RedHill Biopharma Ltd.

STATISTICAL ANALYSIS PLAN (SAP)

Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2/3 Study, in Adult Subjects Hospitalized with Severe SARS-CoV-2 Positive Pneumonia

Study: ABC-201, NCT04467840

Phase: Phase 2/3

Date: 1 September 2021

Version: 2.0

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Prepared by: Michal Klein

Version Control Page

Version:	Version Date:	Protocol Version	Comments
0.3	9-SEP-2020	version 2.0, 2 September 2020	
1.0	24-JAN-2021	version 4.0, 18 January 2021	Changes following additional protocol amendment
2.0	01-SEP-2021	Version 5.0, 15 April, 2021	Changes following protocol amendment and FDA comments. Changes in numbering and hierarchy of secondary endpoints along with removal of the planned multiplicity adjustment for the secondary endpoints. Structural changes to the document to enhance consistency across endpoints, and adding supportive analyses.

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Study: ABC-201

Date: 1 September 2021

Version: 2.0

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Approved by:	
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
COVID-19	Coronavirus Disease of 2019
DB	Double Blind
ECG	Electrocardiogram
EOS	End of Study
FiO2	Fraction of Inspired Oxygen
ITT	Intention to Treat
LAV	Last Available Value
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
PT	Preferred Term
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
TEAE	Treatment Emergent Adverse Event
TESAE	Serious Treatment Emergent Adverse Event

1 PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for RedHill Biopharma Ltd. study ABC-201 (Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2/3 Study, in Adult Subjects Hospitalized with Severe SARS-CoV-2 Positive Pneumonia), and was written in accordance with SOP 100-60-02 (Statistical Analysis Plan Preparation, Review and Approval, Bioforum's Procedure).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol ABC-201, version 5.0, 15 May 2021.
- Case report forms (CRFs) for Study ABC-201.
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports
- COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry, May 2020.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails. Any deviations from the statistical analyses planned in the protocol will be documented in the SAP and any deviations from the statistical analyses planned in the SAP will be documented in the final clinical study report (CSR).

This SAP describes the statistical analyses as foreseen at the time of early initiation of the study. The SAP may be updated during the study conduct and will be finalized before the final database lock and before breaking the blind of the study.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14.

2.2 Secondary

1. To evaluate change on the WHO Ordinal Scale for Clinical Improvement
2. To evaluate the time to recovery defined by improvement to a score of 3 or less on the WHO Ordinal Scale for Clinical Improvement
3. To evaluate the time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or positive pressure ventilation at baseline
4. To evaluate time to discharge from the hospital
5. To evaluate the proportion of patients requiring intubation and mechanical ventilation by Day 42
6. To evaluate mortality 28 and 42 days post-baseline
7. To evaluate the time to two consecutive negative swabs for SARS-CoV-2 by PCR
8. To evaluate the proportion of patients with two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14
9. To evaluate the proportion of patients, with at least one measurement of fever at baseline (defined as temperature >38.0 C [100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14

2.3 Exploratory

1. To assess the change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) over the treatment period of 14 days
2. To assess the change in lymphocyte count over the treatment period of 14 days
3. To evaluate the time to recovery defined by improvement to a score of 1 or less on the WHO Ordinal Scale for Clinical Improvement
4. To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 7
5. To evaluate time to 50% reduction of supplemental oxygen requirement for the subset of subjects who do not require positive pressure ventilation during the study

2.4 Safety

To assess the safety and tolerability of opaganib administered orally at 500 mg Q 12 hours, for up to 14 days, in patients with severe COVID-19 pneumonia.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a phase 2/3 multi-center randomized, double-blind, parallel arm, placebo controlled study, with an adaptive design that will utilize a futility assessment. The study will be performed worldwide in up to approximately 60 clinical sites.

After informed consent is obtained, patients will enter a screening phase for no more than 3 days, to determine eligibility.

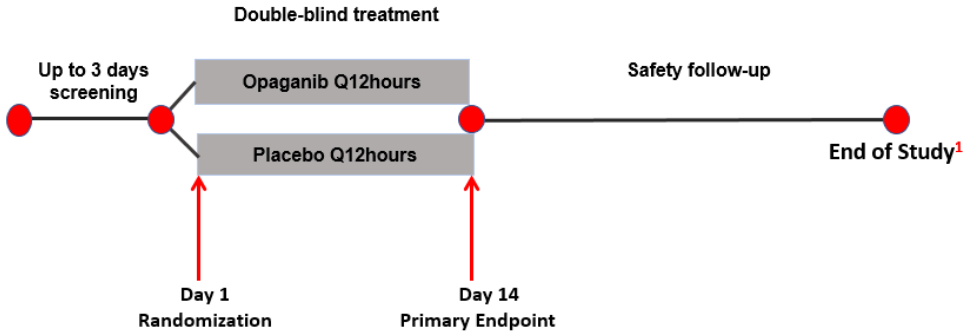
Approximately 464 eligible patients will be randomized and receive either Opaganib added to standard of care, or matching placebo added to standard of care, in a randomization ratio of 1:1. Patients will be stratified based on patients meeting three or more high risk parameters for COVID-19 outcomes at baseline (yes or no) and whether SoC treatment has established efficacy (Yes or No), as specified in section 3.4. Treatment assignments will remain blinded to the patient, investigator and hospital staff, as well as the sponsor.

Study participants will receive either Opaganib 2 x 250 mg capsules (500 mg) every 12 hours, or matching placebo, in addition to standard of care (pharmacological as defined above and/or supportive) at any given institution. Study drug will be administered every day for 14 days (Day 1 to Day 14).

Participants enrolled before the implementation of the 5th protocol amendment, were to be followed up for 28 days after their last dose of study drug, which may occur at Day 14 or after premature study drug discontinuation, based upon patient or physician determination. Starting with protocol v5.0 dated April 15, 2021, all participants enrolled will be followed up for 42 days after first dose of study drug.

The maximum duration of study participation will be up to 45 days (including up to 3 days screening; 14 days of double-blind (DB) treatment and 28 days off-study drug follow-up)/completion of study at Day 42, per final protocol version 5.0).

The study schema is presented below and Visit-specific procedures and assessments are outlined in Table 1.



[1]Participants enrolled before the implementation of the 5th protocol amendment, were to be followed up for 28 days after their last dose of study drug, which may occur at Day 14 or after premature study drug discontinuation, based upon patient or physician determination. Starting with protocol v5.0 dated April 15, 2021, all participants enrolled will be followed up for 42 days after first dose of study drug.

Table 1: Study Procedures and Assessments

Assessments		Study Days															
	-3 *to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Early Term	EOS[12]
ICF signed	X																
Inclusion/exclusion criteria	X	X															
Demographics; medical and surgical history	X	X															
Review concomitant medication(s)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X
Review of adverse events[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO questionnaire[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X
Oxygen flow (L/min)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X
Height and Weight[4]	X																
HbA1c	X																
Pharyngeal viral sample[5]	X	X			X			X			X				X	X	X
12-lead ECG[6]	X	X															
Chest X-ray or CT scan[7]	X																
Serum chemistry[8]	X	X			X			X			X				X		

Hematology (CBC with differential)[9]	X	X			X			X			X				X		
Assessments		Study Days															
	-3 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Early Term	Day 42 F/U[12]
D-dimer, cardiac troponin, CRP, LDH, ferritin[10]	X							X							X		
Urinalysis	X																
Serum or urine pregnancy test[11]	X																

[1] Protocol defined End of Treatment (EOT) occurs on Day 14. For subjects that are discharged from the hospital prior to Day 14, these assessments will be performed at the day of discharge and on a daily basis via phone until Day 14.

[2]daily assessments whilst patient is hospitalized; vital signs = temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter and recording of supplemental oxygen requirement as oxygen flow (L/min) and FiO2 estimate; special attention to the possibility of neuropsychiatric (e.g. anxiety, agitation, insomnia), and cardiopulmonary abnormalities (e.g. tachycardia, palpitations, chest pain, syncope)

[3] For WHO questionnaire (WHO ordinal scale for clinical improvement) -refer to Appendix 1

[4]record weight if even if just by patient estimate

[5] In screening, pharyngeal samples for SARS-CoV-2 PCR to be collected up to 7 days prior to screening. During treatment, samples are collected every 3 days±1 day, other than a confirmatory negative swab at least 24 hours after the first and a Day 14 swab if not confirmed negative prior. Once two confirmed negative swabs are obtained, no further testing need be done. For patients having nasopharyngeal swabs, the same nostril must be used during the study. In countries where regulatory guidelines do not require a negative swab in order for a patient to be discharged from the hospital, reasonable efforts will be made to arrange for testing to be performed either at an external clinic or at the subject's home.

[6] Screening ECG is required. Additionally, all patients will have a 12-lead electrocardiogram prior to the first study drug administration on Day 1 and approximately 3 hours after the first dose. If patients are on monitors (including telemetry or Holter monitors), investigators are encouraged to collect QT interval data.

[7] In screening chest X-ray or CT scan (performed up to 7 days prior to randomization). Chest X-ray or CT scan, lab draws will be at the discretion of the Investigator depending on patient clinical condition

[8] Every 3 days ± 1 day. Serum Chemistries will include at a minimum albumin, alkaline phosphatase, ALT, AST, bicarbonate, total bilirubin, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, sodium, uric acid.

[9] CBC with differential once every 3 days ±1 day

[10] CRP=C-reactive protein, LDH=lactate dehydrogenase, cardiac troponin (Troponin C, I or T, but must be consistent for each patient throughout the study), D-dimer, ferritin, once weekly ±2 days

[11] women of childbearing potential; serum or urine pregnancy test must be negative within 3 days prior to randomization

[12] The follow-up visit should be performed wherever possible but may be performed by telephone if returning to the hospital site is not feasible per Investigator and/or patient decision. Only AEs, WHO questionnaire, concomitant medications and oxygen flow will be collected by telephone. For participants enrolled before the implementation of the 5th protocol amendment, EOS visit was scheduled 28 days after their last dose of study drug, which may occur at Day 14 or after premature study drug discontinuation. Starting with protocol v5.0 dated April 15, 2021, EOS was scheduled at 42 days after first dose of study drug.

* Laboratory values and other diagnostic tests that have been obtained prior to the ICF being signed may be used if within the time allotted for the screening period.

3.2 Study Endpoints

3.2.1 General rules and definitions

3.2.1.1 Definition of Sustained Success

This section describes the general strategy for deriving the set of study endpoints who focus on an improvement/desired health outcome event. These include the primary efficacy endpoint (percentage of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14) and the secondary endpoint #1 (percentage of patients with ≥2 category improvement on the WHO Ordinal Scale for Clinical Improvement by day 14), which aim to compare between study arms the proportion of subjects with favorable type of event (within Day 14 timeframe), and the secondary endpoints #2 (time to recovery), #3 (time to low oxygen flow) and #4 (time to discharge from the hospital), which involve comparison of the time to the occurrence of a favorable event (within specified timeframe).

For the primary endpoint and the secondary endpoints listed above, we will denote the *event* of interest as 'Success', and correspondingly, a 'Failure' *event* will denote subject's status that shows lack of Success.

For all these endpoints, it is required that a Success event will be sustained throughout the study and therefore an initial Success followed by a Failure event occurring by EOS visit will be negated by this Failure and will not be considered Success anymore.

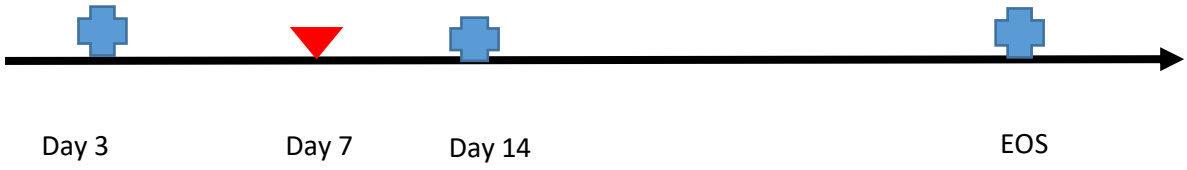
Endpoint-specific Failure events will be listed at the subsequent relevant endpoint definition (section 3.2.1 and 3.2.2, for the primary endpoint and the secondary endpoints, respectively), and in addition, for all the considered endpoints:

- Death during the study will be regarded as Failure event.
- An Early discontinuation from the study (e.g. loss to follow-up, subject withdrawal) will be considered as missing data and subject's ultimate Sustained Success/Failure status will be imputed as follows: the primary analysis of each endpoint will employ worst-case imputation in which subject's ultimate status is ***Failure***. A sensitivity analysis will employ a different imputation strategy where subject's ultimate status will be determined based on ***Observed data while on study (LOCF approach)***. With this approach, a subject who achieved an initial success by the required timeframe and subsequently never experienced a Failure event before early termination of the study

will be considered as Failure in the primary analysis of these endpoints, but as Sustained Success in the sensitivity analysis. A subject whose status just before early termination was already that failed to achieve the required Sustained success, will be imputed as Failure in both the primary and the sensitivity analyses.

For the binary endpoints requiring deriving subject's ultimate Success/Failure response at the end of a specific time-frame (primary endpoint and secondary endpoint #1), a *subject* will be counted as Success if achieved Success by the required timeframe which was also sustained until the end of study visit, and Failure otherwise.

A time to Success endpoint will be defined as the time (in days) from study Day 1 to the earliest day at which a subject achieves a Success that meets the rules defined above. Those subjects who failed to achieve this will be assigned a censored time at the end of the time-frame. For example, for a hypothetical scenario as displayed below, of a subject who had initial success on Day 3 (blue + sign) followed by failure event on Day 7 (red triangle) and later achieved success on Day 14: as no additional failure events were recorded and EOS was performed as planned showing Success as well, we will define this subject as achieved the required Success (maintained through EOS) on Day 14.



3.2.1.2 Biomarker-based endpoints

For the PCR-based secondary and exploratory endpoints and exploratory temperature-based endpoint, Success is not required to be maintained by EOS visit and analysis will be based on observed data while on study only, without imputations. It is acknowledged that as subjects rarely perform laboratory or temperature testing after discharge, these endpoints are expected to provide only limited information. Endpoint-specific derivations will be provided in the relevant sections below (sections 3.2.33.2.4).

3.2.1.3 Handling initiation of a new investigational therapy on a different formal clinical protocol for COVID-19

For all endpoints derivation, If a subject initiates a new investigational therapy on a different formal clinical protocol for COVID-19 during participation in this study, the subject will be followed for true outcomes so that data under the new therapy will be included.

3.2.2 Primary efficacy endpoint

The primary efficacy objective of the study is to evaluate the percentage of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14.

The primary efficacy endpoint will be defined per patient as a binary ("Success"/"Failure") variable, indicating if a subject is no longer requiring supplemental oxygen, for at least 24 hours (the 'Success' event) by treatment Day 14. Any subject reported as not requiring supplemental oxygen on any given study day will be counted as a subject who has not required oxygen for at least 24 hours, based on the instructions to sites to enter the highest oxygen requirement for each study day. Discharge from hospital without supplemental oxygen requirement before or at Day 14 is also considered Success event (note, when discharge occurs exactly on Day 14 and subject is reported requiring supplemental oxygen on day 13, then information on being oxygen-free through the entire discharge date is required to meet Success definition). To note, subjects who are discharged from hospital on supplemental oxygen are expected to be followed up by the study site daily and thus can be considered a success only if for any given study day (prior to Day 14), the highest supplemental oxygen requirement is none.

According to the general approach and rules set in Section 3.2.1.1, a subject is required to achieve a Success by Day 14, that will be maintained throughout EOS (Sustained Success), in order to be counted as Success for the primary endpoint analysis.

The applicable Failure events that can negate initial success events are:

- Resumption of any type of supplemental oxygen.
- Re-admission after discharge from hospital, for supplemental oxygen, for covid-19 related reason.
- Death (occurring by EOS visit).

A blinded review of the adverse event data will be performed to identify re-admissions satisfying failure event per bullet 2 above. If it cannot be determined if AE involved supplemental oxygen for covid-19 related reason or not, a worst-case assumption will be employed, of a Failure event.

Handling of Missing data in determination of Success status will be in accordance to section 3.2.1.1 above.

In addition to the primary endpoint, in order to assess when Sustained Success event occurred, an endpoint of time to no longer requiring supplemental oxygen for at least 24 hours by Day 14 will be calculated as well. This time to event endpoint will be defined in accordance to the approach set in section 3.2.1.1, as the number of days from Day 1 until the earliest day at which a subject reaches Sustained Success, and all subjects with "Failure" status will be assigned a censored time at 14 days. As an example, if a subject reached Sustained Success at Day 4 (that is no failure events occurred between day 4 and EOS visit), time to success will be calculated as 4 days. To note, when partial data in supplemental oxygen records inform that subject is discharged without supplemental oxygen yet the oxygenation status throughout this day up to discharge hour is unknown,

and subject was reported to require supplemental on the previous day, the Success date will be taken as the discharge succeeding day (as only then the 24 hours confirmation can be fulfilled).

3.2.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. **The percentage of patients with ≥2 category improvement on the WHO Ordinal Scale for Clinical Improvement by day 14.**

This endpoint will be defined per subject as a binary ("Success" / "Failure") variable with "Success" indicating that a subject has an improvement of 2 or more on the WHO Ordinal Scale compared to baseline. Patients who have been discharged alive, will be counted as Success, depending on baselines score, as discharge is associated with score<3 (to note, baseline WHO score of 5 is study inclusion criteria). The time frame for this end point is from day 1 until day 14.

The WHO questionnaire (WHO ordinal scale for clinical improvement) –is provided in Appendix 1

According to the general approach and rules set in Section 3.2.1.1, a subject is required to achieve a Success by Day 14, that will be sustained by EOS, in order to be counted as Success for the primary analysis of this endpoint. The applicable Failure events that can negate initial success events are:

- Death (occurring by EOS visit).
- Regression in WHO improvement to less than 2 levels.

Refer to 13.1APPENDIX 1: WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT for the scoring definitions and conventions for inferring WHO improvement in the absence of explicit score.

Handling of Missing data in determination of Success status will be in accordance to section 3.2.1.1 above.

2. **Time to recovery as defined by improvement to a score of 3 or less on the WHO Ordinal Scale for Clinical Improvement**

This time to event endpoint is defined within the time frame of 14 days and will be calculated as the number of days from Day 1 of study medication until the earliest date of score 3 or less on WHO scale – the success event, or Day 14.

For this time to Success endpoint, in accordance with the general approach and rules set in Section 3.2.1.1, a subject is required to achieve a Success by Day 14, that will be sustained by EOS, in order to be counted as Success for the primary analysis of this endpoint. The applicable Failure events that can negate initial success events are:

- Death (occurring by EOS visit).
- Worsening of WHO score to a score of 4 or higher.

Those subjects who will fail to achieve Success within Day 14 will be assigned a censored time at Day 14.

Refer to 13.1APPENDIX 1: WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT for the scoring definitions and conventions for inferring WHO score of 3 (or less) in the absence of explicit score.

Handling of Missing data in determination of Success status will be in accordance to section 3.2.1.1 above.

3. Time to low oxygen flow via low flow nasal cannula or simple face mask from high oxygen flow via high flow nasal cannula, non-rebreather (reservoir) face mask or positive pressure ventilation at baseline

This time to event endpoint, where event of interest is a desired outcome is defined within the time frame of 14 days and will be defined similarly to secondary endpoint #2, where now the event of interest is recording of a low oxygen flow via low flow nasal cannula or simple face mask received before Day 14.

The applicable Failure events to determine Sustained Success status for this endpoint are:

- Re-need of high-flow oxygen, positive pressure ventilation or mechanical ventilation,
- Re-admission after discharge from hospital, for high-flow oxygen, positive pressure ventilation or mechanical ventilation (as will be captured as an SAE),
- Death (occurring by EOS visit).

Identification of a low flow oxygenation will be made through the type of apparatus used. As an inclusion criteria into the study required high flow oxygenation at baseline, all patients will be included in this analysis unless there was a protocol violation of this inclusion criteria and the patient was on low flow nasal cannulas or a simple face mask at the time of randomization (or, conversely, was intubated prior to the first treatment). Specifically, subjects enrolled prior to version 5 of the protocol receiving oxygen via face mask with an oxygen flow of >5L/min, will not be included in this endpoint analysis.

4. Time to discharge from the hospital.

This time to event endpoint where discharge from hospital, the event of interest, is a desired outcome, will be defined similarly to secondary endpoint #2, yet with a time frame of 42 days. To note, the time frame for describing the data is Day 42, however as by 42 days most subjects from both arms are expected to be discharged, treatment effect estimation will be primarily focused within day 14 timeframe.

The applicable Failure events to determine Sustained Success status for this endpoint are:

- Re-admission after discharge from hospital (as captured in AE log) for COVID-19-related reasons. If reason cannot be determined, it will be regarded as COVID-19 related.
- Death (occurring by EOS visit).

5. The percentage of patients requiring intubation and mechanical ventilation by day 42.

This endpoint will be defined per subject as a binary ("Failure" / "Success") variable indicating "Failure" if a subject required intubation and mechanical ventilation ***or died*** before End of safety follow-up period (Day 28 post-last dose of therapy/Day 42 from the first dose, as applicable for the subject, per the protocol amendment under which informed consent was signed).

An early discontinuation from the study (e.g. loss to follow-up, subject withdrawal) or failure to complete the EOS visit, will be considered as missing data and will be handled as follows:

In the primary analysis, a worst-case imputation will be employed so that subject will be considered as ***Failure***.

A sensitivity analysis will employ a different strategy, in which the percentage of patients requiring intubation and mechanical ventilation or death by day 42 will be estimated using time to event analysis, in which subjects early terminating the study before experiencing intubation/failure will be assigned a right-censored Failure time at their last valid observation date (e.g. last oxygen observation date). In addition, for this analysis:

- Patients who experienced intubation/death will be assigned a Failure time equal to the treatment days between Day 1 and their Failure time ("Failure"),
- Patients who successfully completed the study without experiencing intubation/death will be assigned a Right-censored failure time at their End of Study contact date ("Censored").

6. Mortality due to any cause at Days 28 and 42 after baseline

These binary endpoints will be defined per subject as a binary ("Failure" / "Success") variables with "Failure" indicating that a subject had died within 28 treatment days from first dose date or by EOS visit (namely Day 28 post-last dose of therapy/Day 42 from the first dose, as applicable), respectively. "Success" will be assigned for patients known alive at the target time.

Derivation for these mortality endpoints for both the primary and sensitivity analysis will be performed according to the same approach defined for endpoint # 5 above, now with Death as event of interest.

7. **Time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart.**

This endpoint will be defined only for patients who were positive for SARS-Cov-2 by PCR at screening or 7 days prior to screening. According with the note on biomarker-driven endpoints given in Section 1, due to the rarity of PCR testings post discharge, an observed data approach will be utilized in derivation this time to event endpoint where event of interest is a desired outcome which is recording of two consecutive negative swabs for SARS-CoV-2 by PCR by Day 14. Time will be calculated as the number of days from Day 1 of study medication until the first time Success is recorded (the earliest date of the two swabs), and if no success will be recorded, subjects will be censored at the latest PCR test before day 14 date.

8. **The percentage of patients with at least two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14.**

This endpoint will be defined only for patients who were positive for SARS-Cov-2 by PCR at screening or 7 days prior to screening. This PCR-based binary success endpoint will be defined according to Section 1 using the observed data approach. For this purpose, only those patients with at least two post-baseline PCR tests will be analyzed, and subjects will be classified based on testings performed by Day 14 if the results of the latest PCR testing by Day 14 will be classified as Success/Failure, where success is recording of two consecutive negative swabs for SARS-CoV-2 by PCR by Day 14, or not.

9. **The percentage of patients with at least one measurement of fever at baseline (defined as temperature >38.0 C [100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14.**

This endpoint will be defined only for patients who had fever at baseline (i.e at least one measurement of temperature >38.0C [100.4F]), with at least one temperature testing post-baseline. In accordance to Section 1, this binary endpoint will be calculated based on observed data approach This binary endpoint where event of interest is a desired outcome will be defined as Success/Failure based on subject's latest temperature measurement by Day 14, and Success will be assigned if subject was afebrile on this test and Failure otherwise. Death by Day 14 will not be considered Success despite possible previous success.

3.2.4 Exploratory Endpoints

Exploratory endpoints will include:

1. **The changes in systemic markers of inflammation: D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) from baseline at Day 14 for the opaganib arm as compared to the placebo arm.**

2. **The change in lymphocyte count from baseline at Day 14 for the opaganib arm as compared to the placebo arm**.

   The biomarkers above were planned to be collected at Screening visit and then once every 3 days and Day 14 visits. As was noted in Section 1,3.2.1.2 these assessments are mostly available only up to patient's discharge, often before Day 14 visit, and an observed data approach will be utilized. Therefore, a Last Available Value up to and including day 14 (LAVD14) will be calculated and analyzed.

3. **Time to recovery as defined by improvement to a score of 1 or less on the WHO Ordinal Scale for Clinical Improvement for the opaganib arm as compared to the placebo arm**

This time to event endpoint is defined within the time frame of 14 days and will be calculated as the number of days from Day 1 of study medication until the earliest date of score 1 or less on WHO scale – the success event, or Day 14.

For this time to Success endpoint, in accordance with the general approach and rules set in Section 3.2.1.1, a subject is required to achieve a Success by Day 14, that will be sustained by EOS, in order to be counted as Success for the primary analysis of this endpoint.

The applicable Failure events that can negate initial success events are:

- Death (occurring by EOS visit).
- Worsening of WHO score to a score of 2 or higher.

Those subjects who will fail to achieve Success within Day 14 will be assigned a censored time at Day 14.

Because the reality is that follow-up data collected at the EOS visit do not capture the difference between WHO 1 and 2 with regard to all Covid-19 impacted aspects of daily life (i.e. not just need for supplemental oxygen), determining initial success or sustainability of this endpoint for any patient who did not achieve a score of 1 prior to discharge may be impossible, resulting in large amount of missing data. Therefore missing data due to discharge from hospital will be right censored at discharge date and not defined as Failure event. Those subjects who have missing data for identifying discharge will be considered as Failures.

4. **The percentage of patients no longer requiring supplemental oxygen for at least 24 hours by Day 7 for the opaganib arm as compared to the placebo arm.**

This end point will be defined similar to the primary end point within the time frame of 7 days.

5. **Time to 50% reduction of supplemental oxygen requirement for the subset of subjects who do not receive positive pressure ventilation (non-invasive or invasive) at baseline for opaganib arm as compared to the placebo arm.**

This time to event endpoint, where event of interest is a desired outcome is defined within the time frame of 14 days and will be defined similarly to secondary endpoint #2, where now the event of interest is reaching a value of supplemental oxygen, which is at least 50% lower than the baseline value.

The applicable Failure events to determine Sustained Success status for this endpoint are:

- Requirement of supplemental oxygen value which is does not show 50% increase relative to baseline, or, positive pressure ventilation or intubation and mechanical ventilation,
- Re-admission after discharge from hospital, for high-flow oxygen, positive pressure ventilation or intubation and mechanical ventilation (as will be captured as an SAE),
- Death (occurring by EOS visit).

This time to event endpoint is defined for a subset of patients who do not receive positive pressure ventilation (non-invasive or invasive, and met inclusion criteria #3 according to Version 5 of the protocol) at baseline.

3.2.5 Safety Endpoints

The safety and tolerability endpoints will include:

- Treatment Emergent Adverse Events (TEAEs) and serious Adverse events (SAEs)
- Laboratory tests
- vital signs
- ECG

3.3 Sample Size and Power Considerations

It is planned to randomize approximately 464 eligible patients into the double-blind treatment phase, to receive either opaganib added to standard of care (n=232), or matching placebo added to standard of care (n=232). The sample size calculation was based on powering the study with respect to the primary analysis of the primary efficacy endpoint of proportions of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14. It was assumed that the treatment success rate at 14 days in the control arm would be 40% and that opaganib is expected to provide absolute 15% increase of this rate, to a success rate of 55%. A total of 464 subjects provides 90% power to detect the assumed difference in success rate, using chi square test, at a two-sided α=0.05 level of significance. This sample size calculation takes into account a

planned non-binding futility analysis to be performed after at least 135 patients in the study have been evaluated for the primary endpoint.

3.4 Randomization and Blinding

A total of 464 patients will be randomized, using 1:1 assignment ratio and receive either Opaganib added to standard of care (232 patients), or matching placebo added to standard of care (232 patients).

Stratification will be done based on:
1) whether the patients meet three or more high risk parameters for COVID-19 outcomes at baseline (yes or no).

This will be determined by: age at screening ≥60 years, (yes or no); male, (yes or no); HbA1c at screening ≥6.5 or on active treatment with insulin or oral hypoglycemics (yes or no); hypoxemia without commensurate increased work of breathing (yes or no); known underlying chronic lung disease (yes or no); known cardiovascular disease or hypertension (yes or no); BMI ≥ 28.0 kg/m2 (yes or no); known renal disease (yes or no).

2) Whether SoC treatment has established efficacy (yes or no)

Treatment assignments will remain blinded to the patient, investigator and hospital staff, as well as the sponsor.

3.5 Sequence of Planned Analyses

3.5.1 Interim Analyses

One futility analysis when a total of 135 subjects have had day 14 evaluation is planned. The futility criteria will be primarily based on the primary endpoint, and will further involve key clinical secondary endpoints such that futility can only be declared if the primary AND all key secondary endpoints cross the boundary. The analysis will be conducted by an independent unblinded statistician who is charged to reporting to the DMC, who will inform the DMC of the futility outcome: a single statement saying if boundary has or has not been crossed. No unblinded data will be shared in any outcome case. Strict procedures will be employed to maintain the confidentiality of the interim results.. The futility analysis is further detailed in section 5.6.

3.5.2 Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed only after the last patient has completed the study and database have been locked. The randomization codes will not be unblinded until this SAP has been signed and approved. Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

4 ANALYSIS POPULATIONS

This section describes the analysis populations defined for the study.

4.1 Screened

The Screened population will include all subjects who underwent screening, defined by date of informed consent.

4.2 Intention to Treat (ITT)

The ITT population will include all randomized subjects. In this population, treatment will be assigned based upon the treatment to which patients were randomized regardless of which treatment they actually received.

4.3 Modified ITT (mITT)

This population consists of all patients that were randomized and treated with at least one dose (even partial) of study drug.

4.4 Baseline High Flow Treated (BLHF Treated)

This population consists of subset of mITT population who met entry criteria #3 (The patient requires, prior to first dose of study drug, high flow supplemental oxygen or positive pressure ventilation, or is receiving oxygen via non-rebreather or reservoir mask, capable of delivering high concentrations of oxygen). Patients who require mechanical ventilation or no longer require at least high flow supplemental oxygen (as defined in entry criterion #3) prior to receiving the first dose of study drug will not be included in this analysis set.

4.5 Per Protocol (PP)

This Population will consist of subjects that were randomized, treated with at least one dose of study drug who further meet PP Criteria. These criteria will be based on inclusion and exclusion criteria and major protocol violations during the study that may confound the interpretation of the analyses as determined on blinded review by the medical monitor or his designate. A blinded review before database lock will be applied to define this population.

4.6 Safety

The safety population will include all randomized patients who receive at least one dose of study medication.

In the ITT, mITT, BLHF Treated and the PP populations, treatment will be assigned based upon the treatment to which subjects were randomized regardless of which treatment they actually received. In the Safety population, treatment will be assigned based upon the treatment patients actually receive regardless of the treatment to which they were randomized.

5 GENERAL ASPECTS FOR DATA ANALYSIS

5.1 General

The following is a list of general reporting conventions:

1. Descriptive statistics for continuous variables include n (number of non-missing observations), mean, standard deviation (SD), standard error of the mean (SE), median, minimum, and maximum.
2. Means and medians will be reported with 1 more digit than the precision of the captured data. Standard deviations and confidence intervals will be reported at 2 more digits than the precision of the data. Minimum and maximum will be reported to the same level of precision as the original observations.
3. Descriptive statistics for categorical variables will include counts (n) and percentages (%) and will be presented in the form of n (%).
4. Percentages will be reported with 1 decimal place.
5. No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5, then round down; if ≥ 5, then round up.
6. Unless otherwise noted, all statistical analyses will be conducted with a significance level (α) of 0.05 and utilize two-sided testing.
7. All data collected will be presented in the by-subject data listings, sorted by subject and by time point, where appropriate.

If departures from these general conventions are present in the specific evaluation sections of this SAP, then those will take precedence over the above general conventions.

5.2 Specification of Baseline Values

In general, Baseline will be defined for each subject as the last available, valid, non-missing assessment before first study drug dose.

5.3 Multiple Comparisons and Multiplicity

The overall study-wise type I error will be 5%. The non-binding futility analysis does not increase type 1 error probability and thus does not impact final analysis significance level (Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics, November 2019).

The primary endpoint will utilize the overall allowed type 1 error. There is no planned adjustment for multiple comparisons in any secondary or exploratory endpoints analyses and their evaluation will aim at further enhancing the understanding of the beneficial effect of Opaganib.

5.4 Handling Withdrawals and Missing Data

The primary endpoint, the binary secondary efficacy endpoint #1 and the time to event secondary endpoint #2, #3 and #4 are all involving the identification of a Sustained improvement/beneficial event. Early termination from study is considered missing data with regard to determining ultimate Success status in these endpoints and the general strategy for handling it is detailed in section 3.2.1.1, employing a worst-case Failure imputation in the primary analysis along with a 'while on study' observed data approach as a sensitivity analysis. To note, death by EOS visit in the above listed endpoints is not considered Missing data and is counted as Failure event by definition.

Efficacy Secondary endpoints # 5 and #6 are binary endpoints concerning the occurrence of a severe negative-impact health event of interest, by a certain time-point. In both, early termination of study follow-up alive before a Failure event had a chance to occur will be handled via worst-case imputation in the primary analysis along with a sensitivity analysis estimating the cumulative incidence of Failure by a certain time point using time to event methods, where early termination is regarded as right censored Failure time, as defined in Section5

It should be noted that End of Study follow up visit has been defined as 28 days after last dose for subjects enrolled prior to version 5 of the protocol ('Day 28' visit) and as Day 42 after the first dose – following protocol amendment 5. Therefore, subjects should not be considered to have missing day 42 assessment if performed their scheduled 'Day 28' visit as planned.

In this relative short-period study, because the EOS visit is the only scheduled visit after Day 14 visit, it is expected that all completing subjects will have EOS visit, while missing EOS visit will be associated with an Early termination status. It is noted though that missing EOS visit (or missing information in this visit) will bear same application as early termination.

PCR-based and temperature-based secondary efficacy and exploratory endpoints are expected to have high rates of missing data due to discharge from hospital and a strategy to employ 'while on study' observed data will be employed as explained in section 3.2.1.2.

Missing data for exploratory endpoints not covered above (i.e not PCR-based) are defined and handled within the endpoint-specific definition in Section 3.2.4.

Generally, no imputation will be performed for safety endpoints unless stated otherwise in the specific endpoint analysis.

5.5 Study days and visit windows

Throughout this SAP, the following terms and conventions will be applied for this protocol scheduled for of 14 **treatment days** (each includes morning and evening takes) and an overall up to 42 **study days.** Scheduled Visit names are named using the relevant planned **Study day.**

Derived **study** days will be calculated relative to the **Study day 1** date whereas **treatment** days will be derived relative to the **Treatment day 1** date.

Whereas **Study day 1** refers to the date of the *1*st *dose*, for deriving the first treatment day (**Treatment day 1**), refers to the date of when uptake of both 1st morning & evening doses is due, which depends if 1st study dose was a Morning or an Evening administration. The Study day 1 and Treatment day 1 will be equivalent for those subjects enrolled to take their 1 study dose at the Morning but differs for those subjects who due to the pandemic constraints were enrolled to take their first study dose only at the Evening administration, leading to expected completion of 1st treatment day at study day 2. In this later case, Treatment Day 1 date will be equivalent to Study day 2 date. For those randomized subjects who never started study treatment, both study day 1 and treatment day 1 will be referring to the Randomization date.

The efficacy endpoints are based on endpoint-specific **Timeframes**, (detailed in Section 3.2). These timeframes will be defined using **Treatment days**, as defined above. It should be noted that vital signs assessments were also to be taken on study day 15 (the 14'th treatment day), for those subjects who started treatment only at Evening. Summary By-**Treatment day** tables of the efficacy measurements data will be provided .

Listings will include all collected data, and will provide both Study day and Treatment day information. For **by-visit** summaries, assessments at 'Day 1' visit refer to time before first dose of study drug (baseline), and assessments performed on 'Day 2' visit and subsequent visits refer to days after first dose date.

When the EOS visit is included in by-visit summaries, no distinction will be made between those visits completed as scheduled under Version 5 of the protocol and those performed per version 5 protocol.

In case assessments are done at the Early Termination visit, these assessments will be used as data for the scheduled assessment day closest to the early termination time point and as relevant per end point, in case the corresponding data are missing from this assessment day. Generally, measurement taken at unscheduled visits will not be included in by-visit descriptive analyses, however will be otherwise included in 'any time post baseline' analyses and will be included in data listings.

5.6 Futility analysis

One futility analysis when about a total of 135 subjects have had day 14 evaluations is planned.

5.6.1 Outline

The futility analysis will be performed in two steps:

Step 1: primary endpoint analysis

For the primary endpoint, the futility rule is based on performing a statistical test to compare the proportion of **success**, for opaganib versus placebo. The stopping rule boundary for the **primary endpoint** is present in section 5.6.2 below.

In the case that this futility boundary is crossed, sensitivity analyses will be performed on the primary endpoint to ensure that this result is robust, according to specifications provided in Section 5.6.3 below.

If the sensitivity analyses substantiate the futility conclusion with respect to the primary endpoint, then the following step 2 will be performed.

Step 2: key secondary outcomes analysis

In the face of the unpredicted nature of the disease and pandemic situation, it is required that in the case that futility conclusion is reached with regard to the primary endpoint, the final conclusion of study futility will be declared after inspecting key secondary outcomes, as listed below:

1. Time to no longer requiring supplemental oxygen for at least 24 hours (timeframe Day 14)
2. Time to ≥2 category improvement on the WHO Ordinal Scale (timeframe: day 14);
3. Proportion need intubation and mechanical ventilation (timeframe: 14 days)
4. Time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or positive pressure ventilation, if high oxygen flow is not an available option (timeframe Day 14)

Assessed hierarchically, If **ANY** of the observed treatment effects on these endpoints comparing opaganib to placebo is in the **right** direction (beneficial), then study will be concluded as **NOT** futile. If on the other hand all effects are trending in the wrong direction, then the study will be concluded as Futile.

To note, observed effect is regarded as trending in the right direction when **HR>1** for endpoints #1, #2 and #4and when observed % in Opaganib – % in placebo <0 (opaganib numerically need less), for endpoint #2 .

5.6.2 Primary endpoint Futility boundary

The stopping rule for the primary endpoint was chosen so that futility will be recommended if the interim result is trending in the **wrong** direction, and is such that the **conditional probability** of statistically significant result if continue to the end of the study, given interim data so far, and assuming that the future patients will follow the design **40% and 55%** success rates for control and opaganib, respectively, is lower **than 30%.**

The futility stopping rule can be expressed equivalently in terms of:

1. Observed success rate difference: futility boundary will be crossed if placebo has excess of 12.3% success rate over opaganib.
2. The statistical test Z value: futility boundary will be crossed if Z<-1.428.
3. To note, if interim result is such that the futility rule is crossed, the probability for study to turn out to be successful (significant) should continue to the end if the future results will follow the **observed** rates (rather than those hypothesized at design), is almost 0.

The equivalent stopping rules for the primary endpoint are summarized in the following table:

		Futility **stopping rule** (equivalent forms): stop if		
Information at interim	Number of patients	success rate difference (opaganib-placebo)	**Conditional power** (CP) assuming the **design** effect	Z value
135/464=29%	135	Diff<-12.3%	CP <30%	Z<-1.428

The operating characteristics of the plan are presented in terms of false-stopping (risk), and correct-stopping (that is power to stop a futile treatment) probabilities.

Probability to stop at interim	
under H_1 (false-stopping)	under H_0 (correct-stopping)
<0.01%	~8%

5.6.3 Sensitivity analyses for the primary endpoint

Per the protocol and SAP, The primary analysis for the primary endpoint is the Cochran Mantel-Haenzel (CMH) test to compare the proportion of success between the two groups, a stratified test using the study stratification factors as used for randomization, applied on the mITT population. Treatment effect is estimated by the corresponding stratified risk difference. Thus, step 1 of the futility analysis plan will employ the primary analysis specified above. In accordance rules set above if the CMH Z statistic <-1.428 and stratified risk difference<-12.3%, this analysis will indicate futility.

To note, this rule will be employed even if different number than 135 patients are included in analysis.

If the boundary has been crossed then the following sensitivity analyses for the primary endpoint will be performed:

•Repeat the stratified analysis using strata values according to baseline (instead of those known at time of randomization)

•Perform crude analysis: simple risk difference test

•If important baseline imbalance appear, perform adjusted analysis (using logistic regression)..

•Impute missing data as ‘NOT failures’ and repeat the stratified and crude analyses above

•Repeat the stratified and crude analysis without potential outlier site 115 data.

In case in ALL the sensitivity analyses the futility boundary is crossed for the primary endpoint, then it will be regarded as substantiated futility outcome and Step two of outline should be performed, as defined in the outline.

5.6.4 Results dissemination

The independent statistician reporting to the DMC will perform the futility analysis as outlined above. Only a futile/non-futile statement (without unblinded results) will be included in the closed report, that can be passed on as a recommendation to the Sponsor.

Important note: the futility analysis is non-binding such that if boundary is crossed yet other consideration lead to continuation of the trial, it will not impact the study type 1 error.

6 STUDY POPULATION

6.1 General

Study population summaries will be presented by treatment group and overall unless otherwise noted.

6.2 Patient Disposition

The subject disposition will be summarized as follows and presented for each treatment group and overall, unless otherwise specified. Summary will include all screened subjects. The percentages will be calculated from the ITT population, unless otherwise specified.

- The number of all screened subjects (i.e. the number of subjects in the Screened population), presented only for overall group
- The number (%) of subjects who were not eligible for the study (% calculated from the Screened population), including the distribution of reasons for not eligible for the study, presented only for overall group
- The number (%) of subjects screened but not randomized, if applicable (% calculated from the Screened population), presented only for overall group
- The number of randomized subjects (i.e. the number of subjects in the ITT population)
- The number (%) of randomized but not treated subjects, if applicable
- The number (%) of subjects in the Safety population (i.e. treated subjects)
- The number (%) of subjects in the mITT population
- The number (%) of subjects in the BLHF Treated population
- The number (%) of subjects in the PP population
- The number (%) of subjects who completed the study treatment according to protocol
- The number (%) of subjects who discontinued the study treatment prematurely, including the distribution of reasons for premature discontinuation
- The number (%) of subjects who completed the study
- The number (%) of subjects who discontinued the study prematurely, including the distribution of reasons for premature discontinuation

6.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics including the stratification factors will be summarized by treatment group and overall using ITT, mITT and Safety populations. Summaries will be presented with the appropriate descriptive statistics as specified in section 5.1 above.

The following will be provided:

Demographics:

- Age (years) (continuous)
- Sex: Male, Female, Not Specified (categorical)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, (categorical)

- Race: White, American Indian or Alaska native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other (categorical)

Baseline characteristics:

- Smoking status: Never, Former, Current (categorical)
- Weight
- BMI
- Height
- Vital signs including supplemental oxygen requirement
- HBA1C

Stratification factors (categorical):

- Whether SoC treatment has established efficacy (Yes versus No). For both stratification factors, both values used for randomization and those recorded in the eCRF at baseline (possibly corrected/updated) values will be presented.
- High or low risk (i.e meet three or more high risk factors for COVID-19 outcomes) (Yes versus No)

COVID-19 Risk Factors (only values as recorded at eCRF at baseline will be presented):

- age at screening, ≥60 years of age, (yes or no);
- male, (yes or no);
- Diabetes Mellitus status at screening: HbA1c at screening≥6.5 or on active treatment with insulin or oral hypoglycemics (yes or no));
- hypoxemia without commensurate increased work of breathing (yes or no);
- known underlying chronic lung disease (yes or no);
- known cardiovascular disease or hypertension (yes or no);
- BMI ≥ 28.0 kg/m2 (yes or no);
- known renal disease (yes or no).

6.4 **Covid-19 Disease Information**

Disease information will be summarized by treatment group and overall using ITT, mITT, and Safety populations. Summaries will be presented with descriptive statistics as specified in section 5.1 above

- Time from onset of symptoms to Hospitalization (Days)
- Time from onset of symptoms to diagnosis (Days)
- Time from onset of symptoms to randomization (Days)
- Time from diagnosis to hospitalization (Days)
- Time from diagnosis to supplemental oxygen (Days)
- Time from diagnosis to randomization (Days)
- Time from hospitalization to supplemental oxygen (Days)

6.5 Medical and Surgical History

Medical history data will be summarized by treatment group and overall using mITT and Safety populations. All medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with at least one medical history term will be summarized by System Organ Class (SOC) and by Preferred Term (PT) within SOC for each treatment group and overall. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

All medical and surgical history data will be listed.

6.6 Prior Medications

Prior medications will include all recorded medications and supplements a patient was taking during the screening period that were stopped prior to administration of the study drug.

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred terms (PT) from the World Health Organization Drug Dictionary (WHO-DD). Prior medications data will be summarized by treatment group and overall using mITT and Safety populations. The number and percentage of subjects with at least one medication term will be summarized by ATC Level 4 category and by PT within an ATC Level 4 for each treatment group and overall. The table will be sorted by overall descending frequency of ATC Level 4 and then, within an ATC Level 4, by overall descending frequency of PT.

Distribution of SoC medications, as identified by on a blinded review, at baseline will be presented by group. Number and percentage of subjects with at least one SoC medication per each category will be calculated and sorted by overall descending frequency of the SoC category.

In addition, all prior medications data will be listed.

6.7 Electrocardiography

Electrocardiogram findings (normal, abnormal, and missing) at screening will be summarized using appropriate descriptive statistics, and will be presented for the Safety population.

In addition, all screening ECG results data will be listed.

6.8 Physical Examinations

Physical examination findings (normal, abnormal, and missing) at baseline will be summarized by treatment group and overall using Safety population. Summaries will be presented using appropriate descriptive statistics.

6.9 Chest X-Ray or CT scan

Screening Chest X-ray or CT scan findings (normal, abnormal, and missing) will be summarized by treatment group and overall using Safety population. Summaries will be presented using appropriate descriptive statistics.

In addition, all screening chest X-ray and CT scan data will be listed.

6.10 Protocol Violations

All protocol violations will be tabulated presenting incidence (count and percentage) of subjects with deviation category for each group, and data will be listed as well.

7 EFFICACY ANALYSIS

7.1 General Considerations for efficacy evaluation

7.1.1 Populations for analysis

The analysis of the primary efficacy endpoints will be performed on the ITT, mITT, BLHF Treated and PP populations, with the mITT population serving as the primary analysis population. The secondary efficacy endpoints will be analyzed using the mITT, BLHF Treated and PP populations, unless otherwise noted for a specific endpoint.

Summaries will be presented by treatment group to which subjects were randomized.

7.1.2 Stratification

Stratified analysis will employ values of stratification factors used for randomization, where sensitivity analysis will be conducted using the updated/corrected values known at baseline.

7.1.3 Covariates

The comparability of the baseline risk factors for COVID-19 (listed on section 6.3) between groups will be assessed during the Final analysis and statistical procedures (as appropriate for Binary or time-to-event endpoint), to control for the possible impact of factors that appear to be imbalanced, will be performed as a robustness analysis.

7.1.4 Subgroups

Opaganib treatment effect for specific endpoint will be assessed to confirm comparability of effect across baseline SoC regimen strata. As strata may involve small number of subjects, crude analysis (no further stratification) will be performed, as adequate.

7.1.5 Use of effective anti-COVID 19 SOC treatments

Descriptive statistics including frequency and timing (relative to study day 1) of initiation of each type of effective anti-COVID-19 SoC treatment, will be presented by each group. Subjects already exposed to specific treatment before or on Day 1 will be counted as users as well with associated time to initiation of 0 days.

7.2 Primary Efficacy Endpoint Analysis

The primary endpoint aims at comparing the percentage of patients no longer requiring supplemental oxygen, for at least 24 hours by treatment Day 14 as defined in section 3.2.1, between Opaganib and placebo. The primary analysis will be based on the Modified Intent to Treat population (mITT) as defined in section 4.3.

This binary endpoint will be analyzed as follows: the number of subjects having "Success" event will be summarized using counts and percentages for each group.

A 95% confidence interval will be constructed for the proportion of success in each group. A Cochran Mantel-Haenzel (CMH) test will compare the proportion of success between the two groups, using the study stratification factors as used for randomization, and corresponding stratified risk difference estimate will be presented with 95% confidence interval.

The significance level for this test will be two-sided 5%.

The SAS syntax for the above calculations is provided in appendix 1.

A listing providing details on derivation of the primary endpoint will be provided.

7.2.1 Sensitivity and supportive analyses

Sensitivity and supportive analyses for the primary endpoint analysis will address the following aspects:

7.2.1.1 Sensitivity analysis for the imputation of missing data due to early study discontinuation.

The primary endpoint analysis imputed all early discontinuation from the study (or missing EOS visit/data) as Failures, even if a Sustained Success has been observed prior to termination. However in this sensitivity analysis an imputation using Observed data while on study (LOCF approach) will be used, as explained in Section 3.2.1.

7.2.1.2 Sensitivity analyses using other populations

As described in Section 7.1.1.

7.2.1.3 Sensitivity analysis account for stratification error

As described in Section 7.1.2.

7.2.1.4 Sensitivity analysis to account for baseline characteristics adjustment

In accordance with Section 7.1.3, difference between the treatment and control groups (the treatment effect for the primary endpoint) when controlling for possible imbalance in baseline risk factors will be analyzed by evaluating the odds ratio for Success obtained from estimating a multiple logistic regression model that include treatment effect along with the factors appear to be imbalanced as explanatory variables..

7.2.1.5 Subgroup analysis to account for SoC regimen

opaganib treatment effect will be assessed to confirm comparability of effect across these strata, according to Section7.1.4. Post-hoc subgroup analysis by treatments that started before or after Day 1 may be performed as deemed applicable.

7.2.1.6 Companion analysis: time to longer requiring supplemental oxygen for at least 24 hours, time frame of 14 days

Kaplan-Meier plot by treatment arm will be presented along with corresponding median estimates. The stratified Cox proportional hazards regression model estimate of the hazard ratio (HR) along with 95% confidence interval, comparing Opaganib versus control group will be provided.

To note, both the primary analysis and the sensitivity analysis for missing data will undergo the analyses in section 7.2.1.2 to 7.2.1.6.

7.3 Secondary Efficacy Endpoint Analysis

This section describes the analyses to be performed on the secondary efficacy endpoints, **based on endpoints definition provided in section 3.2.3**.

The secondary efficacy endpoints will be primarily analyzed using the mITT as primary analysis and will undergo sensitivity analyses for Missing data as applicable in endpoint–specific definition, and both the primary derivation and the sensitivity for missing data derivation will undergo the sensitivity analyses for Populations, Covariates and Subgroups (per sections 7.1), as applicable.

1. The percentage of patients with ≥2 category improvement on the WHO Ordinal Scale for Clinical Improvement by day 14.

This binary endpoint (“success”/”failure”) will be analyzed as follows: the number of subjects with “success” and “failure” will be summarized using counts and percentages for each group. A 95% confidence interval will be constructed for the proportion of event of interest (“success”) in each group. A Cochran Mantel-Haenzel (CMH) test will compare the proportion of success between the two groups, using the study stratification factors used for randomization, and corresponding stratified risk difference estimate will be presented with 95% confidence interval.

2. Time to recovery as defined by improvement to a score of 3 or less on the WHO Ordinal Scale for Clinical Improvement

This time to event endpoint will be analyzed using the stratified Log-rank test as well as the stratified Cox proportional hazards regression model estimates the hazard ratio (HR) along with 95% confidence interval, comparing opaganib versus control group. Kaplan-Meier plot by treatment arm will be presented and based on it the cumulative incidence of event of interest will be estimated for each group and the for their difference along with

95% confidence interval for each group at day 7 and at day 14. Median time and 95% confidence interval will be estimated using the KM curve for each group.

3. The time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula, non-rebreather (reservoir) face mask or positive pressure ventilation, if high oxygen flow is not an available option.

This time to event end point will be analyzed using the same analytical methods as the secondary end point #2, where the event of interest now is time to low oxygen flow via nasal cannula.

4. Time to discharge from the hospital.

Kaplan-Meier plot by treatment arm will be presented and based on it the cumulative incidence of discharge from hospital will be estimated along with 95% confidence interval for each group and the for their difference at day 7, day 14, day 28 and day 42 time points. Median time and 95% confidence interval will be estimated using the KM curve for each group.

Stratified Log-rank test as well as the stratified Cox proportional hazards regression model estimates the hazard ratio (HR) along with 95% confidence interval, will be used to compare opaganib with the control group, only through 14 days. For this purpose, any discharge time beyond 14 days will be censored at day=14. Restricted means at day 14 will also be provided for each group.

5. The percentage of patients requiring intubation and mechanical ventilation by day 42

According to section 3.2.3, the primary analysis will employ binary variable (“Failure”/”Success”), where event of interest is any intubation and mechanical ventilation or death or early termination from study. This binary variable will be analyzed using the same analytical methods for binary outcome as the first secondary endpoint, where now the event of interest is any Failure.

As a sensitivity analysis for missing data, the Kaplan-Meier method will be used to estimate the cumulative incidence of a composite failure of intubation and mechanical ventilation/death at day 42, when early termination and subjects completing the study successfully without failure are censored at their last contact date, as explained in Section 3.2.3 for this endpoint. The Cumulative Incidence of failure at day 42 and their difference will be provided, along with a 95% confidence interval for the between-group comparison. Additional time points will also be described (e.g. day 14, day 28) and Kaplan Meier curves of time to event through Day 42 will also be provided

A table will be provided presenting the number (%) of each of the failure events comprising the composite intubation/death/early termination binary variable used for the primary analysis of this endpoint. Subjects with Failure event will be classified into one

of 3 mutually exclusive categories: any intubation and mechanical ventilation, death without intubation and early termination.

6. Mortality due to any cause at Days 28 and 42 after baseline

These mortality endpoints will be analyzed according to the same approach defined for endpoint # 5 above, now with Death as event of interest. Kaplan Meier curves of time to death through Day 42 will also be provided.

7. Time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart

This time to event end point will be analyzed using the same analytical methods as the secondary end point #2, where the event of interest now is time to two consecutive negative swabs for SARS-CoV-2 by PCR. No sensitivity analyses will be performed for this endpoint.

8. The percentage of patients with at least two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14

This binary end point ("Success" / "Failure") will be analyzed using similar methods as those specified for the first secondary endpoint and according to the endpoint definitions in section 3.2.2. As noted in endpoint definition, death at any time prior to day 14 will be counted as Failure. No sensitivity analyses will be performed for this endpoint.

9. The percentage of patients with at least one measurement of fever at baseline (defined as temperature >38.0 C[100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14.

This binary end point ("Success" / "Failure") will be analyzed using similar methods as those specified for the 7th secondary endpoint and according to the endpoint definitions in section 3.2.2. No sensitivity analyses will be performed for this endpoint.

7.4 Exploratory Endpoint analysis

This section describes the analyses to be performed on the Exploratory efficacy endpoints, **based on endpoints definition provided in section 3.2.4.** All analyses will be based on the mITT population unless otherwise specified in endpoint definition. There are no planned sensitivity analyses for these endpoints.

1. The change in Systemic markers of inflammation (D-dimer,cardiac troponin C-reactive protein [CRP], lactate dehydrogenase [LDH], and ferritin) from baseline at Day 14 for the opaganib arm as compared to the placebo arm

Descriptive statistics for raw values and changes from baseline will be provided for Day 7, Day 14 and Last Available Value up to and including day 14 (LAVD14). The non-parametric Wilcoxon rank sum test will be used to compare the defined latest timepoint.

2. The change in lymphocyte count from baseline at Day 14 for the opaganib arm as compared to the placebo arm

This endpoint will be analyzed as specified above (exploratory endpoint #1).

3. Time to recovery as defined by improvement to a score of 1 or less on the WHO Ordinal Scale for Clinical Improvement for the opaganib arm as compared to the placebo arm

This time to event end point will be analyzed using the same analytical methods as the secondary end point #2 where the event of interest now refer to a score of 1 or less (instead of 3 or less). Sensitivity analysis will not be applied here.

4. The percentage of patients no longer requiring supplemental oxygen for at least 24 hours by Day 7 for the opaganib arm as compared to the placebo arm

This end point will be analyzed using the same analytical methods applied for the primary end point but within the time frame of 7 days. Sensitivity analysis will not be applied here.

5. Time to 50% reduction of supplemental oxygen requirement for the subset of subjects who do not receive positive pressure ventilation (non-invasive or invasive) for opaganib arm as compared to the placebo arm

This time to event end point will be analyzed using the same analytical methods as the secondary end point #2, where the event of interest now is time to 50% reduction in supplemental oxygen requirement. Sensitivity analysis will not be applied here.

8 SAFETY ANALYSIS

8.1 General

The safety population will be used for all safety analyses. Summaries will be presented by treatment group as actually received unless otherwise specified.

8.2 Study Drug Administration

8.2.1 Exposure to study drug

The following information will be summarized by treatment group:

- Duration of treatment (days treated) will be calculated as the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1). Duration of treatment (days) will be summarized using appropriate descriptive statistics for continuous variable (section 5.1 above).
- The number and proportion of subjects with at least one dose reduction, and the total number of dose reduction will be tabulated.

8.2.2 Treatment Compliance

Compliance with the prescribed study treatment will be assessed per subject, continuously from treatment initiation to end of treatment. The drug accountability log of returned study bottles will be used to evaluate the number of capsules used, unused and lost (recorded by site personnel). In addition, the Dose Missed/Reduced Log, which captures on a daily basis all missed or modified doses and reasons for modification, will be used to more accurately assess compliance.

Compliance rates will be presented as percentages, and subject-level compliance rates will be computed as follows: ([actual number of twice-daily doses taken minus reduced or missed] ÷ [expected number of twice-daily doses taken]) x 100.

Compliance rates will be summarized using appropriate descriptive statistics for continuous variable (section 5.1 above).

Compliance will also be categorized as ≤80% or >80% and will be summarized using counts and percentages.

Subject-level compliance details will be presented in a single data listing, incorporating count of dispensed (28 capsules) and returned capsules, number of expected vs. actual doses taken, occurrence of and reasons for missed and reduced doses, computed compliance rates and AEs leading to change in dose.

8.3 Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded according to the revised NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0). If an AE is not listed in the NCI-CTCAE v.5.0, then the Physician will use the terms: mild/Grade 1, moderate/Grade 2, severe/grade 3, life-threatening or disabling/Grade 4, or death

related/Grade 5 to describe the maximum intensity of the AE, as specified in the protocol (section 17.2).

Only Treatment Emergent Adverse Events (TEAEs) will be summarized. TEAEs are defined as all AEs that start on or after the date of first dose.

The following summaries will be provided:

- An overall summary that will include the number and percentage of subjects with:
  - any TEAEs; any serious TEAE (TESAE);
  - TEAEs will be presented by grade;
  - any treatment related (treatment related is defined as Possibly, Probably and related) related TEAEs, also missing relationship will be regarded as treatment related); any treatment related TESAE;
  - any TEAE resulting in dose reduced; any TEAE resulting in drug withdrawn (drug withdrawn or stopped)
  - any TEAE with an outcome of death
- Summaries by System Organ Class (SOC) and by Preferred Term (PT) within SOC will present the number and percentages of patients: experiencing any TEAEs; any TESAE; any grade 3 or above TEAE; any grade 3 or above TESAE; any treatment related TEAE; any treatment related TESAE; any TEAE resulting in dose reduced; any TEAE resulting in drug withdrawn or stopped; any AE with an outcome of death.
- Summary of TEAEs by SOC and PT and by maximum severity
- Summary of TEAEs by SOC and PT by maximal Relationship to Treatment

In summaries by SOC and PT, subjects are counted only once in each SOC category, and only once in each preferred term category.

In addition, characteristics of all TEAEs and TESAEs for all subjects will be presented in detail across multiple subject-level data listings. All AEs will be listed, regardless of whether they were treatment emergent. Listings for deaths, serious adverse events, adverse events leading to treatment withdrawal.

8.3.1 Protocol Defined Adverse Events of Special interest

The following adverse events are defined as of special interest.

- a sudden and clinically important increase in oxygen requirements
- a rapid decline in clinical status leading to intubation and mechanical ventilation
- clinically important increases in inflammatory markers
- Neuropsychiatric AEs

Adverse events of interest will be summarized using counts and percentages and a Listing will be provided.

8.4 Clinical Laboratory Tests

Laboratory assessments, providing indication of safety, include serum chemistry (Glucose, Blood Urea Nitrogen, Sodium, Chloride, Creatinine, Potassium, Calcium, Uric Acid, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Bicarbonate) and and hematology (Red blood cell count, Hemoglobin, Hematocrit, Platelets, White blood cell count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) will be collected. Scheduled visits for serum chemistry parameters were screening and then once weekly (at Day 7 and at Day 14), and from version 3 of the protocol were changed to every 3 days. Hematology parameters scheduled visits are: Screening visit and then every 3 days. Urinalysis is scheduled to be collected only in Screening visit.

Laboratory results will be assessed versus normal ranges (provided locally for each site) and abnormal results will be further classified as clinically significant (Yes/No). In addition, results will be graded using the NCI CTCAE v5.0 criteria.

Hematology and chemistry laboratory tests will be presented at baseline, and every 3 days up to Day 14. Laboratory tests results and changes from baseline to each visit including Last available value up to and including day 14 (LAVD14) will be summarized using descriptive statistics for continuous variables.

The incidence of abnormal results and of clinically significant abnormal results will be summarized for laboratory data using frequencies and percentages, per analyte, time-point, including LAVD14 and 'any time post-baseline' time point.

Shifts (below, within, and above the normal range) from baseline to each visit, LAVD14 - and 'any time post-baseline' will be summarized using patient counts. Similarly, shifts in interpreted result (normal, abnormal high clinically significant result, and abnormal low clinically significant) will be provided. In shift analysis to any time during study, the worst outcome in both directions (Low, High) will be considered (A subject may be counted both as a shift to High and as a shift to Low, if experienced both events during the study).

In addition, laboratory tests will be summarized by maximal toxicity grade.

Denominators for percentages will equal the number of subjects in the safety population providing data for specific time point.

Listings for clinically significant abnormal laboratory data will be presented.

8.5 Vital Signs

Vital signs (temperature, blood pressure, pulse rate, respiratory rate, oxygen saturation, FiO2) will be collected during screening visit, at Day 1, and daily whilst the subject is hospitalized, at End of treatment visit and at Safety follow-up visit.

Summary statistics for vital signs values and changes from baseline will be presented at baseline (Day 1), and at each scheduled visits (Day 2-13, LAVD14, end of treatment, safety follow up). The incidence of clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

A listing for clinically significant abnormal vital signs will be presented.

8.6 Supplemental oxygen requirement

Supplemental oxygen requirement will be collected during screening visit, at Day 1, and on daily basis. For subjects discharged from the hospital prior to Day 14, this assessment will be performed on a daily basis after discharge, via phone until Day 14. It is expected though, based on a previously completed study, that towards end of treatment period, available data will be predominantly from the more severe patients, still hospitalized. Therefore we will also be evaluating outcomes at the last available observation (LAVD14, up to and including day 14) time point. Lastly, data will be collected as well at the scheduled EOS visit. Descriptive statistics of required supplemental oxygen, type, type of positive ventilation, flow rate and percent oxygen in the gas mixture by scheduled visit per above including change from baseline for oxygen flow rate will be provided. The number and percentage of subjects with no requirement will be provided for each visit as well. Listings of all supplemental oxygen requirement evaluation will also be provided..

8.7 Electrocardiography

12-lead electrocardiogram will be performed for all subjects during screening visit, day 1 and at Day 14 visit. For patients on concomitant chloroquine /hydroxychloroquine /mefloquine (for subjects enrolled before protocol amendment #5 and for all patients following this amendment, the 12-lead ECG will be repeated after 3 hours (±30mins) of initial dose, on Day 2 and Day 4).

Incidence of abnormal result and of abnormal clinically significant results any time during the study will be summarized using appropriate descriptive statistics. Summaries may be provided separately for the subjects on concomitant chloroquine/hydroxychloroquine/mefloquine/ azithromycin.

A listing for clinically significant abnormal results will be presented.

8.8 Concomitant medications

Concomitant medications will include all medications that started, or were continuing, during or after administration of the study drug. All concomitant medications and supportive therapy administered starting Day 1 and until the final off-study drug follow-up visit will be recorded on the appropriate eCRF page. In the case of partial or missing dates such that it is not possible to determine if medication is concomitant, it will be regarded as such.

All concomitant medications will be coded using the WHO Drug. The number and percentage of subjects with at least one medication term will be summarized by ATC Level 4 category and by PT within an ATC Level 4 for each treatment group. Patients are counted only once in each ATC Level 4, and only once in each preferred term category.

The distribution of patient's **baseline** SoC regimen for COVID-19 will be summarized and presented by group.

Distribution of **post baseline** use of COVID -19 SoC treatment will be presented by each group, providing the number and percentage of subjects with at least one use by SoC group, where patients will be counted only once per SoC category.

Descriptive statistics of the days from the study first dose date to the initiation of post-baseline SoC treatment will be presented for each SoC COVID-19 treatment category, were the first SoC medication start time will be used for the analysis.

Similar analysis including the distribution and the time to initiation will be performed for **any time use** (**before or post** the study first dose) of SoC COVID-19 treatment (as described on 7.2.1.5) .

Identification and categorization of SoC for COVID-19 medications will be done by blinded review of medications prior to data base lock.

9 OTHER ANALYSES

9.1 Viral swab for SARS-CoV-2 PCR test

Pharyngeal samples for SARS-CoV-2 PCR will be collected up to 7 days prior to screening and every 3 days until 2 negatives are obtained otherwise another one on day 14 will be done. Efficacy analysis of this outcome is described in Section 3.2.2. Listings of results will also be provided.

9.2 WHO ordinal scale for clinical improvement assessment

WHO ordinal scale for clinical improvement assessment will be done on Screening visit, and on days 1-14 including at Safety follow-up visit. Efficacy analysis of this outcome is described in Section 3.2.2. Descriptive statistics of the continuous values including change from baseline and distribution of the categorical values will be presented by treatment day (including the Last Available Observation before day 14). Listing of the questionnaire will be provided.

10 Change from last SAP version and from protocol

The list below describes the known changes in this SAP relative to the statistical methods provisioned in the protocol:

Endpoints hierarchy:

The protocol specified an hierarchical approach for the control of type I error will due to the secondary endpoints, who were to be tested in an hierarchal manner according to their protocol defined order, following success in the primary endpoint. The SAP defines that no type 1 error control will be applied for the secondary endpoints, and their numbering has been changed (see section 5.3).

Approach to addressing early termination of study in derivation of secondary endpoints:

In the protocol, it has been read as a different approach will be used for the secondary endpoints versus the primary endpoint, where Failure imputation (worst-case) will be applied for the primary endpoint and censoring at time of study termination along with application of time to event methodology for estimating cumulative incidence was to applied fo the various secondary endpoints. In the SAP, a unified conservative approach was applied, where for the clinical secondary endpoints, early termination would now be imputed as Failure (worst-case) as well. The analytical methods has been updated accordingly in the SAP.

Analysis of endpoint percent of patients requiring intubation and mechanical ventilation by day 42:

In the protocol, death was to be handled as censoring event for the primary analysis of this endpoint and as competing risk event for the sensitivity analysis. In the SAP, death was incorporated as a Failure event, leading to the composite endpoint of intubation and ventilation/death (refer to section 3.2.3 for more details).

Populations:

The mITT population now includes the broader population of all subjects who were randomized and treated with at least one study dose , whereas the population definition included the additional requirement of meeting study entry criteria #3 and exclusion of patients who require mechanical ventilation or no longer require supplemental oxygen prior to receiving the first dose of study drug

The BLHF treated population has been added.

Primary endpoint sensitivity analysis:

The following sensitivity analyses were cancelled:

- Negation of achieved Day 14 success by a post-day 14 failure event.
- Negation of achieved Day 14 success by any post-success failure
- Missing data due to early discontinuation of follow-up before achieving success (prior to day 14).
- Joining a different clinical trial prior to day 14 while patients do not withdraw consent from being followed up under ABC-201 protocol.

A sensitivity analysis treating missing data due to early study termination using an 'while on study' approach has been added, consistent across all endpoints, as defined in the SAP.

The above list of changes from protocol also applies to the Changes from previous SAP version, and in addition, the updated SAP has been re-structured to enhance consistency in approaches across endpoints derivation and analysis.

In addition, the term treatment day versus study day has been clarified and it has been established that all efficacy endpoints will be defined in terms of Treatment day (please refer to section 5.5).

A derived additional timepoint has been defined for by-visit descriptive summaries and for biomarker analyses, the Last Available Value by day 14.

11 STATISTICAL SOFTWARE

All summary tables, figures, listings and statistical analyses will be generated using SAS® software, version 9.3 or later.

12 LIST OF SUMMARIES AND LISTINGS

The list of summary tables, figures and listings, along with further details will be provided in a separate document.

13 APPENDECIES

13.1 APPENDIX 1: WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Note: While there is a designated form to collect the WHO score per the Scheduled activities table (Table 1), the link between the patient's clinical status and scores definition allows inferring patient's score at a certain day even when score is not provided explicitly. These include:

- From the day after the subject is discharged alive from hospital, unless there is adverse event indicating otherwise, the patient is regarded ambulatory , and thus scored <=2.
- Any report on requirement of supplemental oxygen while patient is still hospitalized indicate that patient's status is score 4 or more, depending on procedure used low or high flow oxygenation, etc).
- As long as the patient is hospitalized, and as a conservative measure also at day of discharge, the patient can be regarded as having score of 3 or more, depending on oxygenation used on that specific date.

13.2 APPENDIX 2: SAS CODES

- The following is a generic SAS syntax for binary endpoint analysis. It performs the stratified CMH test and provides the associated adjusted risk difference.

```
ods output CMH =cmh(where=(Statistic=2))
CommonPdiff =COMMONRISKDIFF(where=(Method='Mantel-Haenszel'));
proc freq data=data ;
   tables strata1*strata2*group10*outcome01 /nopct nocol cmh
COMMONRISKDIFF(col=2)  ;
run;
** COMMONRISKDIFF requests the common (stratified) risk difference,
where the risk difference is the difference between
the row 1 proportion and the row 2 proportion in a  table.
```

- The following is a generic SAS syntax for estimating and comparing the cumulative incidence of event at a certain time-point based on Kaplan-Meier method (applicable for the sensitivity analysis of endpoint #5 and endpoint #6):

(a) Estimate per group, with confidence interval

```
ods output ProductLimitEstimates   = ProductLimitEstimates;
Proc lifetest data=data timelist=14 28 42 reduceout outsurv=outsurv ;
 time TIME*CNSR(1);
 strata  trt01p;
quit;

data outsurv;
set outsurv;
CI=1-survival;
CI_low=1-sdf_ucl;
CI_high=1-sdf_lcl;
run;
```

(b) Estimate difference between groups, with confidence interval (testing no difference).

```
data ProductLimitEstimates;
set ProductLimitEstimates;
VAR=(STDERR*STDERR);
run;

proc transpose data=ProductLimitEstimates out=tFAILURE prefix=FAIL;
var Failure  ;
id trt01;
by timelist;
run;

data tFAILURE;
set tFAILURE;
FAILDif=FailTRT-FailPBO;
label FAILDif="Difference in FAILURE rate";
run;
```

```
proc transpose data=ProductLimitEstimates out=tVAR prefix=VAR;
var  VAR ;
id trt01;
by timelist;
run;

data SEdiff;
set tVAR;
VarDiff=VARTRT+VARPBO;
SEDiff=sqrt(VarDiff);
label SEDiff="SE of Difference in FAILURE rate";
run;

data diffs;
merge tFAILURE SEdiff;
by timelist;
za=probit(0.975);
D=SEDiff*za;
Diff_Low=FAILDif-D;
Diff_Upper=FAILDif+D;
run;
```