COVER PAGE for ABC-110 STATISTICAL ANALYSIS PLAN (SAP)

The following document is the SAP of study ABC-110:

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

Dated 13 Dec 2020

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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 2a Study, in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia

Study: ABC-110

Phase: Phase 2a/Proof of Concept

Date: 13-December-2020

Version: 3

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Version Control Page

Version:	Version Date:	Comments
1	12-MAY-2020	Initial version
2	16-JULY-2020	Amendment following FDA recommendations
3	**25**-Oct-2020	Amendment following sponsor request for subgroup additions
4	**13**-DEC-2020	Final clarification prior to unblinding for primary outcomes results (early unblinding)

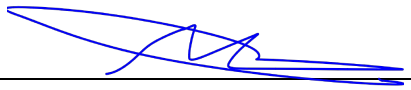
STATISTICAL ANALYSIS PLAN APPROVAL FORM

Study: ABC-110

SAP Date: 13-December-2020

SAP Version:

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

APPROVALS	
Approved by: 	13/DEC/2020
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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
DB	Double Blind
DM	Data Management
HFNC	High flow nasal canula
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
PEEP	Positive End Expiratory Pressure
PT	Preferred Term
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-110 (Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2a Study, in Adult Subjects Hospitalized with 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-110, version 1.2,30 August 2020.
- Case report forms (CRFs) for Study ABC-110.
- 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.
- Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, Guidance for Industry, June 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).

Version 1 of the SAP describes the statistical analyses as foreseen at the time of planning the study and version 2 incorporates an amendment responding to FDA recommendations received prior to study initiation, including additional clarifications and edits made early during initiation of study. Version 3 of the SAP include final clarifications and updates based on blinded data review and is finalized before the first database lock and before breaking the blind of the study. Any changes made after this event will be documented in the final CSR. First database lock refers to the event of locking all data up to and including Day 14 visit, enabling the final analysis of the Primary endpoint and those Secondary endpoints with timeframe of 14 days.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the total oxygen requirement (area under the curve) using daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14)

2.2 Secondary

1. To evaluate the time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min
2. To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14
3. To evaluate the proportion of afebrile patients at Day 14
4. To evaluate the time to negative swabs for SARS-CoV-2 by PCR
5. To evaluate the proportion of patients with negative swabs for SARS-CoV-2 by PCR at Day 14
6. To evaluate the need for intubation and mechanical ventilation by Day 14
7. To evaluate the time to mechanical ventilation
8. 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
9. To evaluate mortality 30 days post-baseline

2.3 Exploratory

To assess the change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin)

2.4 Safety

To assess the safety and tolerability of opaganib administered orally at 500 mg Q 12 hours, for up to 2 weeks, in patients with COVID-19 pneumonia.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a phase 2a, proof of concept, multi-center randomized double-blind, parallel arm, placebo controlled study.

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

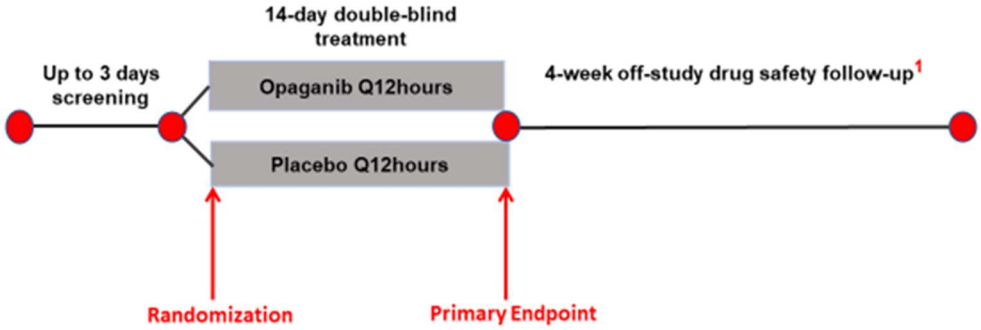
Approximately 40 eligible patients will be randomized to receive either opaganib added to standard of care, or matching placebo added to standard of care, in a randomization ratio of 1:1. Patients will be stratified based on a minimization algorithm, as specified in section 3.4. Treatment assignments will remain blinded to the patient, investigator and hospital staff, as well as the sponsor. As there is currently no consensus for a definitive treatment specifically targeting the SARS-CoV-2 virus causing COVID-19 (K. Wilson, 2020), standard of care will refer to regional, institutional or physician directed therapies, that may be implemented during the COVID-19 pandemic.

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 and/or supportive). Study drug will be administered every day for 14 days (Day 1 to Day 14), unless the patient has been discharged from the hospital without requiring supplemental oxygen, in which case study drug will only be administered to Day 10.

All participants will be followed up for 4 weeks after their last dose of study drug, which may occur at the end of the 2-week double-blind treatment phase or after premature study drug discontinuation, based upon patient or physician determination.

The maximum duration of study participation will be 45 days (including up to 3 days screening; 2 weeks double-blind (DB) phase and 4-weeks off-study drug follow-up).

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



[1] Off-study drug follow-up starts when study drug is stopped per protocol or after discontinuation per patient or physician decision

Table 1: Study Procedures and Assessments

Assessments	Screening	Randomization	DB Phase		Early termination	Safety follow-up
	Days -3 - 1	Day 1	Day 7	Day 14		
ICF signed	X					
Inclusion/exclusion criteria	X					
Demographics; medical and surgical history	X					
Review concomitant medication(s)[1]	X	X	X	X	X	X
Review of adverse events[1]		X	X	X	X	X
Physical examination[1]	X		X	X	X	X
Vital signs[1]	X	X	X	X	X	X
Oxygen flow (L/min)[1]	X	X	X	X	X	X
Weight[2]	X					
HbA1c	X					
Pharyngeal viral sample[3]	X	X	X	X	X	X
12-lead ECG[4]	X			X		
Chest X-ray[5]	X					
Serum chemistry	X		X	X		
Hematology (CBC with differential)	X		X	X		
D-dimer, cardiac troponin, CRP, LDH, ferritin[6]	X		X	X		
Urinalysis	X					
Serum pregnancy test[7]	X					

[1] 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)
[2] record weight if patient is ambulatory
[3] pharyngeal samples for SARS-CoV-2 PCR are collected daily, per standard of care. For patients having nasopharyngeal swabs, the same nostril must be used during the study
[4] for patients on concomitant hydroxychloroquine, the 12-lead ECG will be repeated after 3 hours (±30mins) of initial dose, on Day 2 and Day 4
[5] Chest X-ray, lab draws will be at the discretion of the Investigator depending on patient clinical condition
[6] CRP=C-reactive protein, LDH=lactate dehydrogenase
[7] women of childbearing potential; serum pregnancy test must be negative within 3 days prior to randomization.

3.2 Study Endpoints

3.2.1 Primary efficacy endpoint

The primary efficacy objective of the study is to evaluate the effect of Opaganib on total supplemental oxygen requirement (area under the curve) using daily oxygen flow (L/min) measurements for 14 days (Day 1 to Day 14).

The primary efficacy endpoint will calculate for each patient the area under the curve of the supplemental oxygen requirement through day 14, using the trapezoidal rule after subtracting the baseline oxygen requirement at each day.

The following rules will be applied:

- If several values of oxygen requirement (L/min) are recorded in a certain day, then for the primary analysis the highest of these values will be taken.
- Days where no supplementary oxygen was needed, will be recorded as 0.
- Subjects who require intubation and mechanical ventilation, at these days will be assigned the maximal supplemental oxygen flow requirement of 8L/min (or if higher, the maximal value observed in the study).
- For subjects discharged from hospital without requiring supplemental oxygen prior to Day 14, the oxygen requirement (L/min) will be assigned thereafter as 0 for each day to Day 14 (in the rare case that subject will re-hospitalize before Day 14, the new supplemental oxygen data will be collected and used, until day 14).
- For the primary analysis, if a patient dies any time before Day 14), all his/her values (D1-D14) will be assigned at the maximal supplemental oxygen flow requirement of 8L/min, or if higher, the maximal value observed in the study.

For patients discharged from hospital with supplemental oxygen prior to Day 14, or early terminate the treatment before Day 14 while still requiring supplemental oxygen, data on the supplemental oxygen up to Day 14 is expected to be collected. However, in the rare case that all supplemental oxygen values are missing after discharge/treatment discontinuation, the individual AUC will be calculated where the last value is carried forward - until Day 14, or death, if occurred before (note, death event is analyzed as specified above). This approach will be employed also if a patient initiates new investigational therapy for COVID-19 within 14 days, in which case the primary analysis will include only measurement taken under study treatment while the rest of the days will be imputed as noted above. Sensitivity analysis will address this scenario as well. To note, according to blinded data review prior to database lock, no cases of such prohibited investigational therapy was recorded.

3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min

This endpoint will be based on the oxygen flow values used for the primary efficacy endpoint. It will be calculated as the number of days from baseline (Day 1) of study

medication until the first day when the subject reached a value, which is at least 50% lower than the baseline value (the event of interest). Patients who early terminate the study before reaching this reduction will have their time censored at the last valid observation time point. Patients who will die within the followup timeframe will be censored at the time of the end of the follow-up period, thus taking the highly unfavorable possible outcome for this endpoint. The time frame for this endpoint is from Day 1 until end of off-study-drug follow-up. Additional analysis will be performed in the time frame of the 14-day-treatment DB Phase period (sensitivity analysis).
To note, in order to focus this endpoint on sustained success, it implies increase in supplemental oxygen negating initial success would be followed for re-achievement of success. Further note, a patient who reached success but did not have any further data supporting this success (i.e. discharged from hospital still requiring oxygen and no further data supporting success afterwards), may be subject to sensitivity analysis where regarded censored at last evaluable time.

2. The percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14

This endpoint will be defined per subject as a binary ("Success" / "Failure") variable with "Success" indicating that a subject no longer receiving supplemental oxygen for at least 24 hours by Day 14, and “Failure” otherwise. Patients who will die within 14-days will be regarded as “Failure”, corresponding to the highly unfavorable possible outcome.

To note, in order to focus this endpoint on sustained success, it implies need in supplemental oxygen negating initial success would be followed for re-achievement of success.

3. The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart

This time to event endpoint will be calculated as the number of days from baseline (Day 1) of study medication until the first occurrence of two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart (the event of interest). Patients who early terminate the study before reaching this event will have their time censored at the last valid observation time point. Patients who will die within the follow-up timeframe will be censored at the time of the end of the follow-up period, thus taking the highly unfavorable possible outcome for this endpoint. The time frame for this endpoint is from Day 1 until end of off-study-drug follow-up. Additional analysis will be performed in the time frame of the 14-day-treatment DB Phase period (sensitivity analysis).

4. The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart, followed by continued negative swabs

This time to event endpoint will be defined similarly to the 3rd secondary efficacy endpoint, where the event of interest is the first occurrence of two consecutive negative swabs for SARS-CoV-2 by PCR , at least 24 hours apart, followed by continued negative swabs. The time frame for this endpoint is from Day 1 until end of off-study-drug follow-up.

Additional analysis will be performed in the time frame of the 14-day-treatment DB Phase period (sensitivity analysis).

5. The percentage of patients requiring intubation and mechanical ventilation

The percentage of patients requiring intubation and mechanical ventilation by **Day 30** will will be defined per subject as a binary ("Failure" / "Success") variable with "Failure" indicating that a subject had a reported requirement of intubation and mechanical ventilation any time before 30-days following first study dose, and “Success” otherwise. Death during this time frame will be regarded as “Failure” as well.

The percentage of patients requiring intubation and mechanical ventilation by **Day 14** will also be estimated in a similar way. Death before day 14 will be regarded as “Failure” as well.

6. The time to intubation and mechanical ventilation.

This time to event endpoint will be calculated as the number of days from baseline (Day 1 of study medication) until the earliest date of a reported requirement of intubation and mechanical ventilation, or death. Subjects who early terminate the study alive and without such requirement will have their time censored at the last valid observation time point. The time frame for this endpoint is from Day 1 until Day 30 from first dose. Additional analysis will be performed in the time frame of the 14-day-treatment DB Phase period (sensitivity analysis).

7. 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 per subject as a binary ("Success" / "Failure") variable with "Success" indicating that a subject with fever at baseline is reported as afebrile on Day 14. “Failure” will be assigned otherwise.

This endpoint will be calculated only to the population of subject having fever at baseline. Additionally, to address objective # 3 (To evaluate the proportion of afebrile patients at Day 14), endpoint and analysis will be applied to the entire mITT analysis set.

8. Mortality due to any cause at Day 30.

This binary endpoint will be defined per subject as a binary ("Failure" / "Success") variable with "Failure" indicating that a subject had died within 30 days from first dose. “Success” will be assigned for patients known alive at day 30.

3.2.3 Exploratory Endpoints

Exploratory endpoints will include changes from baseline in the systemic markers of inflammation: D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin.

3.2.4 Safety Endpoints

The safety and tolerability endpoints will include reported AEs, laboratory tests, vital signs, ECG, physical examinations, concomitant medications and hospitalization.

Hospitalization endpoints will include days of hospitalization and status of supplementary oxygen requirement at discharge (No/Yes). When calculating days of hospitalization, if a subject dies while hospitalized, the number of days of hospitalization will be imputed as the worst maximal duration of 42 days.

3.3 Sample Size and Power Considerations

It is planned to enroll approximately 40 eligible patients into the double-blind treatment phase, to receive either opaganib added to standard of care (n=20), or matching placebo added to standard of care (n=20). The sample size for this Proof of Concept study was not chosen for statistical consideration, as there are no formal statistical inferences planned. The size of the study is judged adequate for the preliminary evaluation objectives.

3.4 Randomization and Blinding

A total of 40 subjects 18 to 80 years old, inclusive will be randomized, using a 1:1 assignment ratio, to treatment with either Opaganib 500 mg Q12 hour (20 subjects) or Placebo (20 subjects), respectively.

A dynamic randomization using the minimization method will be used in this study by Bioforum's DM vendor. Three stratification factors will be used for the minimization algorithm:

1. Age at screening, ≥70 years of age, (yes or no)
2. HbA1c at screening, ≥6.5, (yes or no);
3. Oxygen requirement at baseline, requiring non-invasive positive pressure ventilation (e.g. via PEEP, BIPAP, CPAP, HFNC), (yes or no)

The minimization algorithm will be programmed by Bioforum Ltd using Viedoc system and will employ the Pocock and Simon (Pocock S.J. and Simon R. 1975) methodology with biased coin probability of 0.8 and 'Range' as the variation method. All stratification factors will use the same weight of importance. If the subject meets the eligibility criteria, he or she will be allocated to Opaganib 500 mg Q12 hour or Placebo at 1:1 ratio respectively. Once the enrollment of the subject is approved, the investigator will assign the subject an ID number (subject number) provided by the Viedoc system after running the algorithm on the subject's stratification information.

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

No formal interim analysis to stop the study early is planned for this proof of concept study.

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. 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. The analysis of the primary endpoint and supporting efficacy secondary analyses can be started once this SAP has been signed, all data up to day 14 (including) has been locked and unblinded. Study personnel involved in data management activities and those engaged in study conduct will remain blinded until the few remaining safety follow-up visits will be performed and all remaining unlocked data (after Day 14) have been cleaned and locked. Only then, formal final analysis for the CSR will be performed. No difference is expected in results of the primary endpoint (and supporting efficacy secondary endpoints noted above), however in case of any difference occur, it will be documented and presented in the CSR as well. Procedures and firewalls have been defined and documented in study files to maintain study integrity during the partial team unbinding.

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.

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 Safety

The safety population will include all randomized patients who receive at least one dose of study medication. In this population, treatment will be assigned based upon the treatment patients actually receive regardless of the treatment to which they were randomized.

4.4 Modified ITT (mITT)

This population consists of all subjects that were randomized and treated with at least one dose of study drug. In this population, treatment will be assigned based upon the treatment to which subjects were randomized regardless of which treatment they actually received.

4.5 Per protocol (PP)

A per protocol population will include those subjects in the mITT population who had no major protocol violation. Criteria for PP protocol will be mainly based on inclusion and exclusion criteria and will be defined before database lock. The list of protocol deviations

precluding patients from PP population has been prepared using blinded review and documented in study files.

5 GENERAL ASPECTS FOR DATA ANALYSIS

5.1 General

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error of the mean, median, minimum, and maximum.

Descriptive statistics for categorical variables include patient counts and percentages.

Summaries of clinically significant abnormal values will include all post baseline values (including scheduled, unscheduled, and early termination visits).

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

This is a proof of concept study for which no formal statistical hypotheses were defined. When presented, nominal p-values will not be interpreted inferentially. The results of the study will be interpreted by the overall pattern of benefits of opaganib.

5.4 Handling Withdrawals and Missing Data

Missing data in the primary endpoint are handled as described in sections 3.2.1 and 7.2. Sections 3.2.2 and 7.3 provides details on handling missing data for the secondary efficacy endpoints. Generally, no imputation will be performed for safety endpoints unless stated otherwise in the specific endpoint analysis. For time to event analysis, early withdrawal (or death before event of interest) will be addressed via right censoring, as described in Sections 3.2.2.

5.5 Study days and visit windows

The study data will be summarized as collected at the scheduled study day during DB and follow-up phases. 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, in case the corresponding data are missing from this assessment day.

5.6 Subgroups

The subgroup of low-flow vs. high-flow oxygen will be define based on the baseline oxygen required type. Subject will be classified with ’High-Flow’ if baseline oxygen

required was positive pressure or high flow nasal cannulas and ‘Low-Flow’ if baseline oxygen required was regular.

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 who completed the study treatment according to protocol (i.e. on day 14 or on day 10 if discharged from the hospital without requiring supplemental oxygen before day 14)
- 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 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)
    - Gender: Male, Female (categorical)
    - Childbearing Potential: Yes, No (categorical, females only)
    - 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)
    - Smoking status: Never, Former, Current (categorical), and packyears
- Stratification factors (categorical):
    - Age (years): <70, ≥70
    - HbA1c at screening: <6.5, ≥6.5o)
    - Oxygen requirement at baseline requiring non-invasive positive pressure ventilation (e.g. via PEEP, BIPAP, CPAP): yes or no
- Vital signs at baseline, including supplemental oxygen requirement

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

- Reason for hospitalization
- 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 History

Medical history data will be summarized by treatment group and overall using ITT and Safety population. 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 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 ITT 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.

In addition, all prior medications data will be listed.

6.7 Electrocardiography

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

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

Chest X-ray 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.

6.10 Protocol Violations

All protocol violations will be listed.

7 EFFICACY ANALYSIS

7.1 General

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

Summaries will be presented by treatment group, unless otherwise noted.

7.2 Primary Efficacy Endpoint Analysis

The primary analysis will be based on the modified Intent to treat population (mITT), which consist of all patients that were randomized and treated with at least one dose of study drug,

The primary analysis will be based on the baseline-adjusted AUC calculated individually for each subject, as defined in section 3.2.1. Descriptive statistics of the baseline-adjusted AUC will be presented by group and group means will be presented along with 95% confidence interval. The difference in means between the groups will be estimated and presented with 95% confidence interval. Plots presenting individual baseline-adjusted AUC will be presented. Difference between group medians with confidence interval will also be estimated using the Hodges-Lehmann statistics and will be presented along with the non-parametric Wilcoxon rank sum test.

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 Missing data

The primary analysis above is based on individual AUC calculation, where in case that all supplemental oxygen values are missing after discharge or early treatment discontinuation that occur while subject still requires supplemental oxygen (before day 14), the last value is carried forward - until Day 14, or death, if occurred before. In addition, worst case imputation is applied for subjects who died any time within 14 days and on days of intubation.
A sensitivity analysis to the above missing data handling approach will be performed using an AUC summary statistics approach, in which groups AUC is calculated from the estimated parameters of a Repeated-Measures model. More specifically, taking as the dependent variable the observed daily oxygen requirement per each subject (change from baseline), a model incorporating factors for group, day (categorical) and group by day interaction will allow estimation of the mean oxygen requirement at each day, for each group. The model will be implemented using the MIXED procedure in SAS software with subject taken as random factor. To confirm that correlation among observations from the same subject are adequately modeled in this MIXED model application, the following correlation structures will be fitted as well: Unspecified (UN) and Autoregressive(1)

(AR(1)). The denominator degrees of freedom will be computed using the Kenward-Roger method. Each group mean AUC will be estimated using a linear combination of the parameter estimates after a model has been fit. Group AUCs and their difference will be presented along with 95% confidence interval.

7.2.1.2 Baseline characteristics adjustment

Estimation of difference between the treatment groups when controlling for the stratification factors and baseline oxygen requirement will be performed, using regression analysis, both for the individual subjects AUC (via Analysis of Covariance) and the group AUC modeling via Repeated measures approach sensitivity analysis.

7.2.1.3 Per protocol analysis

Analysis using the per-protocol population will be performed as supportive analysis.

7.2.1.4 Robustness for outliers

Analysis based on ranked observations will be performed to confirm robustness of the estimated effect for potential outliers.

7.3 Secondary Efficacy Endpoint analysis

This section describes the analyses to be performed on the secondary efficacy endpoints, as defined in section 3.2.2.

The secondary efficacy endpoints will be analysed using the mITT populations unless otherwise noted for a specific endpoint.

1. Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min

This time to event will be analyzed as follows: Cox proportional hazards regression model will be used to estimate the hazard ratio (HR) along with 95% confidence interval, comparing Opaganib versus control group. The model will include treatment group as explanatory variable and supplemental oxygen at baseline as covariates. If possible, the stratification factors will also be included as covariates. Kaplan-Meier plot will be provided for illustration of effect (along with median estimates). Cumulative incidence function of the time to 50% reduction from baseline in supplemental oxygen will be estimated using the Kaplan-Meier estimator and will be used to estimate the 14-days cumulative incidence of 50% reduction event for each group, along with 95% confidence interval.

2. The percentage of patients no longer receiving supplemental oxygen for at least 24 hours 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. Difference in proportions will be estimated and presented along with 95% confidence interval. Exact confidence intervals will be used as needed (otherwise Wilson (Score) limits will be used). In case loss to follow-up before

event will be recorded, the Cumulative Incidence probabilities at 14-days from the starting of treatment will be estimated using time to event analysis (Kaplan-Meier estimator), censoring loss-to follow up patients at last valid observation date. This analysis will censor death on Day 14.

3. The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart

This time to event endpoint will be analyzed using the same methods specified for the first secondary efficacy endpoint (without adjustment for the supplemental oxygen at baseline).

4. The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart, followed by continued negative swabs

This time to event endpoint will be analyzed using the same methods specified for the first secondary efficacy endpoint (without adjustment for the supplemental oxygen at baseline).

5. The percentage of patients requiring intubation and mechanical ventilation

This binary endpoint will be analyzed using the same methods specified for the second secondary efficacy endpoint. The event of interest is defined as "Failure". As defined in section 3.2.2. death will be analyzed as "Failure".

The percentage of patients requiring intubation and mechanical ventilation by Day 14 will be analyzed similarly.

6. The time to intubation and mechanical ventilation.

This time to event endpoint will be analyzed using the same methods specified for the 1st secondary efficacy endpoint (without adjustment for the supplemental oxygen at baseline).

7. 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 endpoint will be analyzed using the same methods specified for the second secondary efficacy endpoint. This analysis will be based on observed case analysis using patients with Day 14 measurement.

8. Mortality due to any cause at Day 30.

This binary endpoint will be analyzed using the same methods specified for the second secondary efficacy endpoint. The event of interest is defined as "Failure". To note, in case that loss to follow up, the associated time to event analysis to derive the 30-days mortality rate will not encounter any competing event. Kaplan Meier curves of time to death through Day 30 will also be provided.

7.4 Exploratory Endpoint analysis

The systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) will be collected at Screening visit and then once weekly at Day 7 and Day 14 visits. These tests will be evaluated versus local site

normal ranges and assessed by the investigator as Clinically Significant (Yes/No). Changes from baseline analysis and other analyses similar to those planned for the Chemistry/Hematology laboratory tests (section 8.4) will be applied.

7.5 Subgroup analysis

The primary and secondary endpoints will be summarized using the low vs. high oxygen flow subgroup as defined on section 5.6 above. The efficacy primary endpoint and 'Time to event' secondary endpoints will be analyzed by subgroup using the methods described in Section 7. Safety analysis may be provided as well, as deemed relevant.

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.

Rules to address safety data analysis of single patient who may have received a flipped treatment due to bottle switches are documented in study files, in which if the patient was initially on placebo but then mistakenly received opaganib, his/her data before and after the switch will be assigned as Placebo and opaganib, respectively, and thus may be counted twice.

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).
- Days on treatment will also be categorized as ≤10days or >10days and will be summarized using counts and percentages.
- 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] ÷ [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, and computed compliance rates.

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/Grade 4, or death/Grade 5 to describe the maximum intensity of the AE, as specified in the protocol (section 15.2).

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);
    - any grade 3 or above TEAE; any grade 3 or above TESAE;
    - 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 treatment related TEAE grade 3 or above;
    - any TEAE resulting in dose reduced; any TEAE resulting in drug withdrawn
    - 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; 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 hematology (Red blood cell count, Hemoglobin, Hematocrit, Platelets, White blood cell count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), and will be collected during Screening visit and then once weekly at Day 7 and Day 14 visits. 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.

Chemistry and Hematology laboratory tests will be presented at baseline, Day 7 and Day 14 visits. Laboratory tests results and changes from baseline to each visit 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 and time-point, including ‘any time post-baseline’ time point.

Shifts (below, within, and above the normal range) from baseline to each visit 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 and oxygen saturation by pulse oximeter) 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, 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 outcome is the target of the primary efficacy endpoint (refer to section 3.2.1. Listings of all supplemental oxygen requirement evaluation will also be provided. Figures will be provided as possible.

8.7 Electrocardiography

12-lead electrocardiogram will be performed for all subjects during screening visit and at Day 14 visit. For patients on concomitant hydroxychloroquine, 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 will be summarized using appropriate descriptive statistics. Summaries may be provided separately for the subjects on concomitant hydroxychloroquine.

8.8 Physical Examinations

Physical examinations will be conducted at screening visit and then daily while subject is hospitalized, at End of treatment visit and at Safety follow-up visit. Any physical examination finding that is judged by the investigator as abnormal (worsening) compared to a baseline value will be considered an adverse event and reported as such. Therefore, no specific summary tables will be provided. Listings of abnormal physical examination will be provided.

8.9 Chest X-ray

Chest X-ray will be performed at Screening visit and subsequently at the discretion of the Investigator depending on subject's clinical condition. Any post baseline finding that is judged by the investigator as abnormal (worsening) compared to a baseline value will be considered an adverse event and reported as such. Listings of abnormal chest X-ray will be provided.

8.10 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.

8.11 Hospitalization

Summary statistics on subject's hospitalization information will be provided. These will include duration of hospitalization and whether the subject is taking supplemental oxygen at discharge.

8.12 Viral swab for SARS-CoV-2 PCR test

Pharyngeal samples for SARS-CoV-2 PCR will be collected per standard of care, every 1-3 days. Efficacy analysis of this outcome is described in Section 7.3. Listings of results will also be provided.

9 STATISTICAL SOFTWARE

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

10 SUMMARY OF CHANGES FROM LAST SAP VERSION AND PROTOCOL SPECIFIED ANALYSES

Version 2 of the SAP incorporates edits to the previous version of the SAP and some deviations in text from the latest version of the Clinical Study Protocol.

These edits/deviations, however, were made in response to the FDA recommendations, and attempts to insert greater detail and provide further clarifications. The most significant changes made to the text in this document are summarized in the table below:

Table 2: Summary of changes in Version 2

Topic	Change description and rationale
Analysis Populations	Per-protocol population was defined to address major protocol deviations that may occur, mainly relating to inclusion/exclusion criteria
Primary efficacy endpoint and analysis	In Section 3.2.1: Originally, it was thought that multiple units will be used for reporting oxygen flow, and thus a placeholder for algorithm to address that was given. Yet, it was confirmed that all oxygen flow values will be reported using the same, L/min unit, therefore referral for further addendum is no longer needed.
	Imputation rules have been edited as follows: • Following FDA recommendation, any death during study will be imputed using maximal supplemental oxygen flow requirement of 8L/min from Day 1 to Day 14 for the primary efficacy endpoint. • In case that higher values than 8L/min will be recorded, the SAP now define that 8L/min or if higher, the maximal value observed in the study will be used. • The SAP now address the scenario that a patient initiates new investigational therapy for COVID-19 within 14 days, in which case the primary analysis will include only measurement taken under study treatment and the rest of the days will be imputed according to imputation rules.
	In the sensitivity analysis (section 7.2.1.1): it was clarified that Change from baseline will be analyzed in the model.
	A supportive per-protocol analysis was added.
Secondary Efficacy Endpoints #1,#2,#5	Following FDA recommendation and in accordance with the newly released COVID-19 guidance to address death as the highly unfavorable possible outcome for efficacy endpoints, the secondary endpoints and associated analyses have been updated accordingly.

Topic	Change description and rationale
Secondary Efficacy endpoint #4	The endpoint was changed based on FDA recommendation, and analysis was subsequently fitted to analyze the resulting time to event endpoint.
Secondary Efficacy endpoint #7	Assessment of Afebrile status at day 14 will be performed also for the entire mITT patients, in addition to the subgroup of patients with fever at baseline, in order to address study objective #3.

Version 3 of the SAP incorporates the below changes relative to the previous version:

Table 3: Summary of changes in Version 3

Topic	Change description and rationale
Primary Efficacy endpoint (Section 3.2.1)	Derivation of endpoint was updated in accordance with FDA earlier recommendation, that death imputation will trigger worst case imputation if occurring any time within the 14 days period rather than any time during study. In addition, it was updated that based on blinded data review, no cases of, and therefore no need to handle, new investigational COVID-19 therapy.
Secondary Efficacy Endpoints #1,#2 (Section 3.2.2)	Text was added to endpoint definition to clarify that endpoint focus on sustained success, rather than success that may be negated by subsequent failure within the time-frame
Secondary efficacy endpoint #5,#6 (Section 3.2.2)	To align with the protocol, endpoint to estimate cumulative incidence of event by 14 days was added, and, the long term time frame was defined as 30-days post first dose. Time frame for the time to event #6 endpoint was correspondingly aligned.
Secondary efficacy endpoint #8 (Section 3.2.2)	In order to align with other endpoints, origin of timeframe was changed to first dose instead of date of randomization.
Sequence of planned analyses (Section 3.5.2)	Details have been provided on database lock and unbinding process.
Subgroup analysis (Sections 5.6 and 7.5)	Pre-definition of subgroup by baseline type of oxygen requirement: low-flow vs. high-flow oxygen.
Primary efficacy endpoint analysis (Section 7.2)	Non-parametric analysis of the individual subjects AUC was added.
	Additional robustness analysis was added, in which analysis will be repeated on ranked transformed data.
	Text was added to clarify that various robustness analysis will be performed for both individual subjects AUC analysis and the group AUC modeling via Repeated measures approach sensitivity analysis.

Topic	Change description and rationale
	In the group AUC modeling via Repeated measures approach sensitivity analysis, analyses to confirm that correlation among observations from the same subject are adequately modeled was added.
Secondary Efficacy endpoint #7 (Section 7.3)	Clarification that analysis of this endpoint will be based on observed case analysis using patients with Day 14 measurement.
Safety analysis general (Section 8.1)	A note on addressing case of patients who may have received a flipped treatment due to bottle switches.

11 REFERENCES

Pocock S.J. and Simon R. (1975) Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115.

12 LIST OF SUMMARIES AND LISTINGS

The list of summary tables, figures and listings as foreseen at study onset is provided below. The final updated list is maintained and recorded at study files.

Summary number	Title	Population
Study Population Summaries		
14.1.1	Patient Disposition	All Screened Patients
14.1.2.1-3	Demographics and Baseline Characteristics (by treatment group and overall)	ITT, mITT and Safety
14.1.2.4-6	Stratification factors at time of Randomization and on eCRF (by treatment group and overall)	ITT, mITT
14.1.3.1-3	Covid-19 Disease Information (by treatment group an overall)	ITT, mITT and Safety
14.1.4.1-2	Medical and Surgical History (by treatment group an overall)	ITT and Safety
14.1.5.1-3	Prior Medications	ITT, mITT and Safety
14.1.6	Baseline ECG Findings (by treatment group and overall)	Safety
14.1.7	Baseline Physical Examination Findings (by treatment group and overall)	Safety
14.1.8	Baseline X-Ray Findings (Normal/Abnormal/Missing)	Safety
Primary Efficacy Endpoint		
14.2.1.1	Primary Endpoint Analysis: Total Supplemental Oxygen Requirement (area under the curve) using Daily Oxygen Flow (L/min) Measurements for 14 Days (Day 1 to Day 14).	mITT
14.2.1.2	Primary Endpoint: Total Supplemental Oxygen Requirement (area under the curve) using Daily Oxygen Flow (L/min) Measurements for 14 Days (Day 1 to Day 14) - Sensitivity Analysis for missing data	mITT
14.2.1.3	Primary Endpoint: Total Supplemental Oxygen Requirement (area under the curve) using Daily Oxygen Flow (L/min) Measurements for 14 Days (Day 1 to Day 14) - Sensitivity Analysis for Baseline Characteristics Adjustment	mITT
14.2.1.4	Daily Oxygen Flow (L/min) Requirement Values and Change from Baseline, by Treatment Group	mITT
Secondary Efficacy endpoints		
14.2.2.1-2	Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min *(two time frames: up to end of follow up; up to Day 14)*	mITT
14.2.3	Percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14	mITT

Summary number	Title	Population
14.2.4.1-2	The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart *(two time frames: up to end of follow up; up to Day 14)*	mITT
14.2.5.1-2	The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart followed by continued negative swabs *(two time frames: up to end of follow up; up to Day 14)*	mITT
14.2.6	Percentage of patients requiring intubation and mechanical ventilation by the end of the 4-week off-study-drug follow-up	mITT
14.2.7.1-2	Time to intubation and mechanical ventilation *(two time frames: up to end of follow up; up to Day 14)*	mITT
14.2.8	The percentage of patients with at least one measurement of fever at baseline, who are afebrile at Day 14	mITT (with Fever at baseline)
14.2.9	The percentage of patients who are afebrile at Day 14	mITT
14.2.10	Mortality due to any cause at Day 30	mITT
Exploratory Efficacy endpoints		
14.2.11.1	Summary of Systemic Markers of Inflammation and Change from Baseline by Visit and Treatment Groups	mITT
14.2.11.2	Systemic Markers of Inflammation Normal/Abnormal and Clinically Interpretations Results by Visit and at Any Post Baseline Time Point and by treatment Group	mITT
14.2.11.3	Shift from baseline to each Visit and 'Any Time Post Baseline' of Systemic Markers of Inflammation Abnormal Values by Treatment Group	mITT
14.2.11.4	Shift from baseline to each Visit and 'Any Time Post Baseline' of Systemic Markers of Inflammation Clinically Interpreted Test Results by Treatment Group	mITT
Exposure and Safety		
14.3.1.1	Study Drug Exposure by Treatment Group	Safety
14.3.1.2	Treatment Compliance by Treatment Group	Safety
14.3.2.1	Summary of Treatment Emergent Adverse Events by Treatment Group	Safety
14.3.2.2	TEAEs by SoC and PT by Treatment Group	Safety
14.3.2.3	TE-SAE by SoC and PT by Treatment Group	Safety
14.3.2.4	Grade 3 or Above TEAE by SoC and PT by Treatment Group	Safety
14.3.2.5	Grade 3 or above TESAE by SoC and PT by Treatment Group	Safety
14.3.2.6	Treatment related TEAE by SoC and PT by Treatment Group	Safety
14.3.2.7	Treatment related TESAE by SoC and PT by Treatment Group	Safety
14.3.2.8	TEAE resulting in dose reduced by SoC and PT by Treatment Group	Safety
14.3.2.9	TEAE resulting in drug withdrawn by SoC and PT by Treatment Group	Safety

Summary number	Title	Population
14.3.2.10	Any TEAE with an outcome of death by SoC and PT by Treatment Group	Safety
14.3.2.11	TEAEs by SOC, PT and Maximum severity by Treatment Group	Safety
14.3.2.12	TEAEs by SOC and PT by maximal Relationship to Treatment by Treatment Group	Safety
14.3.2.13	TEAEs of Special Interest by Treatment Group	Safety
14.3.3.1.1	Chemistry Results and Change from Baseline by Visit and by Treatment Group	Safety
14.3.3.1.2	Chemistry Normal/Abnormal and Clinically Interpretations Results by Visit and at 'Any Post Baseline Time by Treatment Group	Safety
14.3.3.1.3	Shift from baseline to each Visit and 'any time post baseline' for Chemistry Abnormal Values by Treatment Group and Overall	Safety
14.3.3.1.4	Shift From Baseline to each Visit and 'any time post baseline' for Chemistry Clinically Interpreted Test Results, by Treatment Group	Safety
14.3.3.2.1	Hematology Results and Change from Baseline by Visit and by Treatment Group	Safety
14.3.3.2.2	Hematology Normal/Abnormal and Clinically Interpretations Results by Visit and at 'Any Post Baseline Time Point' and by Treatment Group	Safety
14.3.3.2.3	Shift from baseline to each Visit and 'any time post baseline' for Hematology Abnormal Values by Treatment Group and Overall	Safety
14.3.3.2.4	Shift From Baseline to each Visit and 'any time post baseline' for Hematology Clinically Interpreted Test Results, by Treatment Group	Safety
14.3.3.3	Incidence of laboratory toxicity by maximal toxicity grade during study by Treatment Group	Safety
14.3.4.1	Vital signs Results and Change from Baseline by Visit and Treatment Group	Safety
14.3.4.2	Vital Signs Clinically Interpretations Results at any time during study by Treatment Group	Safety
14.3.5.1	ECG Normal/ ABNORMAL and Clinically Interpretations Results by visit and time point by Treatment Group	Safety
14.3.5.2	ECG Normal/ ABNORMAL and Clinically Interpretations Results by visit and time point by Treatment Group for Subjects on concomitant Hydroxychloroquine	Safety: subjects on concomitant Hydroxychloroquine
14.3.6	Concomitant medications by WHO Dictionary ATC Level 4 and PT by Treatment Group	Safety
14.3.7	Hospitalization by Treatment Group	Safety

Individual Patient Data Listings

Listing Number	Title	Population
16.2.1.1	Patients Disposition	All Screened Patients

Listing Number	Title	Population
16.2.1.2	Patients Not Eligible for the Study	All Screened Patients
16.2.1.3	Patient Disposition with reasons for early termination of treatment and early termination of study	ITT
16.2.2	Demographic and Baseline Characteristics	ITT
16.2.3	Covid-19 Disease History	ITT
16.2.4	Medical History	ITT
16.2.5	Prior Medication	ITT
16.2.6	ECG	Safety
16.2.7	Abnormal Physical Examinations	Safety
16.2.8	Protocol Violations	All Screened Patients
16.2.9	Supplemental oxygen requirement and AUC	mITT
16.2.10	Viral swab for SARS-CoV-2 PCR test	mITT
16.2.11.1	Systemic markers of inflammation results	mITT
16.2.11.2	Abnormal systemic markers of inflammation	mITT
16.2.12	Secondary End Points by Subject Derivations	mITT
16.2.13.1	Study Drug Exposure	Safety
16.2.13.2	Study Drug Compliance	Safety
16.2.14.1	All Adverse Events	Safety
16.2.14.2	Adverse Events Resulted in Death	Safety
16.2.14.3	Serious Adverse Events	Safety
16.2.14.4	Adverse Events Leading to Treatment Withdrawal	Safety
16.2.14.5	Special Interest Adverse Events	Safety
16.2.15.1	Chemistry Results	Safety
16.2.15.2	Abnormal Clinically Significant Chemistry Results	Safety
16.2.15.3	Hematology Results	Safety
16.2.15.4	Abnormal Clinically Significant Hematology Results	Safety
16.2.16.1	Vital Signs Results	Safety
16.2.16.2	Clinically Significant Vital Signs	Safety
16.2.17.1	ECG Results	Safety
16.2.17.2	Abnormal ECG Results	Safety
16.2.18	Abnormal Physical Examination	Safety
16.2.19	Abnormal X-Ray Results	Safety

Listing Number	Title	Population
16.2.20	Concomitant medications	Safety
16.2.21	Hospitalization	Safety

Graphs

Graph Number	Title	Population
17.1.1	Dot plot of total oxygen requirement (baseline adjusted AUC) by treatment	mITT
17.1.2	Overlaid individual oxygen requirement -time profiles by treatment	mITT
17.1.3	Boxplots of oxygen requirement by time and treatment	mITT
17.2	Kaplan-Meier Curves of Cumulative Incidence for Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min	mITT
17.3.1	Kaplan-Meier Curves of Cumulative Incidence for Time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart	mITT
17.3.2	Kaplan-Meier Curves of Cumulative Incidence for Time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart, followed by continued negative swabs	mITT
17.4	Kaplan-Meier Curves of Cumulative Incidence for Time to intubation and mechanical ventilation	mITT
17.5	Kaplan-Meier Curves of Time to Death through Day 30	mITT