due to missing follow-up visits.

The missing data pattern for the adjusted 8-point ordinal scale will be summarized and a distribution plot will be used to represent the pattern of missing data for the adjusted 8-point ordinal scale showing the proportion of missing data each day per treatment group.

12.5.3.2 Time to Sustained Hospital Discharge

Time to sustained hospital discharge, will be defined as time to discharge after which no re-hospitalizations due to COVID-19 occur. Please refer to Section 10.12 for further details on this calculation.

Treatment groups will be compared using a stratified log-rank test adjusting for treatment, actual baseline disease severity and region. The size of the treatment effect will be estimated as a hazard ratio, obtained using a Cox proportional hazards regression model and the Cox regression model will include a factor for

randomized treatment, baseline disease severity and region. The estimated hazard ratios for each treatment group will be presented together with the corresponding 95% CI (based on Wald test).

Analysis will be illustrated using a Kaplan-Meier plot and the median time to hospital discharge will be estimated with 95% CIs for each treatment group. Subjects who die prior to Day 60 will be censored at Day 60 and trial withdrawals prior to Day 60 due to other causes than death without fulfilling the event will be censored at day of withdrawal. Subjects still in trial but not discharged from hospital at Day 60 will be censored at their Day 60 trial visit.

12.5.3.3 Oxygen Supplemental Free Days up to Day 29

Oxygen supplemental free days up to Day 29 will be defined as the number days for each subject with a score of ≤4 and no use of COVID-19 related supplemental oxygen. Refer to Section 10.13 for the derivation of number of oxygen free days.

Subjects who die prior to Day 29 will be given a value of -1 days in the analysis. Subjects who withdraw from the trial prior to Day 29 and have missing data will have their data multiply imputed as per Section 10.19.1. Subjects who chronically used supplemental oxygen prior to their COVID-19 illness will be considered oxygen free when they return to the same level of oxygen support they had been using prior to COVID-19.

Treatment groups will be compared using the Wilcoxon rank-sum test (using p-values) and the treatment difference will be expressed as the Hodges-Lehmann difference in median number of days with 95% CIs. All collected data post treatment will be used. Summary statistics for the number of oxygen free days will also be presented for each treatment group. A cumulative distribution plot of the number of oxygen free days by treatment arm will also be produced.

12.5.3.4 Subjects Free of Respiratory Failure at Day 15

Subjects free of respiratory failure is defined as subject with an ordinal scale score of ≤5 at Day 15. A subject is considered a responder for this endpoint if they have a value of ≤5 at Day 15.

Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region (as described in Appendix 2). Missing data due to trial withdrawals will be multiply imputed as per Section 10.19.1. Subjects who die prior to Day 15 will be considered non-responders in the analysis. The adjusted proportions as calculated from Ge et al., 2011 and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

12.5.3.5 Subjects discharged and free of supplemental oxygen at Day 15

For this endpoint a subject will be considered a responder in the analysis if the subject has a score of ≤2 on the ordinal scale and they are free of supplemental oxygen use at Day 15. Refer to Section 10.10 for details on the classification of subjects as free of supplemental oxygen use at a visit.

Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region (as described in Appendix 2). Missing data due to trial withdrawals will be multiply imputed as per Section 10.19.1. Subjects who die prior to Day 15 will be considered non-responders in the analysis. The adjusted proportions as calculated from Ge et al., 2011 and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

12.5.3.6 Sensitivity Analyses

In order to test the assumptions underpinning the key secondary endpoint analysis the following sensitivity analysis will be performed.

Time to sustained hospital discharge

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Repeat of the analysis in Section 12.5.3.2 on the ITT where non-COVID-19 related re-admissions are treated as re-admissions due to COVID-19 in the analysis and missing data will be imputed using multiple imputation as described in Section 10.19.1. The median time to sustained discharge will be estimated for each imputed dataset and the average value across each imputed dataset will be presented.

Oxygen Supplemental Free Days up to Day 29

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

4) An ANOVA model will be fitted for the number of days oxygen free as a response and actual baseline ordinal scale, region and treatment group as factors in the model. This model will be implemented on the imputed datasets as per Section 10.19.1 with the LS means and SEs from the ANOVA models combined using Rubin's Rule (Rubin, 1987).

Subject free of Respiratory Failure at Day 15

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

Subjects discharged and free of supplemental oxygen at day 15

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

12.5.3.7 Supplementary Analyses

Additional analyses examining the consistency of the intervention effect for the key secondary endpoints will be performed for the subgroups as per Section 12.5.2.4 using the ITT.

12.5.4 Other Secondary Endpoints

Other secondary endpoints assessing proportion of subjects will be compared using similar logistic regression models as described in Appendix 2 with the treatment effect expressed as a difference in proportions. Difference in proportions by treatment (intervention – placebo) will be estimated and 95% CI will be provided. Death prior to endpoint readout will be handled as worst case, that is subject will be assumed to be in mechanical ventilator need, or to be in oxygen need, or not to have fulfilled an improvement of 1 or 2 units. Subjects in ventilator need at readout will be considered in oxygen need. Unless otherwise specified missing data will not be multiply imputed. These secondary endpoints include:

1) Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29. Missing data will be imputed as per Section 10.19.1.

2) Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, ECMO or supplemental oxygen use at Days 8, 15, 22, 29 and 60. Missing data will be imputed as per Section 10.19.1.

3) Proportions of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60. This will be based on the complete case (where deaths are considered in category 8 following date of death). This will be the actual recorded 8-point ordinal scale and not the adjusted scale. This analysis will be descriptive only.

4) Proportions of subjects in each category of the adjusted 8-point ordinal scale at Days 8, 15, 22, 29 and 60. This will be based on the average of values from each imputed dataset created per the analysis in Section 10.19.1.

5) Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60. Deaths will be considered in ICU following date of death. Only documented ICU stay will be considered. Subjects with no documented ICU stay will be included as 0 days.

6) Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60. Missing data will be imputed as per Section 10.19.1.

7) Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60. This data will be imputed as per Section 10.19.1.

Respiratory failure free days up to Day 60 (refer to Section 10.14) will be analyzed as using a Wilcoxon rank-sum test per the key secondary endpoint oxygen supplemental free days up to Day 29.

All-cause mortality up to Days 8, 15, 22 and 29 will be presented. The proportion dead and censored at these timepoints will be calculated.

Endpoints assessing duration of event will be compared between treatments using the Wilcoxon rank sum test. These endpoints are:

1) Duration of hospitalization, including re-hospitalization, up to Day 60 (see Section 10.15).

2) Duration of hospitalization up to Day 60 including re-hospitalization for any reason (COVID-19 and non-COVID-19) and missing data will be imputed using multiple imputation (see Section 10.15 and 10.19.1).

3) Duration of intensive care unit stay, including re-admission, up to Day 60 (see Section 10.16).

4) Duration of invasive mechanical ventilation/ECMO use, up to Day 60 (see Section 10.17).

The change from baseline in SpO_2/FiO_2 at Day 15 will be compared between treatment groups with analysis of covariance (ANCOVA) models with treatment, baseline disease severity, and region as factors, and baseline SpO_2/FiO_2 as a covariate. The adjusted mean difference between treatments will be given together with 95% CIs and associated 2-sided p-value. For information on the assignment of values of FiO_2 for use in the calculation of this ratio refer to Section 10.18. Only subjects with baseline and Day 15 data such that this ratio can be calculated will be included in the analysis.

All secondary endpoints will be assessed on the ITT population.

12.5.5 Exploratory Endpoint Analyses

The change from baseline in CRP and LDH at Day 15 will be compared between treatment groups using an ANCOVA model. Model for CRP and LDH will be multiplicative. CRP and LDH data for all visits will be log-transformed prior to the analysis and the change from baseline for CRP and LDH at each visit will be expressed as a baseline ratio in the analysis. This baseline ratio (log(CRP/LDH at Day 15/Baseline CRP/LDH) will be compared with ANCOVA models adjusting for treatment, baseline disease severity and region as factors and log-transformed baseline CRP or LDH as a covariate.

No imputation for missing data will be performed for exploratory endpoints. The analysis will be performed on the ITT population. The result will then be back-transformed to the linear scale. The back-transformed

geometric mean for both treatment groups as well as the geometric mean ratio (C21 vs Placebo) will be reported together with the 95% confidence intervals. The 2-sided p-value will be presented.

12.6 Safety Analyses

12.6.1 Adverse Events

All AEs will be coded using MedDRA Version 24.0 or later. A TEAE is defined in Section 10.6. Only TEAEs will be included in AE summaries unless otherwise specified. All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed. All AE summary tables will be provided for each treatment and total group in the SS.

All AE summaries will include the number and percentage of subjects in each category. For the calculation of the incidence of events, subjects will only be counted once within the events. For summaries and PT, subjects will be counted once per unique PT and SOC. The number of events in each category will also be presented. For summaries by SOC and PT tables should be sorted in descending order of SOC and then PT by subject counts in the total group.

An overall summary of treatment-emergent adverse events will be presented for the following categories:

- Any TEAEs
- Any Serious Adverse events (SAE)
- Severe TEAEs
- Related TEAEs
- TEAEs pattern (continuous, intermittent, single event)
- TEAEs leading to discontinuation of IMP
- TEAEs leading to trial withdrawal
- TEAE with outcome of death (events with outcome of Fatal on the AE CRF page)

The risk difference between treatments will be calculated for the above categories (except for TEAEs patterns) for the comparison of treatment groups and will be presented together with the 95% Wald asymptotic CI for this risk difference. Risk difference will also be presented for selected SOC and PT if deemed of interest prior to lock.

In addition, the following summaries by SOC and PT will be produced:

- TEAEs
- SAE
- Related TEAEs
- Related SAEs
- Severe TEAEs
- TEAEs leading to discontinuation of IMP
- TEAEs leading to trial withdrawal
- AEs leading to death
- Related AEs leading to death
- TEAEs occurring in 5% of subjects (based on PT) in any treatment arm
- Non-Serious TEAEs occurring in 5% of subjects (based on PT) in any treatment arm

A tabulation of TEAEs, categorized by relationship to IMP, will also be presented. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that SOC or PT. Then the relationship to IMP is dichotomized into related or not related as defined in Section 10.6.

A summary of events reported, categorized by severity (mild, moderate or severe as recorded on the AE CRF page), will also be provided. Subjects with multiple events within a particular body system or PT will be counted under the category of their most severe event within that body system or PT.

A further tabulation presenting the preferred terms for the events in descending order of frequency for the treatment group will also be presented.

Listing of AEs leading to death, IMP discontinuation, trial discontinuation and SAEs will be provided. If a subject has missing severity or seriousness in the database they will be treated as worst-case i.e. severe and serious respectively.

12.6.2 Deaths and Serious Adverse Events

Death, SAEs, and IMP-related SAEs will be summarized as in Section 12.6.1. Tabulations will be provided by SOC and PT and listings will be prepared for SAES and AEs leading to death.

12.6.3 Laboratory Data

Laboratory test results will be reported in International System of Units (SI) units. Additionally, summaries will be present for parameters in US units. Only central lab data will be included in the table summaries.

Laboratory values and change from baseline will be summarized using descriptive statistics by time point and treatment group. Laboratory assessments will be grouped for summary as shown in Table 5.

Standard ranges from the central laboratory will be used for the laboratory analysis. The assessment as to if a lab test is low, high, normal as applicable will be derived using the standard ranges for central lab data.

Shift tables of the post-baseline value to high, low, normal will be presented by treatment group, reference range and time point. For categorical urinalysis parameters shift tables will present shifts to normal and abnormal values. Additionally, plots showing the shift from baseline to the maximum/minimum post-baseline value will be presented.

Positive pregnancy results and dip-stick urinalysis results will be provided in a listing.

Table 5. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count (thrombocytic particle concentration) Hemoglobin Hematocrit (erythrocyte volume fraction) Mean corpuscular volume (MCV)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen (BUN) Glucose, fasting Potassium Sodium	Aspartate transaminase (AST) Alanine transferase (ALT) Alkaline phosphatase (ALP) Albumin

Laboratory Tests	Parameters	
	Calcium Ferritin Prothrombin time (PT) International Normalized Ratio (INR) activated partial thromboplastin time (aPTT)	Total and direct bilirubin Serum creatinine eGFR CRP LDH
Routine urinalysis	• pH, glucose, protein, ketones, bilirubin, urobilinogen, and specific gravity by dipstick • Microscopic examination (per investigator judgment)	
Pregnancy testing	• Highly sensitive urine or serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)	

12.6.4 Vital Signs

Observed values and change from baseline in vital signs will be summarized by time point and treatment group in the SS using descriptive statistics. Parameters to be summarized are body temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Systolic and diastolic blood pressure will have three readings per visit, the average of the three readings will be used as the analysis value for the visit (note if any of the three readings are missing, the average of non-missing readings will be used).

Body temperature can be measured in degree Celsius or Fahrenheit. In order to summarize body temperature by descriptive statistics, body temperature collected in Fahrenheit will be converted to Celsius prior to the analysis.

Vital signs will be listed in the SS.

12.6.5 Physical Examinations, ECGs, and Other Observations Related to Safety

The physical examination system will be summarized as “normal”, “abnormal” with sub category for abnormal events that are clinically significant and the number and percentages of subjects in each category by body system will be presented by time point and treatment group in SS. The assessment of the exam is as reported in the Physical Examination (Body System) CRF page. All physical examination data will be listed.

ECG will only be performed at screening and unscheduled visits. ECG will be summarized for screening, unscheduled visits and “any post-baseline assessment” by treatment group in the SS.

12.7 Pharmacokinetics Analyses

All C21 plasma concentration data collected in this trial may be included in population PK and population PK/PD analyses with the objective of exploring the impact of covariates (e.g., body weight and age) on the PK of C21, or the relationship between the C21 exposure and selected efficacy and safety endpoints. If the PK population is not sufficient for analysis data will be listed only.

Blood PK samples will be collected before the first IMP administration (pre-dose) and 30 minutes, 1, 2, 3, 4, and 6 hours after the first IMP administration. Any population PK and population PK/PD analyses will be reported separately. Due to the unblinding nature of the data, PK analyses will be conducted after unblinding of the trial.

12.7.1 Pharmacokinetic Concentrations

Plasma C21 concentrations below the quantifiable limit (BQL) will be set to ½ the lower limit of quantification (LLOQ) in the computation of mean concentration values. Descriptive statistics (number of subjects,

arithmetic mean, geometric mean, standard deviation, coefficient of variation of the geometric mean, median, minimum, and maximum) will summarize the plasma concentrations by C21 at pre-dose, 30 minutes, 1, 2, 3, 4 and 6 hours post treatment. If 50% of the subjects at a given time point have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum, with the exception of maximum all other statistics will be missing. A figure displaying the mean plasma concentrations over time will be produced.

12.7.2 Pharmacokinetic Parameters

The plasma C21 concentration data will be analyzed by non-compartmental methods with WinNonlin® (WNL) version 8.1 or higher unless stated otherwise and the following parameters will be derived and summarized:

- Cmax – Observed maximum plasma concentration of C21, expressed in concentration units.
- t_{max} – Time to reach C_{max} following first dose of IMP, expressed in time units. If C_{max} occurs at more than one time point t_{max} will be assigned to the first occurrence of C_{max}.
- $AUC_{(0-6)}$ – Area under the plasma concentration curve from time zero to 6 hours. The below conditions will be followed:
    - Actual time will be used for calculating $AUC_{(0-6)}$
    - If the 6 hour sample was not taken then $AUC_{(0-6)}$ will not be calculated
    - $AUC_{(0-6)}$ will be calculated by WNL using extrapolation to actual time when there is a valid λ_z and the 24 hour sample is BQL and the concentrations thereafter are also BQL.
- $AUC_{(0-inf)}$ – Area under the plasma concentration-time curve from time zero extrapolated to infinity. Adjusted r^2 for $t_{1/2}$ greater than 0.8 and AUC%Extrap ≤ 20% are required to obtain a reliable estimation of $AUC_{(0-inf)}$. $AUC_{(0-inf)}$ will be included in analysis/summaries only if these two criteria are met.
- AUC_{last} – Area under the plasma concentration curve from time zero to the last quantifiable concentration.
- $t_{1/2}$ – Apparent terminal half-life, expressed in time units. Adjusted r^2 greater than 0.8 is required to obtain a reliable $t_{1/2}$. $t_{1/2}$ will be included in analysis/summaries only if this regression criteria is met (all values will be listed).
- C6 – Actual plasma concentration of C21 at 6 hours after IMP administration (C6 will be analyzed using SAS® version 9.4 or higher)

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be used to summarize the calculated PK parameters by treatment. For t_{max}, only median, min and max will be presented.

AUCs will be calculated using linear up/ log down (or the linear-log trapezoidal method). The linear trapezoidal method will be employed while concentrations are increasing up to t_{max}. The logarithmic trapezoidal method will be employed after t_{max} while concentrations are decreasing. The minimum requirement for calculation of AUCs will be three consecutive plasma concentrations above the LLOQ and at least one following C_{max}.

13.0 References

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BQL	Below the quantifiable limit
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extra Corporeal Membrane Oxygenation
EWD	Early Withdrawal
FiO_2	Fraction of Inspired Oxygen
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention-to-Treat Analysis Set
IXRS	Interactive Web/Voice Response System
LDH	Lactate dehydrogenase
LLOQ	Lower Limit of Quantification
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PP	Per Protocol Analysis Set
PSO	PRA/ICON system of record
PTs	Preferred Terms
SAP	Statistical Analysis Plan

SAE	Serious Adverse Event
SE	Standard Error
SD	Standard Deviation
SI	System of Unit
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SpO_2	Peripheral Capillary Oxygen Saturation
TEAE	Treatment-Emergent Adverse Event
WHODRUG	World Health Organization Drug Dictionary
WNL	WinNonLin

Appendix 1: Estimand Attributes

Table 6: Trial Endpoints and Estimands

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Primary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Primary Endpoint: - All-cause mortality up to Day 60					
Time to day of death from any cause	Subjects in the ITT analysis set	C21	All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in time to all-cause mortality at Day 60 and 95% CI	Stratified log-rank test will be used to compare treatments. Hazard Ratios for death with 95% CIs will be estimated using Cox regression to demonstrate the size of the treatment effect. Subjects who do not have the event before or at Day 60 will be censored at the time of withdrawal/Day 60 follow-up in this analysis. A Kaplan-Meier plot will be produced.
Sensitivity Analysis of Primary Estimand for the Primary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set. No missing data will be imputed. 2) As primary except the population level summary will be difference in proportions and 95% CI and estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Subjects with missing data at Day 60 will have data imputed as per Section 10.19.2. **Supplementary Analysis** of Primary Estimand for the Primary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.2.4). No missing data will be imputed.					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Time to sustained hospital discharge up to Day 60					
The first occurrence of a score of 2 or below whereafter the score stays ≤2 for the remainder of the 60 days trial period	Subjects in the ITT analysis set	C21	Deaths will not be treated as missing data. They will be considered censored at Day 60 (i.e. worst case) in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in median time to discharge and 95% CI	Stratified log-rank test. Kaplan-Meier difference in median time to sustained hospital discharge with 95% CIs will be estimated. Subjects who do not have the event before or at Day 60 will be censored at last day in study or day 60 if completing the study.
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except all re-admissions (COVID-19 and non-COVID-19) will be included. 3) As primary except missing data will be imputed as per Section 10.19.1. **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Supplemental oxygen free days up to Day 29					
The number of days between Day 1 and Day 29 with a score of ≤4 on the 8-point ordinal scale and with no documented use of COVID-19 related supplemental oxygen	Subjects in the ITT analysis set	C21	Deaths occurring before Day 29 will not be treated as missing data. They will be considered with -1 days in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in median number of days without supplementary oxygen and 95% CI	The Hodges-Lehmann median estimated of the difference in days between treatments with 95% CIs. Missing data will be imputed using multiple imputation (refer to Section 10.19.1)
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation 4) As primary except the analysis will us an ANOVA model **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15					
Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15	Subjects in the ITT analysis set	C21	Deaths occurring before Day 15 will not be treated as missing data. They will be considered as not free of respiratory failure in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in proportions and 95% CI	Estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Missing data due to subject discontinuations from the trial will be imputed using multiple imputation (refer to Section 10.19.1).
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15					
The proportion of subjects with a score of ≤2 on the 8-point ordinal scale and free of COVID-19 related supplemental oxygen use at Day 15	Subjects in the ITT analysis set	C21	Deaths occurring before Day 15 will not be treated as missing data. They will be considered as not discharged in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in proportions and 95% CI	Estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Missing data will be imputed using multiple imputation (refer to Section 10.19.1)
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Appendix 2: Logistic Regression for Analysis

As a sensitivity analysis for the primary endpoint and as the primary analysis for select key secondary endpoints, the proportion of responders between treatment groups will be compared using a logistic regression model adjusting for randomized treatment, actual baseline disease severity and region. The Fisher scoring algorithm will be used for maximum likelihood estimation of the regression parameters and the covariance matrix.

The estimated difference between treatments will be calculated using a weighted estimator for the risk difference. The delta method will be used to calculate the standard error for this difference and the associated 95% CI (Ge et al. 2011).

The risk difference is calculated from the fitted logistic regression model as:

$$Difference\ (d) = \sum_{i} \frac{(\hat{P}_{ti} - \hat{P}_{ci})}{n}$$

Where $\hat{P}_{ti}$ and $\hat{P}_{ci}$ are the i^{th} elements of

$$\hat{P}_t = logit^{-1}(X_t b)$$
$$\hat{P}_c = logit^{-1}(X_c b)$$

n is the number of subjects in the analysis, b is the maximum likelihood estimate of the regression coefficients from the fitted logistic regression model, X is the covariate matrix of the parameter estimates, X_t is a new covariate matrix from X adjusting the column corresponding to treatment so all subjects are treated, X_c is the new covariate matrix from X adjusting the column corresponding to treatment so all subjects are in the control. $\hat{P}_{ti}$ is the estimated probability of response to treatment for subject i and $\hat{P}_{ci}$ is the estimated probability of response to control for subject i.

The delta method to calculate the standard error and associated CI is as follows:

$$d_t = \frac{(A_t' X_t)}{n}$$
$$d_c = \frac{(A_c' X_c)}{n}$$
$$SE(d) = \sqrt{d_t V d_t' + d_c V d_c' - 2 d_c V d_t'}$$
$$CI\ for\ the\ estimation = d \pm z_{(1-\frac{\alpha}{2})}\ SE(d)$$

Where V is the estimated variance-covariance matrix from the fitted logistic regression and A_t and A_c are the vectors defined as:

$$A_{ti} = \hat{P}_{ti}(1 - \hat{P}_{ti})$$
$$A_{ci} = \hat{P}_{ci}(1 - \hat{P}_{ci})$$

Appendix 3: Imputation of FiO_2 values

If the value of FiO_2 is missing when the type of low flow device and oxygen flow is given, the below values will be used as the value of FiO_2 in the analysis. For example if a subject at a visit has a low flow device type of "Open Mask" with oxygen flow of 5 L/min, for analysis purposes a value of 40(%) for FiO_2 will be used.

It should be noted that sites are permitted to enter a range of values. For example if a site states the subject is on a low flow nasal cannula with oxygen flow of 3, the site can enter a range of FiO_2 from 28 to 36. No adjustments will be made in the analysis for site entered values to align with the below literature. Sites are also permitted to enter values that are outside the values presented in the reference tables (for example nasal cannula > 15 L/min).

- **Low Flow Nasal Cannula (Simon et al., 2016)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1	24
2	28
3	32
4	36
5	40
6-15	44

- **Low Flow Open Mask (Simon et al., 2016)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1	24
2	28
3	32
4	36
5	40
6-7	50
8-15	60

- **Venturi Mask (Batool and Garg., 2017)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
2 (blue)	24
4 (white)	28
6 (orange)	31
8 (yellow)	35
10 (red)	40
15 (green)	60

- **Partial Rebreather Mask (Batool and Garg., 2017)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
6	60
8	70
10	80

- **Non-rebreather Mask (MEDEST, 2020)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
10-15 L/min	80-100
Both flaps removed	80-85
One flap removed	85-90
Both flaps in place	95-100

- **Small Diffuser (OxyMask) (Paul et al., 2009)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1.5	25
2	30
2.5	37
3	42
5	58
10	74
15	80

Appendix 4: Blinded Data Review Meeting Specification

Details on which important Protocol deviations will lead to exclusion from the PP and other analysis considerations that must be discussed in a blinded manner will be documented in the "VCRC2108-C21008 Blinded Data Review Meeting Specification_v1.0".

VCRC2108-C21008
Blinded Data Review

Appendix 5: Endpoint Derivation Details

Endpoint	Calculation	Handling of Death	Handling of Missing Data
All-Cause Mortality (Primary Analysis)	Date of event is the date of death Subjects without event will be censored at the time of completion/study discontinuation	n/a	n/a
All-Cause Mortality (Sensitivity Analysis including Multiple Imputation)	Proportion of deaths is the number of subjects with an ordinal scale value of 8 at Day 60	n/a	Missing data at Day 60 will be imputed.
Time to Sustained hospital discharge (Primary Analysis)	Date of event is the last date of discharge (for initial hospitalization or re-hospitalization for COVID-19 reasons) as recorded on the hospitalization form for subjects. If a subject has the event and subsequently withdraws (for reasons other than death) the subject will be treated as having the event If subject does not have event prior to completion/discontinuation the subject is censored at date of completion/discharge (for reasons other than death)	Subjects are treated as worst case (Day 60 is value used in analysis)	n/a
Time to Sustained hospital discharge (Sensitivity Analysis including Multiple Imputation)	Date of event is the last date of discharge (for initial hospitalization or re-hospitalization for any reason) as recorded on the hospitalization form for subjects with no missing data. For subjects with missing data, such that the event occurs at an imputed visit (≤2 ordinal scale occurs after which all subsequent visits stay at ≤2), time to sustained discharge will be the relative day of the imputed visit. For subject with Imputed data, if subjects discharges prior to missing data being observed and imputed values indicate the subject stays discharged (≤2), the last date of discharge recorded in the hospitalization form will be used For subjects with no event based on imputed and missing data, subjects will be censored at date of completion/Day 60.	Subjects are treated as worst case (Day 60 is value used in analysis)	Missing data will be multiple imputed
Number of days oxygen free up to Day 29	Sum of all ordinal scale values of 1, 3, 4 up to Day 29	Death treated as -1	Missing data will be multiple imputed

Endpoint	Calculation	Handling of Death	Handling of Missing Data
Free of Respiratory Failure	Responder is defined as having an ordinal scale value of ≤5 at a visit	No special rules (death will be a non-responder as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects discharged from hospital and free of Supplemental Oxygen Use	Responder is defined as have a value of 1 on the adjusted ordinal scale at a visit	No special rules (death will be a non-responder as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects on Non-Invasive Mechanical Ventilation, Invasive Mechanical Ventilation, ECMO or with Supplemental Oxygen Use	Subjects with event has a score of ≥ 5 on the ordinal scale	No special rules (death will be a event as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects needing ICU stay	Subjects who have a record for ICU stay on the hospitalization CRF	Counted as in ICU from date of death	No
Subjects on Invasive or Mechanical Ventilation or ECMO	Subjects with event has a score of ≥ 7 on the ordinal scale	No special rules (death will be a event as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Number of Respiratory Failure free days up to Day 60	Sum of all days where ordinal scale is ≤5 from Day 2 up to Day 29; Day 60. For days between Day 29 and Day 60 refer to Section 10.14.	Days from death treated as respiratory failure	Missing data will be multiply imputed
Duration of hospitalization	Duration: end date of hospitalization-start date of hospitalization +1 Sum all individual hospitalizations and re- hospitalization for COVID-19 together If a subject discontinues trial following discharge for reasons other than death, the duration will be calculated as normal and no additional days added If a subject discontinues prior to discharge 60 days will be used in the analysis	Subjects that die will be treated as in hospital from date of death	N

Endpoint	Calculation	Handling of Death	Handling of Missing Data
Duration of hospitalization (Sensitivity analysis)	Duration: end date of hospitalization-start date of hospitalization +1; Sum all induvial hospitalization (including all re- hospitalization) together If a subject has missing data following date of discharge and imputed values stay ≤2, then subject will not have any further days added to the duration. If subject has missing data following date of discharge and imputed values are >2, the duration of hospitalization will be the sum of the observed durations plus the count of the days where the values are >2. If subject has missing data and was not discharged, if the imputed values indicate no discharge then the subject will have a duration of hospitalization derived as: Day 60/study completion – start date of hospitalization +1 If subject has missing data and was not discharged and imputed values indicate discharge the subject will have a duration of hospitalization derived as: relative day of last ordinal scale value >2 – start date of hospitalization +1. If a subject has impute data indicating further hospitalizations following the initial discharge, the count of the days where the ordinal scale value is >2 will be summed together and added to the duration of the initial hospitalization.	Subjects that die will be treated as in hospital from date of death	Y
Duration of ICU stay	End date of ICU stay -start date +1; sum individual together; discontinues in ICU considered in ICU from day of discontinuation if not in ICU at discharge then no additional days added; no ICU stay a value of 0 used	Subject will be considered in the ICU from the date of death	n/a
Duration of invasive ventilation or ECMO	End date of use-start date of use +1; sum together; discontinue while on, considered on from date of discontinuation; not on and discontinue will not have any other days; subjects with no use be 0	Subject will be considered on ECMO/ from the date of death	n/a

Signature /Date:	DocuSigned by: Cecilia Gauslandt AC2E3DABD5E2467... 8/24/2022
PRA/ICON plc.	
Biostatistician / Title:	Kamara Lynch / Senior Biostatistician
Signature /Date:	DocuSigned by: Kamara Lynch 1B2ED5FAA2A54EF...

2.0 Change History

Version/Date	Change Log
0.05	Created as new
0.1	Updates following Sponsor Comments on draft v0.05
0.15	Updated to remove line referring to block size
0.2	Updated following Sponsor Comments on draft V0.1
0.25	Updated following Sponsor comments on draft v0.2
0.3	Updated per Sponsor and DMC committee members comments; Updated to new template
0.4	Updated per FDA comments on SAP version 0.25 and Sponsor comments on SAP version 0.3
1.0	Stable version
1.1	Significant changes due to sponsor discussions and Protocol Amendment V5.0. All changes were implemented without access to unblinded data from the ongoing trial. 1. The primary endpoint has been changed from proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15 to all-cause mortality up to Day 60. The previous primary endpoint is now considered a key secondary endpoint. Major changes throughout the document to reflect the new primary endpoint for the study. 2. Sample Size has been reduced from 600 to maximum 300 patients. Section 8.0 and Section 8.1 have been updated to reflect the reduced sample size. Power calculations have been updated to incorporate the new primary endpoint. 3. The hierarchy of key secondary endpoints has been adjusted (refer to Section 9.2.1) leading to re-ordering of sections and text within the document for consistency. 4. Section 12.5.2 has changed to reflect the new primary endpoint and the primary analysis to be performed for this endpoint. 5. Hypothesis in Section 12.5.1 has been updated to reflect the new primary endpoint. 6. Removal of sensitivity analysis for key secondary endpoints. Last observation carried forward and adjusted multiple imputation model have been removed as the remaining sensitivity analysis is sufficient to test the underpinning assumptions of the primary analysis for the key secondary endpoints. 7. Reference to an Interim Analysis, planned to occur when 300 subjects reach Day 15 have been removed from multiple sections. The planned Interim Analysis for futility and sample size re-estimation will no longer occur. 8. Added an additional sensitivity analysis for the key secondary endpoint time to sustained discharge, which will perform the analysis using the multiple imputed datasets. Refer to Section 10.12 and 10.19.1 for further details.

9. Updated Section 10.19.1 as follows:
   - Include specific information on how to handle day of death/day of discharge in the multiple imputation.
   - In Step 1 of the imputation process remove the line "And number of discarded datasets between imputations" as this is not relevant as we are performing a single imputation in this step.
   - In Step 2, clarify that the imputation model can only provide possible imputed values based on what is recorded in the data at the timepoint; that imputed values may be inconsistent with other data; rules for rounding the number of imputations; and the option in SAS PROC MI to use for likelihood if maximum likelihood parameters can not be estimated
   - Added in Step 3 Time to Sustained hospital discharge analysis using the multiple imputed dataset.
   - Adjusted in Step 3, the order of endpoints to align with new hierarchy
   - Added in Step 4, detail on the transformation required for log-rank results
10. Updated Section 10.1 definition of baseline for efficacy to include detail on how to handle multiple assessments at the baseline visit (Visit 2- Day 1).
11. Updated Section 10.4 to state that only subjects who are initially dispensed C21 will be assigned C21 as actual treatment. Individual dose administration is not recorded in the database/kit file, only tablets dispensed at the initial dispensing visit are recorded.
12. Updated Section 10.9 to remove the line "If a scheduled visit and an EWD visit occur in the same window, the scheduled visit will be used in the analysis." as this contradicted other rules for visit windowing outlined in this Section. Updated to state that is multiple records exist on the same trial day for Ordinal Scale, the record at the scheduled visit will be recorded for use in the analysis. Updated to state if visit Day 29 occurs on relative day greater than 29, it will be set to be Day 29 in the analysis.
13. Updated Section 10.10 to explicitly state that recorded values of 1 on the 8-point ordinal scale will not be changed to be a value of 2 on the adjusted 8-point ordinal scale.
14. Updated Section 10.13 to define oxygen free days relative to the adjusted 8-point ordinal scale and not the original 8-point ordinal scale.
15. Updated Section 10.18 to include information on how to assign SpO_2 if only one value is available at a visit.
16. Updated Section 12 to state that pooling of stratum may occur and will be defined in a blinded manner prior to database lock.
17. Updated Section 12.3.1 for the total cumulative dose derivation and to add derivation for percentage of doses taken at the hospital.
18. Updated Section 12.6.4 to state that the average of multiple readings at a visit will be used as the analysis value for select vital signs parameters.

	19. Changes to Appendix 1 and definitions of Estimands to reflect the new primary endpoint. 20. Moved Section on Logistic Regression and definitions for this analysis to an Appendix to enable the document to flow better. 21. Minor updates throughout document with no impact on analysis (for example changing the abbreviation of IMP to be Investigational Medicinal Product; ensuring subgroup risk factors for severe COVID-19 is consistently labelled across all sections).
1.2	Updates based on Sponsor comments on Version 1.1: 1. Updated Section 6.1 to align with Protocol v5.0 2. The PK samples will be collected on a subgroup of approximately 10 subjects. Updates throughout the document to reflect a smaller PK sample group. Updated Section 9.5.5 to add details on exclusion from the PK population. Updated 12.7, to remove Q1 and Q3 as due to low number of subjects available for PK analysis, these summary statistics will not be informative. Updated 12.7.2 to add details on the calculation of select PK Parameters. 3. Updated Section 8.1 to align Sample Size derivation with Protocol v5.0. 4. Updated Section 9.5.3 to state that subjects with no follow-up data at Day 60 will be excluded from the Per Protocol analysis set. 5. Updated Section 10.10: - To clarify collected values of 1, 3 and 4 will not be changed even if evidence of supplemental oxygen usage in the data. - To specify that the question " Was COVID-19 related supplemental oxygen for at home use prescribed?" on the hospitalization CRF page will only be considered in the determination of whether a subject was on oxygen or not on the day of discharge if the scheduled ordinal scale value is missing or a value of 2. 6. Added Section in Conventions and Derivations for All-Cause Mortality. 7. Changed the sensitivity analysis for time to sustained hospital discharge such that, the consideration of non-COVID-19 related re-hospitalizations and multiple imputation will be the same sensitivity analysis as re-hospitalization will be a rare event. Updates to Section 10.13, 10.19.1 and 15.5.3.6. 8. Added clarification to Section 10.14, that subjects with missing data will have their data multiply imputed as per Section 10.19.1. 9. Updated the sensitivity analysis for duration of hospitalization to be similar to time to sustained discharge. Updates to Section 10.15, 10.19.1 and 12.5.4. 10. Updated Section 10.18 to provide details on how to assign values of FiO_2 when the value is missing in the data and how to handle the $Sp0_2/FiO_2$ ratio

	calculation when multiple oxygen supplementation usage is given at the same visit. 11. Section 10.19.2 added to discuss multiple imputation for sensitivity analysis for the primary endpoint. 12. Section 10.19.3 updated to describe general approach for tipping point analysis for all key secondary endpoints. 13. Updated Section 10.19.4 to remove the worst case approach for the key secondary endpoint "number of oxygen free days" as this endpoint will have the same worst case analysis approach as other endpoints. 14. Updated Section 12.3.1 to include a rule for cumulative dose derivation for subjects who discontinue treatment and have no returned capsules amount collected and the first dose was in the evening. Updates to this section to use cumulative dose and not 56 in the derivation of % doses taken in hospital. 15. Updated Section 12.5.1 to define notation $S_1(t)$. 16. Per FDA recommendation add Race and Ethnicity as subgroups for the supplementary analyses of the primary and key secondary endpoints (updates to Sections 12.5.2.4 and 12.5.3.7). Updated Section 12.5.3.7 to refer to Section 12.5.2.4 and not repeat text. 17. Updated Section 12.5.3.2 to remove "if a sufficient number meet the endpoint" as due to current blinded data status a significant number of subjects are discharged and hence, this line will no longer be relevant. 18. The Key Secondary Objective in Appendix 1 for key secondary estimands updated to be "To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19" and not "Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19" to align with Protocol version 5.0. 19. Update the endpoints of subjects free of respiratory failure to define free of respiratory failure as a score of ≤5 and not <6 for consistency with how other endpoints are expressed.
1.3	Minor updates due to Sponsor review of Version 1.2
1.4	- Update Section 12.5.4 to clarify presentation of all-cause mortality at Day 8, Day 15, Day 22 and Day 29. - Minor updates on format and grammar throughout document - Clarification added in Section 12.7 that the coefficient of variation is for the geometric mean - Minor edits to Sections 12.1 (removal of line "together with a breakdown of the reason for exclusion from each analysis set"); Section 12.2 (clarification of the Region variable to be presented in output); Section 12.3.2 (update of typo) and Section 12.6.1 (update of typo) to ensure alignment with the tables, listings and figures shells.

1.5	1. Updated Section 6.1 for differences between Protocol V5 and the SAP 2. Section 9.5.3: Update of the Per Protocol Population definition to potentially exclude patients who discontinue treatment. 3. Section 10.10: Updated to state that all concomitant oxygen usage will be considered on oxygen for the purposes of the adjusted 8-point ordinal scale regardless of the reason for use. 4. Section 10.12 updated for definition of time to sustained discharge: a. Update definition to be based on actual discharge date b. Clarification added on the sensitivity analysis using Multiple Imputation 5. Section 10.14 updated for definition of number of respiratory failure free days: a. Clarification on how to handle subjects who die b. Clarification on how to count the days of respiratory failure free between Day 29 and Day 60 6. Section 10.16 updated for duration of ICU stay: a. Clarifying that deaths will always be considered in ICU even if they were not in the ICU at time of death. b. Clarifying that if the ICU start date is prior to treatment start, treatment start date should be used in the analysis for the start date of the of the ICU stay to align the derivation with other duration calculations. 7. Section 10.19.1: a. Subjects who die will be removed from the imputation at Step 2 in the process i.e subjects who die will not have data imputed. b. Updated to add details for MCMC and non-convergence handling c. Updates to add detail on combining results from Cox regression d. Update to clarify calculation of imputations 8. Section 10.19.3: a. Update details on tipping point for Respiratory failure free at Day 15 and number of oxygen free days b. Added tipping point for All Cause Mortality c. Clarified tipping point will only be performed if the main analysis has a significant p-value. 9. Section 12: a. Text added to stated the pooled region will be used. Region and pooled region are used interchangeably throughout the document. b. Added text that factors will be removed form models if appropriate. 10. Section 12.5.2.4: a. Added text on the handling of small subgroups i.e. only presenting subgroup strata with >10% subjects. 11. Section 12.5.5: a. Text updated to clarify the model and statistics presented for log transformed data. 12. Section 12.8: Data considerations added to discuss how to handle data that may not have a full SDV review. 13. Appendix 4: Added an appendix to refer to the Blinded Data review specifications 14. Appendix 5: Added to summarize all derivations for efficacy endpoints
1.6	1. Update per protocol population to specify that subjects who withdraw from treatment due to subject decision prior to Day 11 will be excluded 2. Updated Section 10.19.1 to be clear that the transformed estimates from Ge et al are combined using Rubin's rule

	3. Updated Section 10.19.1 and 12.5.3.6 to specify for the sensitivity analysis for the time to sustained discharge, median will be presented as the average value of the median within each imputed dataset. 4. Updated Section 12.8 to remove discussion on non-sdv'd data as this is no longer relevant to the study.
2.0	1. Removed section on data considerations as no longer a consideration for the study 2. Update version number to version 2.0

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Vicore Pharma Protocol VP-C21-008.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Trial Objectives
- Trial Design
- Trial Estimands
- Analysis Sets
- Conventions and Definitions
- Applicable Trial Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the trial protocol and case report forms (CRF). This version of the plan has been developed using the protocol version 5.0 dated 13-Apr-2022 and CRF version 3. 0 dated 30-Mar-2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The trial is a randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care (SoC) in adult subjects with COVID-19.

This SAP describes the statistical methods used for the final analysis. A final version of the SAP will be issued for sponsor approval prior to database lock, at which point the blinded team members will become unblinded to the actual randomized assignment.

6.1 Changes from Protocol

- The protocol text uses “Major” and not “Important” to describe significant protocol violations. The SAP has been updated to use “Important” to align with CRO terminology. For the purposes of this trial major protocol deviations and important protocol deviations are interchangeable and have the same meaning as in the trial protocol.
- The protocol defines time to sustained discharge as “The first occurrence of a score ≤ 2 whereafter the score stays ≤2 for the remainder of the 60 days trial period”, in the SAP this has been updated to state the time to date of discharge after which subjects are not re-hospitalized for COVID-19 reasons. These definitions are functionally equivalent. Due to how the ordinal scale is handled for other secondary endpoints (the day after discharge is the first value set to be ≤2) it is necessary to update the SAP definition to ensure that the initial day of discharge is used in the analysis for time to sustained discharge.
- Section 9.2 of the Protocol defines the Per Protocol population as: “All subjects in the ITT set without major protocol deviations deemed to have an impact on efficacy readouts. In addition, subjects who prematurely discontinued IMP during the treatment period but continued with data collection in the trial will also be excluded from the PP. Subjects withdrawn from the trial unrelated to trial participation due to extraordinary circumstances (for example subjects lost-to follow up due to unstable geopolitical situation) may also be excluded from the PP set (further specified in the SAP). Subjects will be included in the analyses according to the intervention they were randomized to.”. For the SAP this will be update to exclude subjects with any important protocol deviations impacting efficacy or subjects who discontinue treatment due to subject decision or subjects not treated.

- Section 9.3.3 of the protocol states "Other endpoints assessing proportion of subjects will be compared using similar logistic regression models as for the primary endpoint with the treatment effect expressed as a difference in proportions." however the primary analysis of the primary endpoint does not use a logistic regression model, this SAP clarifies that this is the sensitivity analysis of the primary endpoint.
- Section 9.3.3 of the protocol has the following line "Other endpoints assessing time to event will be compared using the stratified log-rank test similar to time to sustained discharge with similar imputations for missing data". For the endpoint time to sustained discharge, as the primary analysis no missing data is imputed. Further there are no other secondary endpoints that are assessing time to event, due to this, this line in the protocol was not repeated in the SAP.
- Section 9.3.3 of the protocol states "Endpoints assessing duration of event will be compared between treatments using the Wilcoxon rank sum test, with similar imputations for missing data.", however apart from the endpoint "Duration of hospitalizations, including all re-hospitalizations, up to Day 60, no imputation for missing data for duration endpoints is performed.

7.0 Trial Objectives

7.1 Primary Objective

To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19.

7.2 Secondary Objectives

- Evaluate the safety profile of C21 versus placebo as add on to SoC in subjects with COVID-19.
- Characterize the PK profile of C21 in subjects with COVID-19. A subgroup of approximately 10 patients will be used to assess PK.
- Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19.

7.3 Exploratory Objective

- To explore the effect of C21 versus placebo as add on to SoC on inflammation.
- To explore the effect of C21 versus placebo as add on to SoC on lung injury.

8.0 Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter trial to evaluate the efficacy and safety of C21 versus placebo as add-on to the SoC in adult subjects with COVID-19.

The trial will enroll a maximum of 300 randomized subjects, up to 150 per arm (oral C21 100 mg twice a day (b.i.d.) or placebo for 14 days) according to a 1:1 randomization. Randomization occurs at visit 2 (Day 1) and will be stratified by:

- Disease severity (based on the 8-point ordinal scale score at Day 1 with a score of 5 or 6).
- Region (North America, South and Central America, Europe, Asia, Africa).

Approximately 350 subjects will be screened to achieve a maximum of 300 enrolled and randomly assigned subjects to investigational medicinal product (IMP) treatment.

Subjects hospitalized due to ongoing COVID-19 and who have a score of 5 or 6 on the 8-point ordinal scale will be enrolled. The trial consists of 3 consecutive periods (Table 1): a screening period of up to 48 hours, a 2-week IMP treatment period and a follow-up period of up to 7 weeks. Daily visits are required until discharge. Discharged subjects should return to the clinic for the Day 15 visit. Days 8, 22, 29 and 60 visits will be conducted as phone or video visits for all discharged subjects. The trial duration for an individual subject will not exceed 9 weeks. End of trial is defined as the last subject's last follow-up visit.

An independent data monitoring committee (DMC) will actively monitor data from the trial and will review unblinded safety data from the trial after data collection for 15 days on the first 150 randomized subjects. In addition, the DMC members may call for an ad hoc safety review meeting at any time during the trial.

All subjects will undergo a series of efficacy, safety, and laboratory assessments. Laboratory samples will not be collected at Days 3, 5, 8 and 11 if the subject is discharged from hospital prior to the visit. The primary endpoint is all-cause mortality up to Day 60. The key secondary endpoints are time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure at Day 15 and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15. Type 1 errors will be controlled using a fixed sequential testing hierarchy.

Table 1: Schedule of Activities (SoA)

	Screening	IMP Treatment Period				In-patient Stay[1)]	Follow-up Period[2)]			Unsche-duled[3)]
Visit	**V1**	**V2**	**V3-15[1) 4)]**	**V16[4)]**	**EWD[5)]**	**V17-29**	**V30**	**V31**	**V32**	**UV**
Day (Visit window)	Up to 48h prior to V2	Day 1	Days 2-14	Day 15 (+1 day)		Days 16-28	Day 22 (±1 days)	Day 29 (±1 days)	Day 60 (±3 days)	
Eligibility/General										
Informed consent	x									
Eligibility criteria	x	x[6)]								
Demographics	x									
Medical history	x									
IMP and Concomitant Therapy										
Randomization		x								
IMP administration[7)]		x	x							(x)
Check of fasting criteria		x	x							(x)
IMP accountability			x[8)]	x	x					
Previous and concomitant therapy	x	x	x	x	x	x	x	x		(x)
Trial Assessments and Procedures										
8-point ordinal scale	x	x	x	x	x	x	x	x	x	(x)
Supplemental O_2	x	x	x	x	x	x	x	x		(x)
Oxygen saturation	x	x	x	x	x	x				(x)
Hospitalization	x	x	x	x	x	x	x	x	x	(x)
Physical examination	x			x	x					(x)
Body weight and height	x									
Vital signs	x	x	x	x	x	x				(x)
12-lead ECG[9)]	x									(x)
Adverse events	x	x	x	x	x	x	x	x	x[10)]	x
Biochemistry[11)]	x	x[12)]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Haematology[11)]	x	x[12)]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Urinanalysis[11)]	x	x[12)]		x	x					(x)
Pregnancy testing[13)]	x			x	x					(x)
Oropharyngeal swab		x								
Pharmacokinetics[14)]		x								
Blood sample for future exploratory analysis		x[12)]		x	x					

1. Daily visits until discharge. Visits will be re-initiated in case of a COVID-19 related hospital re-admission.
2. Follow-up visits by phone or video.
3. Assessments marked with () will be performed per investigator judgment at e.g., COVID-19 related hospital re-admission after Day 29.
4. Days 8 and 15 visits must be performed for all subjects. If a subject is discharged before Day 8, the Day 8 visit will be done by phone or video. Site assessments e.g., oxygen saturation, vital signs and blood sampling will not be performed.
5. An early withdrawal (EWD) visit should be performed for subjects withdrawn from the trial prior to Day 15 (Visit 16).
6. Re-evaluation of eligibility including evaluation of electrocardiogram (ECG) and laboratory results from screening.
7. IMP is administered b.i.d. from Days 1 to 14.
8. IMP accountability will be performed at hospital discharge.
9. A historical 12-lead ECG is acceptable. The ECG should be ≤2 days old at the time of screening (Visit 1).
10. SAEs only.
11. Blood samples taken at screening will be analyzed locally. Samples taken at Days 1 to 15, or at the EWD visit will be analyzed at a central laboratory. Days 3, 5, 8 and 11 samples will only be collected if the subject is hospitalized.
12. Blood sampling and urinalysis must be performed prior to IMP dosing.
13. Applicable in women of childbearing potential. If positive, the urine dipstick will be followed up by a blood test.
14. Pharmacokinetic (PK) samples will be collected in a subgroup of approximately 10 subjects.

8.1 Sample Size Considerations

The sample size is based on the all-cause mortality up to Day 60. For the placebo (SOC) group, the proportion of subjects dead at Day 60 is estimated to 10% (Marconi et al., 2021).

With 150 evaluable subjects per trial group, there will be an 80% power to detect a difference between C21 and placebo if the proportion of subjects dead at Day 60 in the C21 group is 2.5% (corresponding to a Hazard Ratio of 0.24). In this calculation a 5% withdrawal rate has been assumed. For the actual detection limit (corresponding to 50% power), if 15 subjects die in the placebo group, significance will be seen if at most 6 subjects die in the C21 group.

This assumes using a 2-sided test at a 5% significance level. Analysis will be by intention-to-treat; thus, all randomized subjects should be accounted for in the statistical evaluation.

8.2 Randomization

Subjects will be randomly assigned in a 1:1 ratio to C21 or placebo treatment. Subject randomization will use a randomly permuted block design and stratified by severity of disease (5 or 6) measured by the 8-point ordinal scale score on trial Day 1 and region.

Registration and randomization will take place using a centralized Interactive Web Response System (IXRS) contracted through Almac. At registration, the IXRS will assign a unique subject identification number that will be used on all of that subject's eCRFs and serious adverse event (SAE) report forms.

This is a double-blinded trial, only a few number of the trial team members are not blinded for conduct of the trial or ensuring subject safety purposes. The unblinded team members will include CRO DMC team members (statistician, programmers and project manager), CRO clinical supply program manager, CRO clinical system designer, CRO clinical system developer and CRO safety personnel. Details are provided in the Data Blinding and Documentation Plan.

9.0 Trial Endpoints

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is all-cause mortality up to Day 60.

9.2 Secondary Endpoints

9.2.1 Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- Time to sustained hospital discharge up to Day 60.
- Supplemental oxygen free days up to Day 29.
- Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15.
- Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15.

9.2.2 Other Secondary Efficacy Endpoints

- Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29.
- Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, extra corporeal membrane oxygenation (ECMO) or supplemental oxygen use at Days 8, 15, 22, 29 and 60.
- Proportion of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60.

- Duration of hospitalization, including re-hospitalization, up to Day 60.
- Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60.
- Duration of intensive care unit stay, including re-admission, up to Day 60.
- Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60.
- Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60, and respiratory failure free days up to Day 60.
- All-cause mortality up to Days 8, 15, 22 and 29.
- Change from baseline in peripheral capillary oxygen saturation (SpO_2) / fraction of inspired oxygen (FiO_2) at Day 15.

9.2.3 Secondary Safety Endpoints

- Adverse events (AE)s.
- Serious AEs (SAE)s.
- Changes in safety laboratory assessments.
- Withdrawals due to AEs.
- PK Parameters (on a subset of approximately 10 subjects).

9.3 Exploratory Endpoints

- Change from baseline in CRP (C-reactive protein) at Day 15.
- Change from baseline in lactate dehydrogenase (LDH) at Day 15.

9.4 Estimand Attributes

Appendix 1: Estimand Attributes presents the primary and key secondary trial endpoints and corresponding estimands as specified in the protocol, Section 3. Sensitivity analysis of the primary and key secondary estimands are described in Sections 12.5.2.3 and 12.5.3.6 respectively. Supplementary analysis is described in Section 12.5.2.4 and 12.5.3.7 for the primary and key secondary respectively. The analysis for other secondary and exploratory endpoints will be detailed in Section 12.5.4 and Section 12.5.5 respectively.

9.5 Population Sets

For the purposes of the final analysis, the following analysis sets are defined:

9.5.1 All-Screened-Subjects

The all-screened-subjects analysis set will include all subjects that signed informed consent for the study.

9.5.2 Intention-To-Treat Analysis Set

The Intention-to-treat analysis set (ITT) comprises all randomized subjects. Subjects will be included in the analyses according to the intervention they were randomized to.

9.5.3 Per Protocol Analysis Set

The per protocol analysis set (PP) comprises all subjects in the ITT without important protocol deviations deemed to have an impact on efficacy endpoints. In addition, subjects who prematurely discontinued IMP prior to Day 11 during the treatment period due to "Withdrawal by Subject" or similar will be excluded. Subjects who were randomized and not treated will also be excluded from the PP population.

Prior to database lock and unblinding of the trial, a blinded data review of the important protocol deviations will be performed to identify the important deviations impacting on the efficacy endpoints. Additionally a review of all subjects who discontinue treatment will be performed to assess if they should be excluded from the PP. Subjects excluded together with the reason for exclusion will be documented in a blinded manner prior to database lock. Subjects will be included in the analyses according to the intervention they were randomized to.

9.5.4 Safety Analysis Set

The safety analysis set (SS) is defined as all subjects who are exposed to at least one dose (even partially) of the IMP. Subjects will be analyzed according to the intervention received.

9.5.5 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKS) is defined as subjects who were randomized to C21, exposed to IMP and with at least one post-IMP blood sample with quantifiable C21 concentration collected. Participants may be excluded from the PK analysis population if they have important protocol deviations that are judged to significantly impact the PK analyses. PK sample is limited among a pre-selected number of trial sites in a subgroup of approximately 10 subjects including those randomized to Placebo. Only samples from subjects randomized to C21 will be analyzed and included.

10.0 Conventions and Derivations

10.1 Baseline and Change from Baseline

For Efficacy assessments baseline is defined as the last non-missing assessment obtained prior to randomization. If more than one assessment could be baseline, the record associated with the visit, Visit 2 – Day 1 in the eCRF will be selected as the baseline record for efficacy. For safety assessments it is defined as the last assessment prior to the administration of first dose of IMP. If time of assessment is not collected and the assessment is collected on the same date as the first dose of IMP, the assessment will be assumed to be per protocol i.e. prior to first dose administration.

Change from baseline at any post-baseline time point will be defined as:

$$Change\ from\ baseline = value\ at\ post\ baseline\ time\ point - value\ at\ baseline$$

10.2 Trial Day

Trial Day 1 is defined as the date of first dose of IMP. For subjects whose treatment assignment is randomly assigned but not dosed, Trial Day 1 is defined as the date of randomization assignment. For dates prior to Trial Day 1, the Trial Day is calculated as:

$$Trial\ Day\ =\ (Date\ of\ Interest/Assessment\ -\ Date\ of\ Trial\ Day\ 1)$$

For dates on or post Trial Day 1,

$$Trial\ Day\ =\ (Date\ of\ Interest/Assessment\ -\ Date\ of\ Trial\ Day\ 1)+1$$

10.3 Dates of First and Last Dose of IMP

The date of first dose of IMP will be the earliest date of IMP documented on the Exposure – Dose Administration CRF page. If no date of first dose of IMP is available and the subject was not treated, date of first dose of IMP will be missing and the date of randomization will be used in any calculations requiring treatment start date.

Date of last dose of IMP for hospitalized subjects at Day 14 will be set to the last dose of IMP recorded on the Exposure – Dose Administration CRF page. For discharged subjects prior to the completion of the treatment period, the date of last dose of IMP will be set to the date of treatment completion/discontinuation as recorded on the End of Treatment CRF page. If date of last dose of IMP is not available and subject is lost to follow-up based on End of Treatment CRF page, date of last scheduled visit or date of last telephone contact where a dose is recorded, will be used as the date of last dose of IMP.

10.4 Actual Treatment

Subjects who are initially dispensed C21 will be assigned actual treatment of C21 100 mg b.i.d. This includes subjects who were randomized to placebo.

10.5 Prior and Concomitant Therapy

Prior therapies are defined as those with a start date prior to the first dose of IMP.

Therapies which start prior to the first dose of IMP and are ongoing at the time of first dose of IMP will be summarized as both prior and concomitant therapies.

Concomitant therapies are defined as those started prior to but continuing after randomization or with a start date on or after randomization. For therapies that start prior to but ended on randomization date they will be considered prior therapies only.

10.6 Adverse Events

1) Adverse Event Leading to Discontinuation of Trial

An AE will be classified as an AE leading to discontinuation of the trial if the answer to the question "Did the adverse event cause the subject to be discontinued from the study?" is Yes on the AE CRF page.

2) Adverse Event leading to IMP Withdrawal

An AE will be classified as an AE leading to IMP withdrawal if the answer to the question "Action Taken with Study Treatment" on the AE CRF page is "Drug Withdrawn".

3) IMP-related adverse events

An AE will be classified as related to IMP if the relationship to study treatment is indicated as Related on the AE CRF page. Additionally, if the relationship is missing, then the AE will be deemed IMP-related.

4) Treatment-emergent adverse events (TEAE)

Treatment-emergent adverse event is defined as an event that starts on or after the date of first dose of IMP or worsens after first dose of IMP.

5) Duration of AEs

Duration of AEs will be calculated as AE end date – AE start date + 1. AE duration will only be calculated when complete dates for the start and stop date are provided.

10.7 Imputation of Missing Dates

There will be no imputation of partial and missing dates. Duration of events will not be calculated if start or stop date is partial and listings will display the collected date and not the imputed date. The following rules will be implemented to determine the assignment of AEs as TEAE and therapies as prior and concomitant for the analysis.

In general, in such cases an AE will be considered treatment-emergent, unless there is evidence in the (partial) dates available that it was not treatment-emergent. In particular, in case of missing start dates of AEs, these will be considered treatment-emergent, unless the stop date of the AE is prior to the first dose of IMP. In the case of partially missing start dates, the AE will be considered treatment-emergent, unless the information from the partial dates clearly shows that the AE was not treatment-emergent i.e. the year/month is prior to treatment start date.

For therapies if start date is missing and the end date is prior to the first dose of IMP, the therapy will be considered prior. If start date is missing or partial and the end date is missing or after first dose of IMP, the therapy will be considered both prior and concomitant unless there is evidence in the partial dates that clearly classifies the therapy as prior or concomitant (i.e. start year/month is after the first date of IMP). If end date is partial or missing and start date is after first dose of IMP the therapy will be considered concomitant.

10.8 8-point Ordinal Scale

The clinical status of COVID-19 is scored at each visit according to the 8-point ordinal scale. For hospitalized subjects this will be assessed by the investigator once daily until Day 29. For discharged subjects the 8-point ordinal scale will be assessed at Day 8, Day 15, Day 22, Day 29 and Day 60. Discharged subjects will be assessed for daily supplemental oxygen use since the previous visit. If there was supplemental oxygen use on the days between visits, the subject will be considered to be on oxygen on those days and an 8-point ordinal scale score of 2. For further details on the assessment of supplemental oxygen use for discharged subjects please refer to Section 10.10.

If a subject is discharged, the 8-point ordinal scale will be updated at discharge as an unscheduled visit. If there is a change in clinical status between Day 29 and Day 60 the 8-point ordinal scale score should also be updated. A subject re-hospitalized for a non-COVID-19 related reason should be considered non hospitalized while scoring the clinical status of COVID-19 on the 8-point ordinal scale.

The 8-point ordinal scale is defined in Table 2. In the efficacy analysis for some key secondary endpoints subjects will be considered a responder at a time point if they have achieved a score of ≤ 2 on the 8-point ordinal scale and have no supplemental oxygen use. For the purpose of the analysis an adjusted version of the 8-point ordinal scale will be used which will re-map subjects with a score of 2 and no at home oxygen use at a time point to have a value of 1 on the adjusted 8-point ordinal scale. Subjects with a clinical status of 2 on the 8-point ordinal scale and no oxygen use will be treated as the best case clinical status in all analysis and equivalent to a status of 1 in the analysis. Refer to Table 3 and Section 10.10 for details on determining the oxygen status of a subject at a time point.

Table 2: 8-point Ordinal Scale

1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Table 3: Adjusted 8-point Ordinal Scale for Multiple Imputation

1	Not hospitalized, no limitations on activities; limitation on activities and no home oxygen required
2	Not hospitalized, requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

10.9 Visit Windowing

Subjects are expected to attend daily visits until hospital discharge. Visits will be re-initiated in case of a COVID-19 related hospital re-admission. Subjects who do not discharge will have daily assessments up to Day 29. Subjects who do discharge will have visits Day 8, 15, 22, 29, 60. All subjects will have a follow-up visit at Day 60.

No visit windowing will occur for the 8-point ordinal scale. Daily values for the 8-point ordinal scale will be assigned based on the trial day the assessment occurs i.e. the value recorded on trial day X will be assigned as the value of the ordinal scale at Day X in the analysis. For discharged subjects, information on the oxygen use at home between visits will be entered on the concomitant medication page and the daily 8-point ordinal scale value for discharged subjects will be derived. If a subject has oxygen use on a trial day as per Section 10.10, they will be assigned a value of 2 on the adjusted 8-point ordinal scale (refer to Table 3 in Section 10.8) on the trial days between the oxygen start and end day. If Day 29 occurs on trial day greater than 29, for the analysis purposes a value of Day 29 will be assigned. For Day 60 the value collected at the Day 60 visit will be used in the analysis, even if this did not occur on trial Day 60. All endpoints for the 8-point ordinal scale will summarize Day 8, 15, 22, 29 and were applicable Day 60 time points. If a subject has multiple non-missing ordinal scale assessments on a trial day the assessment that occurred on the scheduled visit per the eCRF will be used in the analysis.

For hospitalized subjects, vital signs, supplemental oxygen use and oxygen saturation will be collected daily. Therefore, no visit windows will be assigned and results in the analysis will be summarized for each trial day up to Day 29. Trial day calculation is defined in Section 10.2. If the trial day an assessment occurs on does not align with the visit trial day in the CRF, the trial day will take precedence in terms of analysis. Laboratory assessments (including CRP and LDH) will be conducted while in hospital but not daily. Analysis visit windows as defined in Table 4 will be used for laboratory assessments. If a subject has multiple assessments in a window, the visit closest to the target day will be selected. For visits that are equally close to the target day, the assessment latest in time will be selected.

An early withdrawal visit (EWD) will be conducted for subjects who discontinue the trial prior to Day 15. This visit will be mapped to analysis visits per Table 4 and to a daily time point based on the trial day the assessment occurs. If a scheduled visit and EWD occur on the same day, the scheduled visit will be used in the analysis for the 8-point ordinal scale.

Table 4: Visit Windowing for Laboratory Assessments and CRP/LDH

Visit	Target Trial Day	Lower Limit	Upper Limit
Baseline	1		1 (pre-baseline)
Day 3	3	1 (post-baseline)	3
Day 5	5	4	6
Day 8	8	7	9
Day 11	11	10	12
Day 15	15	13	16

10.10 Supplemental Oxygen Use

Hospitalized subjects will be assessed on a daily basis for their oxygen use. If a subject is discharged, they may be prescribed supplemental oxygen for at-home use. On each visit following discharge a subject will be assessed if they have used oxygen since the last visit and which days and if they have used supplemental oxygen this will be recorded on the concomitant medication page of the CRF. Subjects who have used supplemental oxygen since the previous visit will also be assessed if they are still on oxygen at the visit.

If a subject has a scheduled ordinal scale score of 1, 3, or 4 (i.e. free of supplemental oxygen use) and there is evidence of supplemental oxygen usage, the value on the adjusted ordinal scale will not be changed and the investigator's judgement will be considered the most accurate assessment of clinical status. The collected ordinal scale value will be used as the value in the analysis and the subject will be considered free of supplement oxygen usage on the trial day of interest.

For discharged subjects, the daily oxygen use will be derived. If a subject has oxygen use on a trial day they will be assigned a value of 2 on the adjusted 8-point ordinal scale on the trial days between the oxygen start and end day. A discharged subject will be considered to be using supplemental oxygen on a trial day if:

1. The subject has a record at the time point for supplemental oxygen use on the Oxygen supplementation during oxygen saturation measurement page of the CRF.
2. The subject has "Yes" at a time point to the question "Was subject still on COVID-19 related supplemental oxygen at the time of visit" on the Visit page of the CRF for discharged subjects at Day 8, Day 22, Day 29 and Day 60 and on the End of Treatment page for Day 15.
3. If a subject has a missing ordinal scale score on the day of discharge or a value of 2 on the ordinal scale and on the Hospitalization CRF page the question "Was COVID-19 related supplemental oxygen for at home use prescribed?" is Yes then a subject will be considered on supplemental oxygen at discharge and the visit that corresponds with discharge.
4. Subject has a record on the concomitant medication page for post-baseline supplemental oxygen use (preferred term entered as Oxygen and the therapy is concomitant per Section 10.5)

Otherwise the subject will be considered oxygen free at a time point. If the subject has an ordinal scale score of 2 at these time points and is not on supplemental oxygen they will be assigned an adjusted ordinal scale score of 1.

10.11 All-Cause Mortality

All-cause mortality is defined as time to day of death from any cause during the study. Time to all-cause mortality will be defined as:

$$Time\ to\ all\ cause\ mortality\ (days) = Date\ of\ Death\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

where the date of death will correspond to the date of death recorded in the CRF. Subjects without the event will be censored at day of withdrawal/Day 60 follow-up date in this analysis. If a subject is indicated to have died in the data, but date of death is missing, the last available date for the subject in the database will be used as the day of death.

10.12 Time to Sustained Hospital Discharge

Time to sustained hospital discharge is defined as the time to the date of discharge from initial hospitalization or re-hospitalization due to COVID-19 after which the subject is not re-hospitalized for COVID-19 related reasons.

If a subject dies, they will be censored at Day 60, if a subject withdraws (for reasons other than death) from the trial prior to observing the event (i.e. while still hospitalized) they will be censored at the time of withdrawal. If a subject has an event and subsequently withdraws (for reasons other than death), they will be treated as having the event in the analysis. Subjects who complete the trial without the event i.e. are still hospitalized at Day 60, will be censored at Day 60 in the analysis.

The calculation will be as follows:

$$Time\ to\ sustained\ discharge\ (Days) = Date\ of Event\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

where date of event for subjects who discharge will be the date of discharge from hospital (after which the subject is not re-hospitalized for COVID-19 reasons) as recorded on the Hospitalization CRF page. If a subject is re-hospitalized for COVID-19 reasons, the date of event will be the end date of this re-hospitalization (if no subsequent re-hospitalization for COVID-19 reasons).

Additionally, a sensitivity analysis will be performed where all re-hospitalizations are considered as COVID-19 related regardless of the investigator indicated cause. In the sensitivity analysis, date of event for subjects with missing data and no discharge record on the hospitalization form will be the relative day a value of ≤2 is achieved after which a subject has only imputed values of ≤2 for all subsequent visits. If subjects with imputed data have a recorded value of discharge on the hospitalization page and imputed data is ≤2 from this date of discharge, the recorded date of discharge will be used as event date in the calculation. If subjects with imputed data have a recorded value of discharge on the hospitalization page and any imputed data is >2 from this date of discharge, time to sustained discharge will be the relative day a value of ≤2 is achieved after which a subject has an imputed value of ≤2 for all subsequent visits. If a subject with imputed data never observes the event they will be censored at Day 60.

10.13 Number of Oxygen Free Days

Subjects will be considered oxygen free on a trial day if they do not have supplemental oxygen usage on that day. Supplemental oxygen usage is defined in Section 10.10 and subjects will be assessed for supplemental oxygen usage on each post treatment day up to trial Day 29 (i.e. from trial Day 2 to Day 29).

The number of oxygen free days for a subject will be the sum of the number of oxygen free days in hospital and number of oxygen free days at home if applicable. These days do not need to be consecutive. Missing data will be imputed as per Section 10.19.1.

10.14 Number of Respiratory Failure Free Days

The number of days a subject is free of respiratory failure will be the number of days a subject has a score of ≤5 on the ordinal scale post-baseline.

If a subject dies, they will be considered in respiratory failure from the date of death up to Day 60.

For hospitalized subjects this will be the number of days a subject has a score of ≤5 on the 8-point ordinal scale CRF page. Up to Day 29, the adjusted 8-point ordinal scale will be used, for days between Day 29 and Day 60 the following rules will apply:

- If the clinical status on both days is ≥ 6 the subject will be assumed to be in respiratory failure for all days between Day 29 and Day 60.
- If the clinical status on both days is ≤5 and there is no observed data (for example unscheduled visits) indicating a worsening of status the subject will be assumed to be respiratory failure free for all days between Day 29 and Day 60. If there is a worsening of a status such that the ordinal scale has a value of ≥6, the subject will not be considered respiratory failure free from the duration of this status (if duration of status is known).
- If the clinical status at Day 29 is ≥ 6 and Day 60 is ≤5 and the date of the change of status is known, the subject will be counted as respiratory failure free from the date the status improved. If the date of change in status is unknown (for example data is imputed), only Day 60 will be counted as respiratory failure free.
- If the clinical status at Day 29 is ≤5 and Day 60 is ≥6 and the date of the change of status is known, the subject will be counted as respiratory failure free until the date the status worsen. If the date of change in status is unknown (for example data is imputed), only Day 60 will be counted as in respiratory failure.

For discharge subjects, if a subject does not have a change in status up to Day 60 following discharge i.e. they are not re-hospitalized due to a COVID-19 related illness, the number of respiratory failure free days after discharge will be calculated as

$$Respiratory\ Failure\ free\ (days) = Day\ 60\ visit - Date\ of\ Discharge + 1$$

If a subject is re-hospitalized due to a COVID-19 related illness and the ordinal scale on re-admission is ≥ 6 the number of respiratory failure free days after discharge and prior to re-hospitalized will be calculated as

$$Respiratory\ Failure\ free\ (days) = Date\ of\ re - hospitalization - Date\ of\ Discharge$$

The number of respiratory failure free days will be the sum of the days the subjects met the criteria i.e. the number of days a subject has a score of ≤5 on the 8-point ordinal scale while hospitalized and the numbers of days a subject meets the criteria while discharged. These days do not need to be consecutive.

Subjects with missing data will have their data multiply imputed as per Section 10.19.1.

10.15 Duration of Hospitalization

The duration of hospitalization will be calculated as

$$Duration\ (days) = End\ date\ of\ hospitaliztion - Start\ date\ of\ hospitalization + 1$$

The duration of multiple hospitalizations, including re-hospitalizations due to COVID-19 in the period will be summed together to derive the overall duration of hospitalization. For subjects who were hospitalized on the date of first dose of IMP, the date of first dose of IMP will be used as the start date. If a subject is still hospitalized at the end of the 60-day period the date of trial completion will be used.

For subjects who die they will be considered hospitalized from date of death through Day 60. For subjects who discontinue the trial prior to discharge from hospital, the number of days of hospitalization will be set to 60 days (it will be assume they did not discharge from hospital). If a subject discontinues the trial following discharge for reasons other than death and there is no further hospitalization data available then for the purpose of the analysis the subject will be considered to be not re-admitted in the period and no additional imputed days will be added to the number of days recorded on the available assessments.

An additional sensitivity analysis will be performed where missing data will be imputed as per Section 10.19.1, such that subjects who are early withdrawals will have data imputed following withdrawal and

where all re-hospitalizations are considered as COVID-19 related regardless of the investigator indicated cause.

10.16 Duration of ICU Stay

The duration of ICU stay will be calculated as

$$Duration\ (days) = End\ date\ of ICU\ stay - Start\ date\ of\ ICU\ stay + 1$$

The duration of multiple ICU stays in the period will be summed together to derive the overall duration of ICU stay. If a subject dies or discontinues prior to the end of the ICU stay or the subject died and had no ICU stay, the subject will be considered in the ICU from the date of death/discontinuation through Day 60. For subjects who discontinue the trial in hospital but not in ICU or discontinue following discharge they will not have any imputed additional days added to the number of days recorded on the available assessments. If the start date of the ICU stay is prior to treatment start, the treatment start date will be used as the ICU start date in the above derivation. For subjects with no ICU stay a value of 0 days will be used in the analysis. Note that ICU stays associated with re-admission for non-COVID reasons should not contribute to the duration.

10.17 Duration of Invasive Ventilation or ECMO

The duration of invasive ventilation or ECMO use will be calculated as

$$Duration\ (days) = End\ date\ of\ use - Start\ date\ of\ use + 1$$

The duration of multiple invasive ventilation or ECMO use will be summed in the period to derive the overall duration. For subjects who die they will be considered on invasive ventilation or ECMO from date of death through Day 60. Subjects who discontinue the trial prior to discharge from hospital with last ordinal scale assessment of 7 will be considered on invasive ventilation or ECMO from date of discontinuation through Day 60. Subjects who discontinue the trial in hospital with last known status on the 8-point ordinal scale of ≤6 or subjects who discontinue following discharge will be considered not on invasive ventilation or ECMO through Day 60 and will have no additional days added to the number of days recorded on the available assessments. For subjects with no invasive ventilation/ECMO use a value of 0 days will be used in the analysis.

10.18 Data handling for SpO_2 and FiO_2

SpO_2 will be collected on the Oxygen saturation form daily for hospitalized subjects. SpO_2 will be collected twice at a visit and the average of the two assessments will be used as the value in the analysis. If only one assessment is available at a visit this will be the value used in the analysis. Discharged subjects will not have site assessments performed. Day 15 will be the only time point examined for this endpoint.

Subjects on low flow oxygen, high flow device or mechanical ventilation will use the value of FiO_2 as entered on the eCRF by the investigator. Subjects on room air will have a value of 21% for FiO_2 assigned. Subjects on ECMO will not have FiO_2 collected. In this case in the calculation of the SpO_2/FiO_2 ratio the last observation for this ratio prior to the subject moving to ECMO ventilation will be used. If the value of FiO_2 is missing, but information on the type of device and oxygen flow is collected, Appendix 3 will be used to assign a value of FiO_2 to use in the calculation of the SpO_2/FiO_2 ratio.

At a visit a subject may have a SpO_2 reading on an oxygen device and another reading at the same visit on room air. In this case the ratio SpO_2/FiO_2 will be calculated using the on room air value only for SpO_2 and a value of 21% for FiO_2.

10.19 Missing Data

In general, missing safety data will not be imputed. However, safety assessments in the form of <x (i.e. below the lower limit of quantification) or >x (i.e. above the upper limit of quantification) will be imputed as x in the calculation of summary statistics but displayed as <x or >x in the listings. Missing FiO_2 values will be imputed as per Appendix 3.

In all efficacy analysis subjects who die will always be treated as the worst case following the date of death. For endpoints where multiple imputation will not be implemented, subjects who discontinue the trial early will be assessed in the analysis based on their last known status as discussed in Sections 10.15, 10.16 and 10.17. Other missing data will be imputed using multiple imputation as outlined below.

10.19.1 Multiple Imputation

Missing ordinal scale data at scheduled time points will be imputed using multiple imputation. Multiple imputation relies on the assumption of data being missing at random (MAR) i.e. the missingness can be explained by the observed data and missing data does not depend on unobserved data after accounting for observed factors. Subjects will only have missing data imputed for post-baseline scheduled visits (Day 2 to Day 29, Day 60).

The following steps will be used to impute the missing data. Prior to the missing data imputation all observed 8-point ordinal scale data will be re-mapped per Table 3 to ensure discharged subjects with supplemental oxygen use are treated as clinically worse than discharged subjects with no oxygen use. This will also ensure information on at home oxygen use is explicitly contained in the ordinal scale score. The value of the adjusted 8-point ordinal scale to use in the analysis for all days following discharge will be assigned as per Section 10.10. On the day of discharge, the following rules will be used to assign a value of the adjusted ordinal scale:

- If a subject has a scheduled visit with an ordinal scale value other than 2, this value will be used in the analysis for the day of discharge.
- If a subject has a missing assessment or a value of 2 is recorded as the scheduled assessment, a subject will be assigned a value of 1 or 2 on the adjusted 8-point ordinal scale on the day of discharge as outlined in Section 10.10.

If a subject has an ordinal scale value of 8 at any visit or the subject has a date of death, records on or following date of death will be handled as follows in the analysis:

- All days following day of death will be set to 8.
- For the day of death, if the subject has a non-missing value on the ordinal scale that is not a value of 8 this will be the value used in the analysis.
- If a subject has a missing value on the day of death the value of 8 will be used.

Subjects who die will be removed from the Imputation in step 2. Only subjects who have not died will have their data imputed. Following the imputation, data for subjects who died will be included in all imputed datasets as observed.

A random seed of 2188 will be used for all imputation in this analysis.

1. Prior to the imputation, missing data pattern for ordinal scale data will be explored. If the pattern of missing data is non-monotone (for example intermediate missing data due to missing follow-up visits), intermittent missing ordinal scores will be imputed under a missing at random (MAR) model for missing data using a Markov chain Monte Carlo (MCMC) method of imputation to ensure data follows a monotone missing data pattern i.e. if data is missing at Day X it will be missing for all subsequent time points. The 8-point ordinal scale will be imputed using PROC MI with the MCMC impute=MONOTONE specification and specifying the variables in order of scheduled visits (Day 2 up to Day 29, Day 60), in order to partially impute intermediate missing values only.

   A minimum value of 1 and maximum value of 7 will be specified to ensure values are not outside the range of possible ordinal scale scores. Values will be rounded to the nearest whole number and 1,000 burning iterations will be used. Graphical tools will be used to check for any signs of non-convergence and if non-convergence is an issue, the number of burn-in iterations should be increased.

If the model does not converge as values within the minimum/maximum range can not be imputed, the minimum and maximum criteria will be removed. Subjects which have values outside the minimum and maximum will be reviewed and the following process will be followed to obtain convergence:

- For values below the minimum and above the maximum the largest absolute deviation from the minimum/maximum will be determined. The subject with the largest absolute deviation for the non-monotone data will have the data point assigned using last observation carried forward (LOCF)
- The MCMC will be re-run (with minimum/maximum specified). If setting the minimum/maximum results in convergence these results will be used in Step 2 of the MI process. Otherwise the process will be repeated until setting minimum/maximum results in convergence or no further subjects with unrealistic data can have non-monotone data imputed with LOCF.
- If after these steps are applied and there is no convergence, the MCMC will not be used and LOCF will be used for all subjects to impute their non-monotone data.

This step will only be performed if missing data does not follow a monotone missing data pattern. This step assumes data is multivariate normally distributed which will not be the case for ordinal data. However, as the number of non-monotone data is expected to be small, the overall impact of this partial imputation step on the analysis at the time point of interest will be small. Subjects who died will be included in this step. Further it is accepted that values of 1 and 2 may be imputed for non-monotone data prior to the observed date of discharge. No adjustments will be made for this as these values are theoretically possible.

2. Missing 8 point ordinal scale data at time point X will be imputed for subjects who did not die using a logistic regression model with the factors of
    a. Treatment group
    b. Actual baseline ordinal scale score
    c. Region (Pooled)
    d. Age (will not be included in the CLASS statement in the PROC MI)
    e. Post-baseline daily values of adjusted 8-point ordinal scale up to time point X

Values will be restricted to a minimum value of 1 and a maximum value of 7, as values of 8 will not be present in the data per the previous rules outlined. It is noted that at a time point only values of the ordinal scale recorded at the time point will be possible imputed values. Imputed values may be inconsistent with other data, for example it is possible that an imputed value will be 3 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care) even if supplemental oxygen is documented on the concomitant medication page.

The number of imputations will depend on the percentage of missing data to be imputed and will range from a minimum of 20 to a maximum of 50. The number of imputations will increase from the minimum of 20 to the maximum of 50 according to the formula:

$$Number\ of\ imputations = 20 + 1.5 * (m)$$

where m is the proportion of missing data, expressed as a percentage. The smallest integer that is greater than or equal to the number will be used (note this will be based on missing data present following step 1 and will not included subjects who died in the calculation)

By default SAS PROC MI, uses the option "LIKELIHOOD=NOAUGMENT" for the computation of maximum likelihood estimates. If the maximum likelihood parameter estimates do not exist or any warning results from this option, the option "LIKELIHOOD=AUGMENT" will be used to get the maximum likelihood estimates.

3. Imputed values from each of the imputed datasets in step 2, data for subjects who died and non-missing data will be used to calculate the responder status for a subject at a time point for the following endpoints:

Sensitivity Analysis for Time to Sustained Hospital Discharge

For each of the imputed datasets, the time to sustained hospital discharge will be derived. If a subject has an observed or imputed score of ≤2 on the ordinal scale where for all subsequent visits the observed or imputed score stays at or below 2 the earliest occurrence will be considered the time to sustained hospital discharge. Note for subjects with no missing data, the time to sustained discharge will be per the rules in Section 10.12. If a subject was re-hospitalized for a non-COVID-19 related reason, the subject will not be considered discharged during this re-hospitalization period for this analysis. For all subjects who do not have the event or who die, they will be censored at Day 60. The calculation will be as follows:

$$Time\ to\ sustained\ discharge\ (Days) = Date\ of Event\ or\ Censor - Date\ of\ first\ dose\ of\ IMP + 1$$

For subjects where the event occurs on an imputed visit, the value of time to sustained discharge will be set to the trial day of the imputed visit (i.e. if the event first occurs for Day 29 and is an imputed value, the time to sustained discharge will be set to 29). For each of the datasets the analysis (stratified log-rank) as per Section 12.5.3.2 will be implemented.

Number of Days Oxygen Free

A subject will be considered as oxygen free at a time point if the observed and imputed value of the adjusted 8-point ordinal scale is 1, 3 or 4. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.3 will be implemented.

Proportion of subjects free of respiratory failure at Day 8, 15, 22, 29, 60

A subject will be considered a responder at a time point if the value of the 8-point ordinal scale is ≤5. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.4 will be implemented.

Subjects discharged and free of supplemental oxygen at Day 8, 15, 22 and 29

A subject will be considered a responder at a time point if the value of the adjusted 8-point ordinal scale, observed and imputed, is 1. For each of the datasets imputed in step 2, the analysis as specified in Section 12.5.3.5 will be implemented.

Number of Days Free of Respiratory failure

A subject will be considered free of respiratory failure at a time point if the value of the 8-point ordinal scale is ≤5. For details on this derivation refer to Section 10.13. For each of the datasets imputed in step 2, the analysis as per Section 12.5.3.3 will be implemented.

Other Non-Key Secondary Endpoints

For the endpoints of proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, a subject will be considered on invasive mechanical ventilation or ECMO if the imputed value at the time point is ≥ 7.

For the endpoint of proportion of subjects on non-invasive, invasive mechanical ventilation, ECMO or supplemental oxygen use at Days 8, 15, 22, 29 and 60, subjects will be considered on non-invasive, invasive mechanical ventilation, ECMO or supplemental use if they have an imputed or observed score of ≥ 5 at the time point.

For sensitivity analysis for the endpoint of duration of hospitalization, the duration of multiple hospitalizations, including re-hospitalizations due to COVID-19 and non-COVID-19 related reasons in the period will be summed together to derive the overall duration of hospitalization. For subjects with no missing data, duration of hospitalization will be calculated as per Section 10.15. For subjects with missing data following observed discharge date, no additional days will be added for

duration if the imputed values are ≤2 following this date, otherwise if subjects have a value of >2 following last observed discharge, the number of days where the imputed values are >2 will be added to the observed duration. For subjects with missing data with no observed discharge date, if the imputed values are ≤2, then the subject will have the duration of hospitalization calculated as relative day of last value >2 – start date of hospitalization +1. If the subject has multiple values > 2 following the first imputed discharge, the number of days where the imputed value is >2 will be added to the duration. Note that Day 59 should be used in the calculation if imputed Day 29 is >2 and imputed Day 60 ≤ 2. If imputed Day 29≤2 and Day 60>2 only Day 60 will be counted as in hospital.. If a subject does not have the event across the imputed and observed data duration will be calculated as Day 60/study completion – date of initial hospitalization +1.

4. Results from the analysis (log-rank, logistic regression as per Appendix 2, statistics from the analysis for number of days oxygen free as per Section 12.5.3.3 and ANOVA) will be combined using Rubin's rule (Rubin, 1987). Estimates will be combined using PROC MIANALYZE in SAS. Rubin's rule assumes the estimates are asymptotically normally distributed.

   Analysis of Proportions using Logistic Regression (Appendix 2)

   Estimates from the logistic regression are transformed using the method outlined in Appendix 2. The standardized weighted differences, standard errors and the 95% CI based on the delta method (Ge et al, 2011) are approximately normal, no adjustment is required.

   Analysis using Log-Rank

   Estimates from log-rank are based on a chi-square distributed statistic and prior to combining the estimates via Rubin's rule, the estimates will need to be normalized using a Wilson-Hilferty transformation (Moscovici and Ratitch, 2017).

   Analysis using Cox Regression

   For results from Cox regression, the estimates obtained from PROC PHREG are log hazard ratios, and after combining via Rubin's rule, the results will be exponentiated to obtained the hazard ratios and associated confidence intervals (Moscovici and Ratitch, 2017).

   ANOVA

   Estimates from ANOVA are approximately normal and no transformation is required.

10.19.2 Multiple Imputation as a Sensitivity Analysis for the Primary Endpoint

As a sensitivity analysis for the primary endpoint, all-cause mortality at Day 60, missing data for Day 60 will be imputed using a logistic regression model and the proportions of deaths at Day 60 analyzed per Appendix 2. The steps for this multiple imputation will follow Section 10.19.1 with the following exceptions:

- Deaths in the data will be included in the imputation model.
- For Step 1, imputation of non-monotone data using MCMC, the maximum value allowed will be 8
- At the imputation step only missing data for Day 60 will be imputed using the following model:
  - Treatment group
  - Actual baseline ordinal scale score
  - Region (Pooled)
  - Age
  - Last known post-baseline ordinal scale value (for subjects with complete data collection up to Day 60, this will be the value collected at Day 29 analysis visit)

10.19.3 Tipping Point Analysis

To assess the robustness of the efficacy analysis, an additional sensitivity analysis using a tipping point will be performed. Tipping point analysis will be performed for the key secondary endpoints of oxygen supplemental free days up to Day 29, proportion of subjects free of respiratory failure at Day 15, and subjects discharged and free of supplemental oxygen usage at Day 15. A series of analyses will be performed with different values of a shift applied until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that changes the conclusions of the analysis from significant to non-significant will represent the tipping point. The results of the tipping point will be summarized showing the treatment difference, 95% CI and p-values for each level of δ. The analysis will not be performed if the primary efficacy analysis for the endpoints results in a non-significant result.

All-Cause Mortality

For the endpoint all-cause mortality, missing data will be imputed using Section 10.19.2. For each imputed dataset generated, a subject with missing data at Day 60 will be assigned as a death/survival based on the value of the adjusted 8-point ordinal scale. Prior to step 3 (performing the logistic regression analysis on the imputed datasets), a shift will be applied to the number of subjects classified as survivors across the imputed datasets. Among the subjects with missing data in the active arm, the number of survivors in this group will be reduced incrementally across each dataset (i.e. changing the subject from survival status to death status), starting at 1 to a maximum value of the number of subjects with missing data (for example if 10 subjects have a missing data at Day 60 in the active arm, each dataset will have the number of responders reduced from 1 up to 10 in the active arm at Day 60) or until it is not possible to reduce the number of survivors any more in an imputed dataset (i.e all subjects at Day 60 with missing data are set to Death status).

For each incrementally shift in the number of responders across missing data in the active arm, step 3 and step 4 will be performed as in Section 10.19.2. If no tipping point is found by just applying a shift to the number of responders in the active arm, the procedure will be repeated with the number of survivors across subjects with missing data at Day 60 in the placebo arm increased.

The choice of the subject to change from a survivor to death will be done at random. Using the random seed of 150822, each subject with missing data will be assigned a numeric value. The subject's values will be changed incrementally based on the numeric order generated by this process.

Respiratory Failure Free at Day 15/ Discharged and Free of Supplemental Oxygen Usage at Day 15

For these endpoints, a similar approach as all-cause mortality will be applied. For each imputed dataset as generated per Section 10.19.1 a subject will be assigned as a responder/non-responder depending on the value of the adjusted ordinal scale. For each imputed dataset, a shift will be applied to the number of responders across the imputed datasets. Among the subjects with missing data in the active arm, the number of responders in this group will be reduced incrementally across each dataset, starting at 1 to a maximum value of the number of subjects with missing data at Day 15 or until it is not possible to reduce the number of responders any more in an imputed dataset (i.e all subjects at Day 15 with missing data are set to be non-responder). If a shift is not found by just applying to the active arm, a shift will be applied to the Placebo arm (increasing the number of responders). The choice of which subject to change from responder to non-responder will be assigned following the approach for all-cause mortality.

Number of Supplemental Free Days up to Day 29

For the endpoint oxygen supplemental free days up to Day 29, the imputation as described in Section 10.19.1 will be performed and for each imputed dataset the number of days oxygen free will be tabulated. Then for subjects in the active arm with missing data up to Day 29, the number of days oxygen free will be reduced incrementally starting at 1 up to the number of days the subject had a missing value. For each reduction, the analysis as described in step 3 and step 4 in Section 10.19.1 will be performed. If no tipping point is found by just applying a shift to the number of days in the active arm, the procedure will be repeated with the number of days across subjects with missing data in the placebo arm increased.

10.19.4 Worst Case Imputation

In order to assess the robustness of the primary efficacy analysis for selected key secondary endpoints, the worst case analysis will be used which will assign missing data in the active arm using the average of the observed values in the placebo arm at a visit. Likewise for missing values in the placebo arm, the average of the observed values in the active arm at a visit will be used. This analysis will only be considered meaningful if the results of the primary analysis for the key secondary endpoints are significant for C21.

The adjusted ordinal scale value will be used in this analysis and the average will be rounded to the nearest whole number prior to analysis. For the key secondary endpoint of oxygen supplemental free days, death will be given a value of -1, subjects with no post treatment data a value of 0 in the analysis.

11.0 Interim Analyses

No formal interim analysis will be performed in the study. The DMC will review the safety results after the first 150 randomized subjects have completed study up to Day 15.

12.0 Statistical Methods

All statistical analyses will use SAS® version 9.4 or higher. Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% which will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, Standard Deviation (SD), median, Q1, Q3, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, median, Q1, and Q3 to a further decimal place and the SD to two additional decimal places. The maximum number of decimal places will be 4, unless otherwise noted. P-values will be presented to 3 decimal places, with values less than 0.001 presented as <0.001.

In general, all data summaries will be presented by treatment group and overall. Efficacy outputs will not have an overall column. If not stated otherwise, p-values from statistical tests will be two-sided and CIs will be calculated using a 95% CI.

Stratification will be done based on baseline disease severity, that is the score on the ordinal scale at baseline (5 or 6), and region (North America, South and Central America, Europe, Asia, Africa). The actual stratification will be used as factors in the statistical analysis, subjects included in wrong stratum at randomization will be moved to their correct strata belonging in the analyses. Small stratum may be pooled in the analysis. Any pooling of stratum will be agreed prior to unblinding of the database. Region will be pooled as Europe vs the rest of the world (North America, South and Central America, Asia, Africa). For all models where region is a factor (including in the imputation), pooled region will be used. In the text of this document, region will mean pooled region. Factors may be removed from models if the factor is causing an issue with convergence. For subgroup analysis, factors that are aligned with the strata division will be deleted from the model.

Missing data will be handled as described in Section 10.19. The ITT is used to analyze endpoints related to the efficacy objectives, the PP will be used for sensitivity analyses related to efficacy objectives and the SS is used to analyze the endpoints and assessments related to safety. PK analyses will be presented using the PKS.

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in hierarchical order as below:

1. All-cause mortality up to Day 60
2. Time to sustained hospital discharge up to Day 60
3. Supplemental oxygen free days up to Day 29
4. Proportion of subjects free of respiratory failure at Day 15

5. Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15

This means that statistically significant results for the comparison in the higher rank are required to initiate the testing of the next comparison in the lower rank. All analysis will be performed in the above order, however if a statistical comparison is non-significant then all subsequent statistical analysis will be exploratory in nature and no formal conclusions will be drawn. In other words, if the test for endpoint 3 in the above order is non-significant, then endpoints 4 and 5 will be exploratory in nature.

Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.

All data collected during this trial regarding subject characteristics, efficacy and safety will be listed, unless otherwise specified. Screen failures will be excluded from all listings and tables if not otherwise noted. Listings will not show imputed data but will present data as reported.

12.1 Subject Disposition

The number of subjects screened, and the number and percentage of screen failure subjects, together with the reason for screen failure will be presented.

The number and percentage of subjects randomized, not treated and treated in the trial will be presented, with the number and percentage of subjects who prematurely withdrew from the treatment, withdrew from treatment but completed the trial, prematurely withdrew from the trial and a breakdown of the corresponding reasons for treatment and trial withdrawal.

Tabulations of the number and percentage of subjects included in each analysis set. A tabulation of subjects still in the trial at each post-baseline time point will be provided.

Subjects disposition will be listed for all randomized subjects.

12.2 Demographic and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the ITT, SS, and PP. Additionally, a summary of demographic characteristics by actual baseline severity strata will be presented for the ITT.

Descriptive statistics will be provided for

- Sex (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Country
- Actual Region (North America, South and Central America, Europe, Asia, Africa) [Randomized region will be presented if any difference between actual region and randomized]
- Age (years) at informed consent (as collected on the Demographics CRF page),
- Age group (< 65 years, ≥ 65 years)
- Baseline body weight, height, and BMI. BMI will be derived as Weight (in kg)/Height (in m)^2
- Actual Baseline Disease Severity strata (ordinal score 5 or 6 at baseline based on actual value and not randomized)
- Randomized Baseline Disease Severity strata (ordinal score 5 or 6 at baseline based on value used in randomization)

- Presence of Risk factors for Severe COVID-19 (subjects with any medical history preferred terms selected as a risk factor as defined by the investigator on the Medical history page of the CRF will be counted as Yes otherwise subjects will be counted as No)
- Number of Risk Factors (count of unique medical history preferred terms selected as risk factor for severe COVID-19 by the investigator)
- SARS-CoV-2 Variant

A listing for demographics will be provided for ITT.

Medical history conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later. The number and percentage of subjects with each medical history term will be summarized by the MedDRA system organ class (SOC) and preferred term (PT) using the ITT. A listing for medical history presented for the ITT. Additionally medical history indicated by the investigator on the CRF as a risk factor for severe COVID-19 will be summarized by SOC and PT in the ITT.

COVID-19 diagnosis and history will also be summarized for ITT with descriptive statistics presented for the following:

- History of previous COVID-19 infections (Yes, No)
- Time since onset of current COVID-19 signs and symptoms calculated as:

$$Time\ since\ onset\ (days) = Start\ date\ of\ treatment - date\ of\ onset$$

- Time since current COVID-19 diagnosis

$$Time\ since\ diagnosis\ (days) = Start\ date\ of\ treatment - date\ of\ diagnosis$$

- Duration of current hospitalization calculated as:

$$Duration\ (days) = Start\ date\ of\ treatment - Start\ date\ of\ hospitalization$$

  The start date of hospitalization is the start date for records indicated as Initial hospitalization on the COVID-19 Hospitalizations CRF page. Additionally the following categories for duration of current hospitalization in days will be presented :0, 1, 2, 3, 4, 5 days.

- Type of Oxygen Supplementation for current infection at baseline (Low flow oxygen device, High flow oxygen device, non-invasive mechanical ventilation). All types of oxygen supplementation will be presented even if not specifically specified in this list.

Information on COVID-19 diagnosis and history will also be listed for the ITT.

12.3 Treatments

12.3.1 Extent of Trial Drug Exposure

For the IMP, summary statistics will be provided for SS for duration of exposure, total number of dose administrated and total cumulative dose in the treatment period. The number and percentage of subjects who experience at least one overdose on any day during the treatment period will be provided. Any dose of C21 exceeding a total daily dose of 200 mg (i.e., 4 capsules of IMP) is considered an overdose.

The total cumulative dose will be calculated as:

$$Cumulative\ dose\ (mg) = 50x\ (Number\ of\ Capsules\ dispensed\ [56] - Capsules\ returned)$$

The total number of doses administered will be the difference between the number of capsules dispensed [56] and number of capsules returned. If returned amount is missing and the subject is indicated to have completed treatment, they will be treated as taking all capsules. If the subject discontinues treatment and

returned amount is missing, they will be treated as taking capsules as planned up to the day of discontinuation derived as:

$$Cumulative\ dose\ (mg) = 50 * (4 * (duration\ of\ exposure))$$

where duration of exposure for this calculation will be set to a minimum of duration of exposure and 14 days.

If first dose for subject that discontinues treatment and has no returned amount is in the evening (p.m.) the calculation will be as follows:

$$Cumulative\ dose\ (mg) = 50 * (2 + 4 * (duration\ of\ treatment - 1))$$

For these subjects with first dose in the p.m., if duration of exposure is >14 indicating the subject took the full treatment course, the cumulative dose will be assumed to be 56.

The duration of exposure will be derived as:

$$Duration = (Last\ dose\ of\ IMP - First\ dose\ of\ IMP) + 1$$

Duration of exposure will be summarized overall, by subjects whose first dose was in the morning and by subjects whose first dose was an evening dose. Duration of exposure will also be summarized by duration categories, the number of subjects exposed for 1-6 days, 7-13 days and 14+ days.

Overall compliance will be calculated as follows:

$$Treatment\ Compliance\ (\%) = 100 * \frac{Total\ Number\ of\ Doses\ adminstered}{Expected\ Number\ of\ Capusles}$$

For subjects who completed treatment, expected number of capsules will be 56. For subjects who discontinue treatment:

$$Expected\ Number\ of\ Capsules = 4 * Duration\ of\ exposure$$

Compliance will be summarized using the following categories: <80%, 80-90%, >90%.

The percentage of doses taken in hospital will be presented and derived as follows:

$$\%\ of\ Doses\ taken\ = 100 * \frac{56 - Number\ of\ Capsules\ dispensed\ on\ discharge}{Cumulative\ dose\ (total\ capsules\ taken)}$$

For subjects who do not discharge during the treatment period or who discontinue the study prior to discharge from hospital during the treatment period, the % doses taken will be 100%.

The number of doses missed and reason dose missed will be summarized for subjects (this information will only be collected during the hospitalized period). Trial drug exposure will be listed. Drug accountability will also be listed.

12.3.2 Prior and Concomitant Therapies

Therapies received prior and concomitantly with IMP, categorized by medication group and subgroup according to the World Health Organization Drug Dictionary (WHODRUG) Global version March 2021 B3 or later will be summarized using ITT.

Prior and concomitant therapies (see Section 10.5) will be summarized separately using Anatomical Therapeutic Chemical (ATC) levels 2 and 4. The number and percentage of subjects using any therapy will be displayed together with the number and percentage of subjects using at least one therapy within each medication group and subgroup.

A summary of vaccinations will be provided for the ITT. Vaccinations will be collected on the concomitant medication page and will be identified via code review by medics.

12.4 Important Protocol Deviations

Per PRA/ICON processes, protocol deviations data will be entered into the PRA/ICON system of record (PSO), in accordance with the Protocol Deviation Guidance Document. Important protocol deviations are defined in the protocol deviation guidance document. The last approved version of protocol deviation guidance will be finalized before the database lock. The trial team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable subjects throughout the trial, adjusting the deviation criteria as seems appropriate.

Protocol deviation data will be reviewed prior to database lock and important deviations with an impact on efficacy leading to the elimination of subjects from the PP will be identified. The PP must be finalized at the blinded data review meeting (or earlier), prior to database lock.

The number of subjects with Important protocol deviations will be summarized in the ITT by category of violation and by treatment group including subset of Important protocol deviations leading to exclusion from the PP. Site level protocol deviations will be summarized as individual subject level protocol deviations for subjects at the impacted site. All protocol deviations will also be listed using the ITT.

12.5 Efficacy Analysis

12.5.1 Hypothesis Testing Strategy

The objective of the primary efficacy analysis will be to evaluate the efficacy of C21 versus placebo as add on to SoC in subjects with COVID-19 by comparing the all-cause mortality at Day 60. The aim of the efficacy analysis is to demonstrate superiority of C21 over placebo.

The null and alternative hypotheses used to evaluate the efficacy for the primary endpoint are to evaluate the difference in time to all-cause mortality up to study follow-up Day 60 between C21 ($S_1(t)$, survival distribution for C21 over time t) and placebo ($S_2(t)$, survival distribution for placebo over time t).

Null hypothesis i.e. no difference in survival up to Day 60 between the two groups:

$$H_0: S_1(t) = S_2(t)$$

Alternative hypothesis i.e. difference in survival up to Day 60 between the two groups :

$$H_1: S_1(t) \neq S_2(t)$$

The overall 2-sided significance level of 5% will be applied to the primary endpoint and the 2-sided p-value obtained from a log-rank test presented in the outputs.

Analysis of the key secondary endpoints will be performed using a hierarchical testing procedure as defined in Section 12.0. All tests for the key and non-key secondary endpoints will be at the 2-sided significance level of 5% and testing the null hypotheses that there is no difference between C21 and placebo, against the alternative hypothesis that C21 is better than placebo. Efficacy of C21 in comparison to Placebo with respect to the key secondary endpoints will be demonstrated only if efficacy is demonstrated in the primary endpoint otherwise these endpoints will be exploratory only.

12.5.2 Primary Estimand

The estimand of interest is all-cause mortality up to Day 60 defined as the time to day of death from any cause assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or important protocol deviations according to the treatment policy, with subjects with no confirmed death before or at Day 60 being censored at day of withdrawal/Day 60 follow-up (refer to Appendix 1).

Intercurrent events will be handled according to the treatment policy strategy. Treatment policy strategy is defined as the strategy that considers "The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs" (See ICH E9 R1 addendum). All scheduled scores of clinical status will be considered for the analysis, even if collected after the occurrence of intercurrent events of (1) discontinuing IMP, (2) returning to initial treatment and/or (3) initiating a new treatment.

12.5.2.1 Imputation Methods

Missing data will not be imputed for the primary estimand.

12.5.2.2 Primary Analysis

All-cause mortality at Day 60 will be defined as time to day of death from any cause within Day 1 to Day 60 follow-up (refer to Section 10.11). All-cause mortality will be estimated using the Kaplan-Meier methodology where subjects in this analysis without the event will be censored at Day 60 follow-up. Withdrawn subjects without the event will be censored at day of discontinuation (this assumes the censoring is non-informative).

Treatment groups will be compared using a stratified log-rank test adjusting for treatment, actual baseline disease severity and region. The p-value from the stratified log-rank will be presented. The size of the treatment effect will be estimated as a hazard ratio, obtained using a Cox proportional hazards regression model, and the Cox regression model will include a factor for randomized treatment, baseline disease severity and region. The estimated Hazard Ratio comparing C21 to Placebo will be presented together with the corresponding 95% CI (based on Wald test). A Kaplan-Meier plot of time to all-cause mortality will also be produced.

12.5.2.3 Sensitivity Analyses

1. Subjects with any important protocol deviations (as defined in Section 12.4) that impact efficacy, who prematurely discontinue IMP will be excluded from the analysis. In the primary analysis, subjects with important protocol deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect. Additionally, subjects withdrawn from treatment due to patient decision may be excluded. For subjects in the PP, the analysis approach as described in Section 12.5.2.2 for primary analysis will be followed.

2. The proportion of deaths before or at Day 60 between treatment groups will be compared using a logistic regression model adjusting for randomized treatment, actual baseline disease severity and region as per Appendix 2 on the ITT. Subjects with no confirmed death or missing data due to premature withdrawal will have missing data imputed as per Section 10.19.2. The number of deaths at Day 60, the adjusted proportions as calculated from Ge et al., 2011, and the associated statistics (treatment difference (C21-Placebo), SE and CI) will also be presented.

3. Sensitivity to IMP discontinuation: No analysis will be performed to assess the impact of IMP discontinuation. Subjects who prematurely discontinue due to subject decision up to Day 11 will be excluded from the PP set since this is equivalent to less than 80% compliance.

12.5.2.4 Supplementary Analyses

Additional analyses examining the consistency of the intervention effect in the following subgroups using the ITT will be performed. A forest plot and repeat of the analysis as per Section 12.5.2 in the following subgroups will be presented:

- Age group: <65 vs ≥65 years
- Sex: female vs male
- Actual baseline disease severity (8-point ordinal scale 5 or 6 at Day 1)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (Europe, Rest of the World)
- Presence of risk factors for severe COVID-19 (Yes, No)

The subgroup categories may be redefined prior to unblinding the study due to the following reasons:

- If the number of subjects is too small (less than 10% of the ITT population) within a subgroup then only the categories with >10% of subjects will be presented in the output.
- If other subgroups appear to be of interest (for example the medications used as SOC) they will be included in the summary.

12.5.3 Key Secondary Estimands and Multiplicity

The key secondary endpoints will be tested in a hierarchical order following the test of the primary endpoint (see Section 12.0).

Other secondary endpoints will be tested independently without adjustment for multiple tests.

ITT will be used for all key secondary endpoint. Subjects will be included in analyses as randomized. The key secondary endpoints are the time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure at Day 15, and the proportion of subjects discharged and free of supplemental oxygen at Day 15.

12.5.3.1 Missing data

Imputation of data due to intercurrent events (treatment discontinuation due to lack of efficacy, occurrence of important protocol deviation, rescue therapy) will not be performed. Subjects who die will have their missing data set as non-responders in the relevant analysis for all time points of interest following the date of death.

Subjects who discontinue the trial for reasons other than death will have their data multiply imputed as per Section 10.19.1. It is anticipated that missing data will be due to discharged subjects not returning for subsequent scheduled visits, or a worsening of clinical status such that the subject can no longer participate in the trial, or due to missing follow-up visits.

The missing data pattern for the adjusted 8-point ordinal scale will be summarized and a distribution plot will be used to represent the pattern of missing data for the adjusted 8-point ordinal scale showing the proportion of missing data each day per treatment group.

12.5.3.2 Time to Sustained Hospital Discharge

Time to sustained hospital discharge, will be defined as time to discharge after which no re-hospitalizations due to COVID-19 occur. Please refer to Section 10.12 for further details on this calculation.

Treatment groups will be compared using a stratified log-rank test adjusting for treatment, actual baseline disease severity and region. The size of the treatment effect will be estimated as a hazard ratio, obtained using a Cox proportional hazards regression model and the Cox regression model will include a factor for

randomized treatment, baseline disease severity and region. The estimated hazard ratios for each treatment group will be presented together with the corresponding 95% CI (based on Wald test).

Analysis will be illustrated using a Kaplan-Meier plot and the median time to hospital discharge will be estimated with 95% CIs for each treatment group. Subjects who die prior to Day 60 will be censored at Day 60 and trial withdrawals prior to Day 60 due to other causes than death without fulfilling the event will be censored at day of withdrawal. Subjects still in trial but not discharged from hospital at Day 60 will be censored at their Day 60 trial visit.

12.5.3.3 Oxygen Supplemental Free Days up to Day 29

Oxygen supplemental free days up to Day 29 will be defined as the number days for each subject with a score of ≤4 and no use of COVID-19 related supplemental oxygen. Refer to Section 10.13 for the derivation of number of oxygen free days.

Subjects who die prior to Day 29 will be given a value of -1 days in the analysis. Subjects who withdraw from the trial prior to Day 29 and have missing data will have their data multiply imputed as per Section 10.19.1. Subjects who chronically used supplemental oxygen prior to their COVID-19 illness will be considered oxygen free when they return to the same level of oxygen support they had been using prior to COVID-19.

Treatment groups will be compared using the Wilcoxon rank-sum test (using p-values) and the treatment difference will be expressed as the Hodges-Lehmann difference in median number of days with 95% CIs. All collected data post treatment will be used. Summary statistics for the number of oxygen free days will also be presented for each treatment group. A cumulative distribution plot of the number of oxygen free days by treatment arm will also be produced.

12.5.3.4 Subjects Free of Respiratory Failure at Day 15

Subjects free of respiratory failure is defined as subject with an ordinal scale score of ≤5 at Day 15. A subject is considered a responder for this endpoint if they have a value of ≤5 at Day 15.

Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region (as described in Appendix 2). Missing data due to trial withdrawals will be multiply imputed as per Section 10.19.1. Subjects who die prior to Day 15 will be considered non-responders in the analysis. The adjusted proportions as calculated from Ge et al., 2011 and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

12.5.3.5 Subjects discharged and free of supplemental oxygen at Day 15

For this endpoint a subject will be considered a responder in the analysis if the subject has a score of ≤2 on the ordinal scale and they are free of supplemental oxygen use at Day 15. Refer to Section 10.10 for details on the classification of subjects as free of supplemental oxygen use at a visit.

Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region (as described in Appendix 2). Missing data due to trial withdrawals will be multiply imputed as per Section 10.19.1. Subjects who die prior to Day 15 will be considered non-responders in the analysis. The adjusted proportions as calculated from Ge et al., 2011 and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

12.5.3.6 Sensitivity Analyses

In order to test the assumptions underpinning the key secondary endpoint analysis the following sensitivity analysis will be performed.

Time to sustained hospital discharge

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Repeat of the analysis in Section 12.5.3.2 on the ITT where non-COVID-19 related re-admissions are treated as re-admissions due to COVID-19 in the analysis and missing data will be imputed using multiple imputation as described in Section 10.19.1. The median time to sustained discharge will be estimated for each imputed dataset and the average value across each imputed dataset will be presented.

Oxygen Supplemental Free Days up to Day 29

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

4) An ANOVA model will be fitted for the number of days oxygen free as a response and actual baseline ordinal scale, region and treatment group as factors in the model. This model will be implemented on the imputed datasets as per Section 10.19.1 with the LS means and SEs from the ANOVA models combined using Rubin's Rule (Rubin, 1987).

Subject free of Respiratory Failure at Day 15

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

Subjects discharged and free of supplemental oxygen at day 15

1) Repeated on the PP to assess the impact of important protocol deviations related to efficacy on this endpoint.

2) Tipping point analysis for the impact of premature trial discontinuation as described in Section 10.19.3.

3) Worst Case imputation as per Section 10.19.4.

12.5.3.7 Supplementary Analyses

Additional analyses examining the consistency of the intervention effect for the key secondary endpoints will be performed for the subgroups as per Section 12.5.2.4 using the ITT.

12.5.4 Other Secondary Endpoints

Other secondary endpoints assessing proportion of subjects will be compared using similar logistic regression models as described in Appendix 2 with the treatment effect expressed as a difference in proportions. Difference in proportions by treatment (intervention – placebo) will be estimated and 95% CI will be provided. Death prior to endpoint readout will be handled as worst case, that is subject will be assumed to be in mechanical ventilator need, or to be in oxygen need, or not to have fulfilled an improvement of 1 or 2 units. Subjects in ventilator need at readout will be considered in oxygen need. Unless otherwise specified missing data will not be multiply imputed. These secondary endpoints include:

1) Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29. Missing data will be imputed as per Section 10.19.1.

2) Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, ECMO or supplemental oxygen use at Days 8, 15, 22, 29 and 60. Missing data will be imputed as per Section 10.19.1.

3) Proportions of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60. This will be based on the complete case (where deaths are considered in category 8 following date of death). This will be the actual recorded 8-point ordinal scale and not the adjusted scale. This analysis will be descriptive only.

4) Proportions of subjects in each category of the adjusted 8-point ordinal scale at Days 8, 15, 22, 29 and 60. This will be based on the average of values from each imputed dataset created per the analysis in Section 10.19.1.

5) Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60. Deaths will be considered in ICU following date of death. Only documented ICU stay will be considered. Subjects with no documented ICU stay will be included as 0 days.

6) Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60. Missing data will be imputed as per Section 10.19.1.

7) Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60. This data will be imputed as per Section 10.19.1.

Respiratory failure free days up to Day 60 (refer to Section 10.14) will be analyzed as using a Wilcoxon rank-sum test per the key secondary endpoint oxygen supplemental free days up to Day 29.

All-cause mortality up to Days 8, 15, 22 and 29 will be presented. The proportion dead and censored at these timepoints will be calculated.

Endpoints assessing duration of event will be compared between treatments using the Wilcoxon rank sum test. These endpoints are:

1) Duration of hospitalization, including re-hospitalization, up to Day 60 (see Section 10.15).

2) Duration of hospitalization up to Day 60 including re-hospitalization for any reason (COVID-19 and non-COVID-19) and missing data will be imputed using multiple imputation (see Section 10.15 and 10.19.1).

3) Duration of intensive care unit stay, including re-admission, up to Day 60 (see Section 10.16).

4) Duration of invasive mechanical ventilation/ECMO use, up to Day 60 (see Section 10.17).

The change from baseline in SpO_2/FiO_2 at Day 15 will be compared between treatment groups with analysis of covariance (ANCOVA) models with treatment, baseline disease severity, and region as factors, and baseline SpO_2/FiO_2 as a covariate. The adjusted mean difference between treatments will be given together with 95% CIs and associated 2-sided p-value. For information on the assignment of values of FiO_2 for use in the calculation of this ratio refer to Section 10.18. Only subjects with baseline and Day 15 data such that this ratio can be calculated will be included in the analysis.

All secondary endpoints will be assessed on the ITT population.

12.5.5 Exploratory Endpoint Analyses

The change from baseline in CRP and LDH at Day 15 will be compared between treatment groups using an ANCOVA model. Model for CRP and LDH will be multiplicative. CRP and LDH data for all visits will be log-transformed prior to the analysis and the change from baseline for CRP and LDH at each visit will be expressed as a baseline ratio in the analysis. This baseline ratio (log(CRP/LDH at Day 15/Baseline CRP/LDH) will be compared with ANCOVA models adjusting for treatment, baseline disease severity and region as factors and log-transformed baseline CRP or LDH as a covariate.

No imputation for missing data will be performed for exploratory endpoints. The analysis will be performed on the ITT population. The result will then be back-transformed to the linear scale. The back-transformed

geometric mean for both treatment groups as well as the geometric mean ratio (C21 vs Placebo) will be reported together with the 95% confidence intervals. The 2-sided p-value will be presented.

12.6 Safety Analyses

12.6.1 Adverse Events

All AEs will be coded using MedDRA Version 24.0 or later. A TEAE is defined in Section 10.6. Only TEAEs will be included in AE summaries unless otherwise specified. All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed. All AE summary tables will be provided for each treatment and total group in the SS.

All AE summaries will include the number and percentage of subjects in each category. For the calculation of the incidence of events, subjects will only be counted once within the events. For summaries and PT, subjects will be counted once per unique PT and SOC. The number of events in each category will also be presented. For summaries by SOC and PT tables should be sorted in descending order of SOC and then PT by subject counts in the total group.

An overall summary of treatment-emergent adverse events will be presented for the following categories:

- Any TEAEs
- Any Serious Adverse events (SAE)
- Severe TEAEs
- Related TEAEs
- TEAEs pattern (continuous, intermittent, single event)
- TEAEs leading to discontinuation of IMP
- TEAEs leading to trial withdrawal
- TEAE with outcome of death (events with outcome of Fatal on the AE CRF page)

The risk difference between treatments will be calculated for the above categories (except for TEAEs patterns) for the comparison of treatment groups and will be presented together with the 95% Wald asymptotic CI for this risk difference. Risk difference will also be presented for selected SOC and PT if deemed of interest prior to lock.

In addition, the following summaries by SOC and PT will be produced:

- TEAEs
- SAE
- Related TEAEs
- Related SAEs
- Severe TEAEs
- TEAEs leading to discontinuation of IMP
- TEAEs leading to trial withdrawal
- AEs leading to death
- Related AEs leading to death
- TEAEs occurring in 5% of subjects (based on PT) in any treatment arm
- Non-Serious TEAEs occurring in 5% of subjects (based on PT) in any treatment arm

A tabulation of TEAEs, categorized by relationship to IMP, will also be presented. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that SOC or PT. Then the relationship to IMP is dichotomized into related or not related as defined in Section 10.6.

A summary of events reported, categorized by severity (mild, moderate or severe as recorded on the AE CRF page), will also be provided. Subjects with multiple events within a particular body system or PT will be counted under the category of their most severe event within that body system or PT.

A further tabulation presenting the preferred terms for the events in descending order of frequency for the treatment group will also be presented.

Listing of AEs leading to death, IMP discontinuation, trial discontinuation and SAEs will be provided. If a subject has missing severity or seriousness in the database they will be treated as worst-case i.e. severe and serious respectively.

12.6.2 Deaths and Serious Adverse Events

Death, SAEs, and IMP-related SAEs will be summarized as in Section 12.6.1. Tabulations will be provided by SOC and PT and listings will be prepared for SAES and AEs leading to death.

12.6.3 Laboratory Data

Laboratory test results will be reported in International System of Units (SI) units. Additionally, summaries will be present for parameters in US units. Only central lab data will be included in the table summaries.

Laboratory values and change from baseline will be summarized using descriptive statistics by time point and treatment group. Laboratory assessments will be grouped for summary as shown in Table 5.

Standard ranges from the central laboratory will be used for the laboratory analysis. The assessment as to if a lab test is low, high, normal as applicable will be derived using the standard ranges for central lab data.

Shift tables of the post-baseline value to high, low, normal will be presented by treatment group, reference range and time point. For categorical urinalysis parameters shift tables will present shifts to normal and abnormal values. Additionally, plots showing the shift from baseline to the maximum/minimum post-baseline value will be presented.

Positive pregnancy results and dip-stick urinalysis results will be provided in a listing.

Table 5. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count (thrombocytic particle concentration) Hemoglobin Hematocrit (erythrocyte volume fraction) Mean corpuscular volume (MCV)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen (BUN) Glucose, fasting Potassium Sodium	Aspartate transaminase (AST) Alanine transferase (ALT) Alkaline phosphatase (ALP) Albumin

Laboratory Tests	Parameters	
	Calcium Ferritin Prothrombin time (PT) International Normalized Ratio (INR) activated partial thromboplastin time (aPTT)	Total and direct bilirubin Serum creatinine eGFR CRP LDH
Routine urinalysis	• pH, glucose, protein, ketones, bilirubin, urobilinogen, and specific gravity by dipstick • Microscopic examination (per investigator judgment)	
Pregnancy testing	• Highly sensitive urine or serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)	

12.6.4 Vital Signs

Observed values and change from baseline in vital signs will be summarized by time point and treatment group in the SS using descriptive statistics. Parameters to be summarized are body temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Systolic and diastolic blood pressure will have three readings per visit, the average of the three readings will be used as the analysis value for the visit (note if any of the three readings are missing, the average of non-missing readings will be used).

Body temperature can be measured in degree Celsius or Fahrenheit. In order to summarize body temperature by descriptive statistics, body temperature collected in Fahrenheit will be converted to Celsius prior to the analysis.

Vital signs will be listed in the SS.

12.6.5 Physical Examinations, ECGs, and Other Observations Related to Safety

The physical examination system will be summarized as “normal”, “abnormal” with sub category for abnormal events that are clinically significant and the number and percentages of subjects in each category by body system will be presented by time point and treatment group in SS. The assessment of the exam is as reported in the Physical Examination (Body System) CRF page. All physical examination data will be listed.

ECG will only be performed at screening and unscheduled visits. ECG will be summarized for screening, unscheduled visits and “any post-baseline assessment” by treatment group in the SS.

12.7 Pharmacokinetics Analyses

All C21 plasma concentration data collected in this trial may be included in population PK and population PK/PD analyses with the objective of exploring the impact of covariates (e.g., body weight and age) on the PK of C21, or the relationship between the C21 exposure and selected efficacy and safety endpoints. If the PK population is not sufficient for analysis data will be listed only.

Blood PK samples will be collected before the first IMP administration (pre-dose) and 30 minutes, 1, 2, 3, 4, and 6 hours after the first IMP administration. Any population PK and population PK/PD analyses will be reported separately. Due to the unblinding nature of the data, PK analyses will be conducted after unblinding of the trial.

12.7.1 Pharmacokinetic Concentrations

Plasma C21 concentrations below the quantifiable limit (BQL) will be set to ½ the lower limit of quantification (LLOQ) in the computation of mean concentration values. Descriptive statistics (number of subjects,

arithmetic mean, geometric mean, standard deviation, coefficient of variation of the geometric mean, median, minimum, and maximum) will summarize the plasma concentrations by C21 at pre-dose, 30 minutes, 1, 2, 3, 4 and 6 hours post treatment. If 50% of the subjects at a given time point have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum, with the exception of maximum all other statistics will be missing. A figure displaying the mean plasma concentrations over time will be produced.

12.7.2 Pharmacokinetic Parameters

The plasma C21 concentration data will be analyzed by non-compartmental methods with WinNonlin® (WNL) version 8.1 or higher unless stated otherwise and the following parameters will be derived and summarized:

- Cmax – Observed maximum plasma concentration of C21, expressed in concentration units.
- t_{max} – Time to reach C_{max} following first dose of IMP, expressed in time units. If C_{max} occurs at more than one time point t_{max} will be assigned to the first occurrence of C_{max}.
- $AUC_{(0-6)}$ – Area under the plasma concentration curve from time zero to 6 hours. The below conditions will be followed:
    - Actual time will be used for calculating $AUC_{(0-6)}$
    - If the 6 hour sample was not taken then $AUC_{(0-6)}$ will not be calculated
    - $AUC_{(0-6)}$ will be calculated by WNL using extrapolation to actual time when there is a valid λ_z and the 24 hour sample is BQL and the concentrations thereafter are also BQL.
- $AUC_{(0-inf)}$ – Area under the plasma concentration-time curve from time zero extrapolated to infinity. Adjusted r^2 for $t_{1/2}$ greater than 0.8 and AUC%Extrap ≤ 20% are required to obtain a reliable estimation of $AUC_{(0-inf)}$. $AUC_{(0-inf)}$ will be included in analysis/summaries only if these two criteria are met.
- AUC_{last} – Area under the plasma concentration curve from time zero to the last quantifiable concentration.
- $t_{1/2}$ – Apparent terminal half-life, expressed in time units. Adjusted r^2 greater than 0.8 is required to obtain a reliable $t_{1/2}$. $t_{1/2}$ will be included in analysis/summaries only if this regression criteria is met (all values will be listed).
- C6 – Actual plasma concentration of C21 at 6 hours after IMP administration (C6 will be analyzed using SAS® version 9.4 or higher)

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be used to summarize the calculated PK parameters by treatment. For t_{max}, only median, min and max will be presented.

AUCs will be calculated using linear up/ log down (or the linear-log trapezoidal method). The linear trapezoidal method will be employed while concentrations are increasing up to t_{max}. The logarithmic trapezoidal method will be employed after t_{max} while concentrations are decreasing. The minimum requirement for calculation of AUCs will be three consecutive plasma concentrations above the LLOQ and at least one following C_{max}.

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BQL	Below the quantifiable limit
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extra Corporeal Membrane Oxygenation
EWD	Early Withdrawal
FiO_2	Fraction of Inspired Oxygen
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention-to-Treat Analysis Set
IXRS	Interactive Web/Voice Response System
LDH	Lactate dehydrogenase
LLOQ	Lower Limit of Quantification
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PP	Per Protocol Analysis Set
PSO	PRA/ICON system of record
PTs	Preferred Terms
SAP	Statistical Analysis Plan

SAE	Serious Adverse Event
SE	Standard Error
SD	Standard Deviation
SI	System of Unit
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SpO_2	Peripheral Capillary Oxygen Saturation
TEAE	Treatment-Emergent Adverse Event
WHODRUG	World Health Organization Drug Dictionary
WNL	WinNonLin

Appendix 1: Estimand Attributes

Table 6: Trial Endpoints and Estimands

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Primary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Primary Endpoint: - All-cause mortality up to Day 60					
Time to day of death from any cause	Subjects in the ITT analysis set	C21	All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in time to all-cause mortality at Day 60 and 95% CI	Stratified log-rank test will be used to compare treatments. Hazard Ratios for death with 95% CIs will be estimated using Cox regression to demonstrate the size of the treatment effect. Subjects who do not have the event before or at Day 60 will be censored at the time of withdrawal/Day 60 follow-up in this analysis. A Kaplan-Meier plot will be produced.
Sensitivity Analysis of Primary Estimand for the Primary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set. No missing data will be imputed. 2) As primary except the population level summary will be difference in proportions and 95% CI and estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Subjects with missing data at Day 60 will have data imputed as per Section 10.19.2. **Supplementary Analysis** of Primary Estimand for the Primary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.2.4). No missing data will be imputed.					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Time to sustained hospital discharge up to Day 60					
The first occurrence of a score of 2 or below whereafter the score stays ≤2 for the remainder of the 60 days trial period	Subjects in the ITT analysis set	C21	Deaths will not be treated as missing data. They will be considered censored at Day 60 (i.e. worst case) in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in median time to discharge and 95% CI	Stratified log-rank test. Kaplan-Meier difference in median time to sustained hospital discharge with 95% CIs will be estimated. Subjects who do not have the event before or at Day 60 will be censored at last day in study or day 60 if completing the study.
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except all re-admissions (COVID-19 and non-COVID-19) will be included. 3) As primary except missing data will be imputed as per Section 10.19.1. **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Supplemental oxygen free days up to Day 29					
The number of days between Day 1 and Day 29 with a score of ≤4 on the 8-point ordinal scale and with no documented use of COVID-19 related supplemental oxygen	Subjects in the ITT analysis set	C21	Deaths occurring before Day 29 will not be treated as missing data. They will be considered with -1 days in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in median number of days without supplementary oxygen and 95% CI	The Hodges-Lehmann median estimated of the difference in days between treatments with 95% CIs. Missing data will be imputed using multiple imputation (refer to Section 10.19.1)
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation 4) As primary except the analysis will us an ANOVA model **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15					
Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5 at Day 15	Subjects in the ITT analysis set	C21	Deaths occurring before Day 15 will not be treated as missing data. They will be considered as not free of respiratory failure in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in proportions and 95% CI	Estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Missing data due to subject discontinuations from the trial will be imputed using multiple imputation (refer to Section 10.19.1).
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of in interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Estimand					Analysis
Variable of Interest	**Population**	**Treatment of Interest**	**Intercurrent Events**	**Population-level summary**	
Secondary Objective: - To evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19					
Key Secondary Endpoint: - Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15					
The proportion of subjects with a score of ≤2 on the 8-point ordinal scale and free of COVID-19 related supplemental oxygen use at Day 15	Subjects in the ITT analysis set	C21	Deaths occurring before Day 15 will not be treated as missing data. They will be considered as not discharged in the analysis. All other intercurrent events will adopt a treatment policy i.e. the value of the variable of interest is used regardless if an intercurrent event occurs.	Difference in proportions and 95% CI	Estimated difference will be calculated using a weighted estimator based on a logistic regression model. The Standard Error for the difference and the 95% CI will be calculated via the delta method. Missing data will be imputed using multiple imputation (refer to Section 10.19.1)
Sensitivity Analysis of Primary Estimand for the Key Secondary Endpoint: 1) As primary except population of interest will be the Per Protocol Analysis Set 2) As primary except the impact of missing data will be explored using a tipping point analysis 3) As primary except missing data will be imputed using Worst Case imputation **Supplementary Analysis** of Primary Estimand for the Key Secondary Endpoint: 1) As primary expect the analysis will be restricted to subgroups of interest (see Section 12.5.3.7).					

Appendix 2: Logistic Regression for Analysis

As a sensitivity analysis for the primary endpoint and as the primary analysis for select key secondary endpoints, the proportion of responders between treatment groups will be compared using a logistic regression model adjusting for randomized treatment, actual baseline disease severity and region. The Fisher scoring algorithm will be used for maximum likelihood estimation of the regression parameters and the covariance matrix.

The estimated difference between treatments will be calculated using a weighted estimator for the risk difference. The delta method will be used to calculate the standard error for this difference and the associated 95% CI (Ge et al. 2011).

The risk difference is calculated from the fitted logistic regression model as:

$$Difference\ (d) = \sum_{i} \frac{(\hat{P}_{ti} - \hat{P}_{ci})}{n}$$

Where $\hat{P}_{ti}$ and $\hat{P}_{ci}$ are the i^{th} elements of

$$\hat{P}_t = logit^{-1}(X_t b)$$
$$\hat{P}_c = logit^{-1}(X_c b)$$

n is the number of subjects in the analysis, b is the maximum likelihood estimate of the regression coefficients from the fitted logistic regression model, X is the covariate matrix of the parameter estimates, X_t is a new covariate matrix from X adjusting the column corresponding to treatment so all subjects are treated, X_c is the new covariate matrix from X adjusting the column corresponding to treatment so all subjects are in the control. $\hat{P}_{ti}$ is the estimated probability of response to treatment for subject i and $\hat{P}_{ci}$ is the estimated probability of response to control for subject i.

The delta method to calculate the standard error and associated CI is as follows:

$$d_t = \frac{(A_t' X_t)}{n}$$
$$d_c = \frac{(A_c' X_c)}{n}$$
$$SE(d) = \sqrt{d_t V d_t' + d_c V d_c' - 2 d_c V d_t'}$$
$$CI\ for\ the\ estimation = d \pm z_{(1-\frac{\alpha}{2})}\, SE(d)$$

Where V is the estimated variance-covariance matrix from the fitted logistic regression and A_t and A_c are the vectors defined as:

$$A_{ti} = \hat{P}_{ti}(1 - \hat{P}_{ti})$$
$$A_{ci} = \hat{P}_{ci}(1 - \hat{P}_{ci})$$

Appendix 3: Imputation of FiO_2 values

If the value of FiO_2 is missing when the type of low flow device and oxygen flow is given, the below values will be used as the value of FiO_2 in the analysis. For example if a subject at a visit has a low flow device type of "Open Mask" with oxygen flow of 5 L/min, for analysis purposes a value of 40(%) for FiO_2 will be used.

It should be noted that sites are permitted to enter a range of values. For example if a site states the subject is on a low flow nasal cannula with oxygen flow of 3, the site can enter a range of FiO_2 from 28 to 36. No adjustments will be made in the analysis for site entered values to align with the below literature. Sites are also permitted to enter values that are outside the values presented in the reference tables (for example nasal cannula > 15 L/min).

- **Low Flow Nasal Cannula (Simon et al., 2016)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1	24
2	28
3	32
4	36
5	40
6-15	44

- **Low Flow Open Mask (Simon et al., 2016)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1	24
2	28
3	32
4	36
5	40
6-7	50
8-15	60

- **Venturi Mask (Batool and Garg., 2017)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
2 (blue)	24
4 (white)	28
6 (orange)	31
8 (yellow)	35
10 (red)	40
15 (green)	60

- **Partial Rebreather Mask (Batool and Garg., 2017)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
6	60
8	70
10	80

- **Non-rebreather Mask (MEDEST, 2020)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
10-15 L/min	80-100
Both flaps removed	80-85
One flap removed	85-90
Both flaps in place	95-100

- **Small Diffuser (OxyMask) (Paul et al., 2009)**

Oxygen Flow (L/min)	Fraction of Inspired Oxygen (%)
1.5	25
2	30
2.5	37
3	42
5	58
10	74
15	80

Appendix 4: Blinded Data Review Meeting Specification

Details on which important Protocol deviations will lead to exclusion from the PP and other analysis considerations that must be discussed in a blinded manner will be documented in the "VCRC2108-C21008 Blinded Data Review Meeting Specification_v1.0".

VCRC2108-C21008
Blinded Data Review

Appendix 5: Endpoint Derivation Details

Endpoint	Calculation	Handling of Death	Handling of Missing Data
All-Cause Mortality (Primary Analysis)	Date of event is the date of death Subjects without event will be censored at the time of completion/study discontinuation	n/a	n/a
All-Cause Mortality (Sensitivity Analysis including Multiple Imputation)	Proportion of deaths is the number of subjects with an ordinal scale value of 8 at Day 60	n/a	Missing data at Day 60 will be imputed.
Time to Sustained hospital discharge (Primary Analysis)	Date of event is the last date of discharge (for initial hospitalization or re-hospitalization for COVID-19 reasons) as recorded on the hospitalization form for subjects. If a subject has the event and subsequently withdraws (for reasons other than death) the subject will be treated as having the event If subject does not have event prior to completion/discontinuation the subject is censored at date of completion/discharge (for reasons other than death)	Subjects are treated as worst case (Day 60 is value used in analysis)	n/a
Time to Sustained hospital discharge (Sensitivity Analysis including Multiple Imputation)	Date of event is the last date of discharge (for initial hospitalization or re-hospitalization for any reason) as recorded on the hospitalization form for subjects with no missing data. For subjects with missing data, such that the event occurs at an imputed visit (≤2 ordinal scale occurs after which all subsequent visits stay at ≤2), time to sustained discharge will be the relative day of the imputed visit. For subject with Imputed data, if subjects discharges prior to missing data being observed and imputed values indicate the subject stays discharged (≤2), the last date of discharge recorded in the hospitalization form will be used For subjects with no event based on imputed and missing data, subjects will be censored at date of completion/Day 60.	Subjects are treated as worst case (Day 60 is value used in analysis)	Missing data will be multiple imputed
Number of days oxygen free up to Day 29	Sum of all ordinal scale values of 1, 3, 4 up to Day 29	Death treated as -1	Missing data will be multiple imputed

Endpoint	Calculation	Handling of Death	Handling of Missing Data
Free of Respiratory Failure	Responder is defined as having an ordinal scale value of ≤5 at a visit	No special rules (death will be a non-responder as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects discharged from hospital and free of Supplemental Oxygen Use	Responder is defined as have a value of 1 on the adjusted ordinal scale at a visit	No special rules (death will be a non-responder as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects on Non-Invasive Mechanical Ventilation, Invasive Mechanical Ventilation, ECMO or with Supplemental Oxygen Use	Subjects with event has a score of ≥ 5 on the ordinal scale	No special rules (death will be a event as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Subjects needing ICU stay	Subjects who have a record for ICU stay on the hospitalization CRF	Counted as in ICU from date of death	No
Subjects on Invasive or Mechanical Ventilation or ECMO	Subjects with event has a score of ≥ 7 on the ordinal scale	No special rules (death will be a event as will have an ordinal scale value of 8)	Missing data will be multiply imputed
Number of Respiratory Failure free days up to Day 60	Sum of all days where ordinal scale is ≤5 from Day 2 up to Day 29; Day 60. For days between Day 29 and Day 60 refer to Section 10.14.	Days from death treated as respiratory failure	Missing data will be multiply imputed
Duration of hospitalization	Duration: end date of hospitalization-start date of hospitalization +1 Sum all individual hospitalizations and re- hospitalization for COVID-19 together If a subject discontinues trial following discharge for reasons other than death, the duration will be calculated as normal and no additional days added If a subject discontinues prior to discharge 60 days will be used in the analysis	Subjects that die will be treated as in hospital from date of death	N

Endpoint	Calculation	Handling of Death	Handling of Missing Data
Duration of hospitalization (Sensitivity analysis)	Duration: end date of hospitalization-start date of hospitalization +1; Sum all induvial hospitalization (including all re- hospitalization) together If a subject has missing data following date of discharge and imputed values stay ≤2, then subject will not have any further days added to the duration. If subject has missing data following date of discharge and imputed values are >2, the duration of hospitalization will be the sum of the observed durations plus the count of the days where the values are >2. If subject has missing data and was not discharged, if the imputed values indicate no discharge then the subject will have a duration of hospitalization derived as: Day 60/study completion – start date of hospitalization +1 If subject has missing data and was not discharged and imputed values indicate discharge the subject will have a duration of hospitalization derived as: relative day of last ordinal scale value >2 – start date of hospitalization +1. If a subject has impute data indicating further hospitalizations following the initial discharge, the count of the days where the ordinal scale value is >2 will be summed together and added to the duration of the initial hospitalization.	Subjects that die will be treated as in hospital from date of death	Y
Duration of ICU stay	End date of ICU stay -start date +1; sum individual together; discontinues in ICU considered in ICU from day of discontinuation if not in ICU at discharge then no additional days added; no ICU stay a value of 0 used	Subject will be considered in the ICU from the date of death	n/a
Duration of invasive ventilation or ECMO	End date of use-start date of use +1; sum together; discontinue while on, considered on from date of discontinuation; not on and discontinue will not have any other days; subjects with no use be 0	Subject will be considered on ECMO/ from the date of death	n/a