9. STATISTICAL METHODS INTERIM ANALYSIS PLAN

- Statistical Analysis Plan (SAP), Version 1.0, 15 April 2021
- Statistical Analysis Plan, Interim for Final Analysis, Changes to Planned Statistical Analyses Form, 16 March 2022

STATISTICAL ANALYSIS PLAN

AT-03A-001

A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF AT-527 IN SUBJECTS WITH MODERATE COVID-19

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V1.0, 15APR2021

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (dated 15Apr2021) for protocol AT-03A-001.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	15Apr2021	[redacted]	Not Applicable – First Version

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol AT-03A-001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 8.0 (amendment 7) dated 25Feb2021. A separate SAP for the Virology Sub-Study will be written by the [redacted] Pharmacokinetic (PK) group.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary efficacy goal is to significantly reduce Progressive Respiratory Insufficiency (PRI), assessed with the 6-tier scale of increasing levels of respiratory support and defined as a ≥ 2-tier increase in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), within the 14-day study period. The primary efficacy goal is a 50% reduction in the incidence of PRI in active treatment recipients compared to placebo recipients.

2.2. SECONDARY OBJECTIVES

The key secondary objectives are to evaluate the efficacy of AT-527 as compared to placebo in:

- Providing greater reduction in SARS-CoV-2 virus RNA as measured by RT-PCR at specified timepoints.
- Shortening the median time to clinical recovery by at least four days (based on achieving disease resolution in the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Status scale).
- Reduction in progression to respiratory failure or death (RFD), using the 6-point scale.

Other secondary objectives are to compare the active treatment vs. placebo in the following:

- Improvement in overall Clinical Status using the NIAID ordinal scale.
- Reduction in all-cause mortality.

- Shortening in duration of hospitalization for COVID-19.
- Shortening of time to sustained non-detectable SARS-CoV-2.
- Reduction in proportion of subjects SARS-CoV-2 positive at Days 5 and 14.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- Plasma concentrations of AT-527 and metabolites will be monitored in sparse samples collected from subjects with COVID-19.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a phase 2 double-blind, placebo-controlled, randomized treatment study evaluating AT-527 (or placebo) for 5 days in combination with supportive standard of care (SoC) compared to SoC alone in hospitalized/confined subjects with moderate COVID-19 disease and risk factors for poor outcomes. The study will enroll adults, age ≥18 years of age, with moderate COVID-19, not on a ventilator. Subjects must also have at least one of the known common risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes or asthma. Subjects will be documented as SARS-CoV-2 positive in an assay granted Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA).

Moderate disease will be defined by the following:

- Symptoms of lower respiratory infection with COVID-19, with initial symptom onset within 5 days prior to Screening:
    - At least 1 of the following: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
- Clinical signs indicative of lower respiratory infection with COVID-19 (as above), with:
    - SpO2 ≥ 93% on room air or requires ≤ 2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥

93%

Subjects will be randomized 1:1 (active:placebo). Subjects will receive one (1) tablet of 550 mg active drug (or matching placebo) every ~12 hours to complete **5 days** of treatment.

Table A Study Design

Disease Severity	Treatment Duration	Dosing Arms	
Moderate	5 days	active	550 mg AT-527 administered every ~12 hours (10 doses) + SOC
		placebo	AT-527 placebo administered every ~12 hours (10 doses) + SOC

*Randomized 1:1 (active:placebo)

A cohort of 20 subjects will initially be enrolled to preliminarily assess the safety of the 550 mg BID dosing regimen. Enrollment will be paused after the first 20 subjects, until the Data Safety Monitoring Board (DSMB) conducts a safety review. If study stopping criteria are not met, a second cohort of 20 subjects will be enrolled. Again, enrollment will be paused until the DSMB conducts a safety review of these data.

Subsequent pauses in enrollment will accommodate further DSMB reviews of safety data at enrollment milestones of 50% and 75% of the full enrollment target.

For each interim safety review, pooled safety data will be reviewed by the DSMB. The DSMB will alert the Sponsor if there are any safety concerns for active-treated subjects compared to placebo recipients.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6 of the protocol (Table 6-1).

3.3. CHANGES TO ANALYSES FROM PROTOCOL

- "Sparse plasma PK analyses, to assess PK parameters of AT-527 in COVID-19 subjects compared to PK data obtained in healthy human volunteers and HCV subjects" are specified in the protocol Section 8.2.4 but are

not included in this SAP. This is because only subjects diagnosed with COVID-19 are enrolled in this study. Plasma concentrations of study drug will be listed and summarized as applicable. 21DEC2020

- Per Protocol (PP) set will not be used for this study as for COVID-19 studies it is strongly recommended not to perform analyses based on a PP analysis set due to the short duration of the study, expected high number of protocol deviations and based on current regulatory guidelines and advice. 12Feb2021
- Modified Intent-to-Treat (mITT) analysis set is added in order to run the efficacy analysis excluding the subjects with negative SARS-CoV-2 test at baseline and who did not receive treatment. 12Feb2021
- Analysis of CRP (if quantified) is added. 12Feb2021
- Exploratory analysis of COVID-19 symptoms resolution, COVID-19 symptom severity and time to first SARS-CoV-2 negative test is added. 12Feb2021
- Analysis of change from baseline in antibody to SARS-CoV-2 (IgG and IgM). 09Mar2021
- Addition of an exploratory endpoint to run a similar analysis as Primary analysis but with a different threshold (PRI defined as a $\geq$ 1-tier increase from baseline). 09Mar2021
- Analysis of the secondary endpoint proportion of subjects Improving/Worsening from baseline in Clinical status has been updated to include more granularity. 09Mar2021
- Addition of an exploratory Time-weighted average change from baseline in quantitative SARs-CoV-2. 09Mar2021
- Definition of "Duration of hospitalization/confinement for COVID-19" was updated, Status 6 on the NIAID Clinical Status scale will not be considered as hospitalization and subjects with hospital discharge will be included. 09Mar2021
- TEAE definition updated to update the time frame to 28 days after last dose of study drug. 09Mar2021
- Addition of an exploratory endpoint: Level of SARS-CoV-2 infectious virus titer. 12Mar2021

4. PLANNED ANALYSES

4.1. DATA SAFETY MONITORING BOARD

A DSMB SAP, describing the methodology and the presentation of and access to results will be provided by [redacted] as a separate document.

4.2. INTERIM ANALYSIS

An administrative interim analysis will be carried out when the first 70 patients randomized have had follow-up to at least Day 14. The purpose of this analysis is to inform the planning of future clinical studies. The results will not be used to declare evidence of efficacy for the study, but a small alpha spend (0.0001) will be taken for this look. The analysis will be carried out by an independent statistician and interpreted by a small number of members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. It is acknowledged by the Sponsor that disclosure of interim results to members of the Sponsor study team will impact the interpretation of results of subsequent analyses, i.e. efficacy results may be considered as exploratory.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, database lock (DBL), and general study unblinding.

5. ANALYSIS SETS

5.1. ALL SCREENED SUBJECTS ANALYSIS SET

The all screened subjects (SCRN) analysis set will contain all subjects who provide informed consent for this study.

5.2. INTENT-TO-TREAT ANALYSIS SET

The Intent-to-Treat (ITT) analysis set will contain all subjects in the SCRN analysis set who were randomized to study drug.

For analyses and displays based on ITT analysis set, subjects will be classified according to randomized treatment.

5.3. MODIFIED INTENT-TO-TREAT ANALYSIS SET

The Modified Intent-to-Treat (mITT) analysis set will contain subjects in the ITT analysis set with positive qualitative SARS-CoV-2 RT-PCR test result at baseline from the central laboratory and who receive at least one dose of study drug (AT-527 or placebo).

For analyses and displays based on mITT analysis set, subjects will be classified according to randomized treatment.

5.4. SAFETY ANALYSIS SET

The safety (SAF) analysis set will contain all subjects in the SCRN analysis set who receive at least one dose of study drug (AT-527 or placebo). If there is any doubt whether a subject was treated or not, he/she will be assumed treated for the purposes of analysis.

For analyses and displays based on the SAF analysis set, subjects will be classified according to the actual treatment received.

5.5. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic (PK) analysis set will contain all subjects in the SCRN analysis set who were randomized to and received at least one dose of AT-527, and for whom evaluable plasma concentration data are available. Subjects who received placebo will not be included in the PK analysis set. If there is any doubt whether a subject was treated or not, he/she will be assumed treated for the purposes of analysis.

5.6. PROCESS FOR ANALYSIS SET ASSIGNMENT

The analysis sets that will be used to summarize, analyze, and list the data collected during the course of this study

are all defined based on objective criteria only. That is, none of the analysis set definitions included in this SAP contains subjective criteria (e.g., major protocol deviation potentially having an impact on the efficacy data). Hence, the authorization of this SAP will also stand as the agreement and authorization of the inclusion/exclusion of each subject in each analysis set.

6. General Considerations

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of the first dose of study drug, which is defined as Day 1.

Study Day will be computed as follows:

- Study Day = (Date of event –Date of first dose of study drug) + 1 if the date of the event is on or after the date of the first dose of study drug;
- Study Day = (Date of event – Date of first dose of study drug) if the date of the event is prior to the date of the first dose of study drug.

There is no Day 0. In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study drug (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the first dose of study drug coincide, that measurement will be considered pre-baseline. In cases where the time is missing, and the last non-missing measurement and the date of the first dose of study drug coincide, that measurement will be considered pre-baseline.

Adverse event (AE) start date and time is to be collected. Any adverse event with start date and time prior to the date and time of first study drug administration will be considered as a baseline sign/symptom. An adverse event starting on the date of first dose of study drug with missing start time or with start time the same as or after the start time of the first study drug administration will be considered treatment-emergent, i.e. post-baseline.

Medications starting on the date of first dose of study drug will be considered post-baseline.

6.3. Unscheduled Visits, Retests, and Early Termination Data

For by-visit summaries, data recorded at the nominal visit will be analyzed. Unscheduled visits for safety labs and SARS-CoV-2 test will also be included in by-visit summaries (if they have been mapped to a scheduled visit following the rules provided in Table B of Section 6.4) and will contribute to the baseline timepoint and/or worst/maximum/minimum post-baseline value, where required (e.g. shift table).

In case of a retest when retest is defined as having blood sample tested twice, the latest available measurement for that blood sample will be used for the by-visit summaries. In case of a retest when retest is defined as having two blood samples collected on the same day, results from the last blood sample will be used for the by-visit summaries.

Refer to Section 6.4 for the conventions to map unscheduled and early termination data to protocol-defined visit windows. Early termination data might also contribute to the worst/maximum/minimum post-baseline value, where required (e.g. shift table).

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions

Early termination data will be mapped based on the scheduled Study Day of each scheduled visit as specified in the protocol schedule of events.

If early termination data are mapped to a scheduled visit for which data from the scheduled visit are also available (i.e., non-missing), the data collected at the scheduled visit will be used in the by-visit summaries. If early termination data are mapped to a scheduled visit for which data from the scheduled visit are not available (i.e., missing), data from the early termination visit will be used in the by-visit summaries.

Visits assigned as "unscheduled" by labs for safety data and SARS-CoV-2 test will be mapped based on the table below. If there is more than one unscheduled visit in a visit window, the visit closest to the target date will be used in by-visit analyses. If there is a tie between the numbers of days from the target date, the later visit will be used. Unscheduled visits that fall within the protocol-defined visit windows will be summarized in the by-visit analyses only if there is no scheduled visit available in the analysis visit window.

Table B: Analysis Visit Windows

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Analysis visit windows for safety labs and SARS-CoV-2 Test		
Baseline	Day 1	Day -1 or Day 1/before 1st dose
Day 2	Day 2	Day 2 to Day 3
Day 5	Day 5	Day 4 to Day 6
Day 8	Day 8	Day 7 to Day 9
Day 10	Day 10	Day 10 to Day 11
Day 12	Day 12	Day 12 to Day 13
Day 14	Day 14	Day 14 to Day 18
Day 21	Day 21	Day 19 to Day 25
Day 28	Day 28	Day 26 to Day 46
Day 63	Day 63	Day 47 to Day 79

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

- Change from baseline = Test value at post-baseline visit – Baseline value

Percent change from baseline will be calculated as:

- Percent change from baseline (%) = (Change from baseline at post-baseline visit / Baseline value) X 100%

7. STATISTICAL CONSIDERATIONS

For continuous data, descriptive statistics (i.e., n [number of subjects with available data], mean, standard deviation [SD], median, minimum, and maximum values) will be presented by treatment group and visit, when applicable.

For categorical data, the number and percentages of subjects in each category will be presented by treatment group and visit, when applicable

7.1. SAMPLE SIZE CALCULATION

The sample size calculation was based on these assumptions regarding the primary endpoint:

The primary endpoint for this study is the proportion of subjects with PRI, defined as a ≥ 2-tier increase in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), using the 6-tier hierarchical scale of Respiratory Support methods.

The primary efficacy goal is to reduce the incidence of PRI by 50% for active-dosed subjects compared to placebo recipients. The featured timeframe for this primary endpoint analysis will be the 14-day primary study period, with secondary analyses at study Days 10, 21, and 28.

With this study's relatively high-risk COVID-19 subject population (one or more known risk factors for poor outcomes), the study postulate is that 40% of placebo recipients will experience PRI during the 14-day study period, and the efficacy goal is therefore to reduce that incidence of PRI to 20% or less in active recipients.

Assuming PRI rates (PRIR) of 0.4 and 0.2 in the control and experimental arms, respectively, at alpha one-sided of 0.025, and at a power of 0.8, a total of 182 subjects are required at a 1:1 allocation, i.e. 91 per study arm. The study statistical hypotheses are as follows:

- H_0: $Experimental_{PRIR} \geq Control_{PRIR}$
- H_a: $Experimental_{PRIR} < Control_{PRIR}$

The key secondary endpoints will be tested, in order, only if the primary efficacy endpoint meets its success criteria, and each higher endpoint meets its success criteria. This hierarchical testing strategy will preserve study alpha.

First Key Secondary Efficacy Endpoint: Change from baseline in log10 SARS-CoV-2 virus RNA. If 90% of patients have quantifiable viral load at baseline and the standard deviation for change from baseline log10 viral load is 2

log10 copies/mL, then there is at least 85% power to detect a 1 log10 greater reduction in viral load using a two-sided level 0.05 test, i.e. a one-sided level 0.025 test. The corresponding statistical hypotheses are as follows:

- H_0: Experimental change from baseline ≥ Control change from baseline
- Ha: Experimental change from baseline < Control change from baseline

Second Key Secondary Efficacy Endpoint: Median days to Clinical Recovery (MDCR), from randomization to a disease resolution status in the NIAID Clinical Status scale described in the protocol Section 6.9 - i.e. achieving Clinical Status 6, 7, or 8 by Day 14, according to whether the subject is still hospitalized at Day 14 or is an outpatient. Patients without observed clinical recovery will have clinical recovery time assigned as 15 days to preserve the ranks for the comparison.

The power assessment for this endpoint assumed days to clinical recovery in the control and experimental arms have exponential distributions. If the median time to recovery is 12 days for the placebo arm, then a one-sided 0.025 level test has 80% power to detect a 5 day reduction in median recovery time with the experimental arm (i.e. median is 7 days for experimental arm). If these assumptions hold, we would expect to observe approximately 50 and 68 clinical recoveries in the placebo and experimental arms, respectively, during the 14 day follow-up. The study statistical hypotheses are as follows:

- H_0: ExperimentalMDCR ≥ ControlMDCR
- Ha: ExperimentalMDCR< ControlMDCR

Third Key Secondary Efficacy Endpoint: Respiratory failure or death

The next key secondary efficacy endpoint of the study is the proportion of subjects with Respiratory Failure or Death (RFD), for which the featured assessment will be at Day 28, with additional analyses at Days 10, 14, and 63. Assuming the RFD rate (RFDR) is 0.35 and 0.15 in the control and experimental arms, respectively, at alpha one-sided of 0.025, at a total of 182 subjects with a 1:1 allocation, i.e. 91 per study arm, the power is 85%. The study statistical hypotheses are as follows:

- H_0: ExperimentalRFDR ≥ ControlRFDR
- Ha: ExperimentalRFDR< ControlRFDR

7.2. MISSING DATA

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.1.2,16.2.1.2 16.2.1.3 and 16.2.3.6 of this analysis plan.

Missing safety data will not be imputed, except for missing AE severity and relationship data (refer to Section 17.1.1). Partial or completely missing AE and medication dates will be handled as described in APPENDIX 1.

7.3. STATISTICAL TESTS

All statistical tests will be conducted at the two-sided 5% significance level (i.e. 2.5% for one-sided tests), unless otherwise specified in the description of the analyses. Confidence Intervals (CIs) will be two-sided with 95% coverage.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

A sequential gatekeeping strategy will be utilized for the primary and the secondary efficacy endpoints to maintain the one-sided Type 1 error rate at α=0.025. The efficacy objectives will be tested in the following order:

(1) The primary efficacy endpoint of proportion of subjects with PRI in the ITT analysis set will be tested at one sided $\alpha = 0.025$.

(2) If the primary efficacy comparison achieves statistical significance, there may be two comparisons for the first key secondary endpoint. The comparison at Day 5 will be tested first at one-sided α=0.025. If statistical significance is met on the Day 5 comparison, then the quantitative SARS-CoV-2 changes at Day 2 would be formally tested at one-sided α=0.025.

(3) The second key secondary endpoint of median days to clinical recovery will be tested at one sided $\alpha = 0.025$ only if the primary efficacy objective and the first key secondary objective are met for Day 5 and Day 2 (at one-sided α=0.025).

(4) The final key secondary endpoint of proportion of subjects with respiratory failure or death will be tested at one sided $\alpha = 0.025$ only if both the primary efficacy objective and the first and second key secondary objectives are met (at one-sided α=0.025).

Only nominal two-sided p-values will be provided for the other secondary and the exploratory efficacy endpoints.

No statistical testing will be performed for the safety endpoints.

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers. Data from all centers will be pooled together in the analyses and there are no plans to perform an analysis of homogeneity of the results across centers.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The analyses will be adjusted for the following covariates and factors.

- Geographic regions (stratification variable for randomization)
  - North America
  - South America
  - Europe
  - Rest of World
- Baseline quantitative SARS-CoV-2 (virologic endpoints only)

If data are too sparse for one level of the Geographic region factor (i.e., less than 5% of subjects), South America and Rest of World will be combined. If the level is still less than 5% of subjects, then the factor will not be included in the statistical model/test. Determination of the factor(s) to be included into the statistical models/tests will be finalized before the study DBL in a blinded fashion.

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Sections 16.1.5. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The subgroups are:

- Age (years) at informed consent (< 70 and ≥ 70);
- Gender (male and female);
- Geographic region (See Section 7.6);
- Obesity (BMI > 30 kg/m^2 and BMI ≤ 30 kg/m^2) at screening;
- Hypertension co-morbidity at screening (Systolic Blood Pressure (SBP) > 140 and/or Diastolic Blood Pressure (DBP) >90) (yes and no);
- Diabetes co-morbidity at study entry (yes or no);
- Asthma co-morbidity at study entry (yes and no);
- Number of high-risk factors (1, >1) (Obesity at screening, hypertension co-morbidity at screening, diabetes and asthma co-morbidities at study entry);
- Number of comorbidities (1, >1) from Medical History CRF page (including alcohol and drug abuse);
- Time since start of COVID-19 symptoms (< median and ≥ median) (ITT analysis set);
- Time since initial COVID-19 diagnosis to screening (< median and ≥ median) (ITT analysis set);
- Baseline quantitative SARS-CoV-2 (< median and ≥ median) (mITT analysis set).

If data are too sparse for one subgroup (i.e., less than 5% of subjects in the subgroup), neither descriptive statistics nor statistical inferences will be provided for that subgroup, as well as for its complementary subgroup. For example, if only 5% of subjects have obesity, no subgroup analysis will be provided for the subjects with or without obesity.

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

8. OUTPUT PRESENTATIONS

APPENDIX 2 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore, the format and content of the summary tables, figures, and listings to be provided by [redacted] Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Number of subjects screened will be presented overall for the SCRN analysis set. Number and percentage of subjects with screen failure and reason for screen failure will also be presented overall based on the SCRN analysis set. Number of subjects randomized will be presented overall and by treatment group for the SCRN analysis set.

Number and percentages of subjects treated, who completed/discontinued early from treatment (including reason for withdrawal), and who completed/discontinued early from the study (including reason for withdrawal) will be provided overall and by treatment group based on the ITT analysis set.

Similarly, number of subjects included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by treatment group based on the ITT analysis set. A listing showing inclusion and exclusion of each subject from each analysis set, including reason for exclusion, will be provided.

9.2. PROTOCOL DEVIATIONS

All protocol deviations (critical, major, and minor) will be recorded in the clinical trial management system (CTMS) protocol deviations log for the duration of the study (refer to the Protocol Deviations Management Plan for the definition of critical, major, and minor protocol deviations). Site-level identified protocol deviations will be replicated for all subjects ongoing in the study at the site at the time of the protocol deviation and presented in the summary outputs as subject-level protocol deviation unless otherwise indicated at the deviation review meeting before DBL.

Number and percentage of subject with critical and major protocol deviations will be provided overall and by treatment group based on the ITT analysis set for each category of protocol deviations specified in the Protocol Deviations Management Plan.

A listing of protocol deviations identified by the study team (critical, major, and minor) will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – calculated relative to date of consent, as continuous and categorical (<70 and ≥70);
- Gender (male or female);
- Geographic region;
- Childbearing potential for female subjects only (yes or no; and reasons if not of childbearing potential);
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Not Reported, Unknown);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown);
- Weight (kg);
- Body Mass Index (BMI) (kg/m^2);
- Obesity (BMI > 30 kg/m^2 and BMI ≤ 30 kg/m^2);
- Hemoglobin A1c (mmol/mol);
- Hypertension co-morbidity at screening (Systolic Blood Pressure (SBP) > 140 and/or Diastolic Blood Pressure (DBP) >90) (yes and no);
- Quantitative SARS-CoV-2 based on central lab;
- Clinical Status Score;
- Immunoglobulin G (IgG) (if data available);

- Immunoglobulin M (IgM) (if data available);
- Serostatus (positive, negative, indeterminate) (if data available).

The following comorbidities, as captured on the Medical History page of the eCRF, will also be reported for this study:

- Any comorbidity, defined as having any of the comorbidities listed below;
- Diabetes;
- Heart Disease;
- Chronic Lung Disease;
- Chronic Liver Disease;
- Asthma;
- HIV;
- Tuberculosis;
- Alcohol Abuse;
- Drug Abuse.

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics overall and by treatment group based on the SAF analysis set. For categorical demographic and other baseline characteristics, number and percentage of subjects in each category will be provided overall and by treatment group based on the SAF analysis set. No statistical testing will be carried out for demographic or other baseline characteristics.

Demographic, other baseline characteristics, and comorbidities data will be listed.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as follows:

- BMI (kg/m^2) = weight (kg)/ [height $(m)^2$]

11. MEDICAL HISTORY

Medical history is defined as any medical conditions/diseases that started and stopped before screening as well as any medical conditions/diseases that started before screening AND were ongoing at the time of screening.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later and will be summarized by System Organ Class and PT overall and by treatment group based on the SAF. A subject having more than one medical condition/disease within the same System Organ Class/PT will be counted only once for that System Organ Class or PT. In the summary, System Organ Classes will be sorted in alphabetical order and within each System Organ Class, PTs will be sorted in decreasing order of total frequency.

12. DISEASE HISTORY

The following disease history characteristics will be summarized overall and by treatment group based on the SAF analysis set:

- Time since first COVID-19 symptoms onset (days) – calculated relative to Study Day 1 (refer to Section 6.1);
- Time since COVID-19 diagnosis (days) – calculated relative to Study Day 1;
- Hospitalized at study entry;
- Time since hospital admission (days) – calculated relative to Study Day 1;
- Time since ICU/HDU admission (days) for subjects in ICU/HDU at study entry – calculated relative to Study Day 1;
- Presence and severity of each of the following COVID-19 symptoms at study entry:
    - Cough;
    - Fever;
    - Myalgia;
    - Diarrhea;
    - Dyspnea;

- Headache;
- Nausea;
- Vomiting;
- Fatigue/malaise;
- Loss of appetite;
- Loss of smell;
- Loss of taste.

All disease history characteristics will be listed.

12.1. DERIVATIONS

'Time since' disease history characteristics, in days, will be calculated as follows:

- Time since first COVID-19 symptom(s) (days) = (Date of Study Day 1 – Date of first COVID-19 symptom(s) onset); date of onset of COVID-19 symptoms as captured on the Medical History page of the eCRF;
- Time since COVID-19 diagnosis (days) = (Date of Study Day 1 - Date of COVID-19 diagnosis); date of COVID-19 diagnosis as captured on the Medical History page of the eCRF;

13. MEDICATIONS

- Prior medications are defined as any medication that started and stopped prior to the date of Study Day 1
- Concomitant medications are defined as:
  - Any medication that started before the date of Study Day 1 AND ended on the date of Study Day 1 or were ongoing at that time;
  - Any medication that started on or after the date of Study Day 1.

Partially or completely missing medication start and stop dates will be handled as described in APPENDIX 1.

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by treatment group based on the SAF analysis set. A subject having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

No summary will be presented for the post-study medications, but all medications (prior, concomitant, and post-study) will be listed.

14. EXPOSURE TO STUDY DRUG

Duration of exposure to the study drug, in days, will be summarized by treatment group based on the SAF analysis set.

14.1. DERIVATIONS

Duration of exposure, in days, will be calculated as follows:

- Duration of exposure (days) = (Date of last dose of study drug – Date of first dose of study drug) + 1

Interruptions to dosing will not be considered for duration of exposure.

15. EXPOSURE TO STUDY DRUG

Exposure to study drug, as number of doses received, total amount of drug taken (mg) and proportion of planned dose received , will be summarized by treatment group based on the SAF analysis set.

15.1. DERIVATIONS

Proportion of planned dose received will be calculated as follows:

- Proportion = Number of tablets taken / Number of planned tablets

where:

- Number of tablets taken = (total number of tablets dispensed – total number of tablets returned)
- Number of planned tablets = 10

16. EFFICACY ENDPOINTS

Unless otherwise indicated, all efficacy summaries and figures will be presented by treatment group and visit, when appropriate, based on the ITT and mITT analysis set. Method to control the overall type 1 error of the study to 5% is described in Section 7.4.

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint for this study is the proportion of subjects with PRI on or before Day 14. The PRI is defined as a ≥ 2-tier increase from baseline in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), using the 6-tier hierarchical scale of Respiratory Support methods which have the following levels:

- LEVEL 1: Normal oxygenation on room air (SpO2 ≥ 93), no need for supplemental O_2
- LEVEL 2: Persistent hypoxemia on room air (SpO2 < 93) with requirement for low-level supplemental O_2 by nasal cannula or mask (up to 2L/min) to maintain SpO2 ≥ 93
- LEVEL 3: Requirement for higher levels of passive supplemental O_2 by nasal cannula or mask (≥ 2L/min) to maintain SpO2 ≥ 93
- LEVEL 4: Requirement for oxygenation by positive-pressure devices, e.g. Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP) or other non-invasive positive-pressure respiratory support methods to maintain satisfactory oxygenation and/or ventilation
- LEVEL 5: Requires invasive respiratory support (intubated mechanical ventilation or ECMO)
- LEVEL 6: Death

The assessment scores of respiratory support level are collected on the Ordinal Scale of Respiratory Support Level

page of the eCRF (electronic Case Report From).

16.1.2. Missing Data Imputation Method for Primary Efficacy Endpoint

First, subjects will be declared as PRI if they have a ≥ 2 increase observed up to and including Day 14, even if they have some days with missing values; as long as one day has ≥ 2 increase they are considered PRI.

If subjects had NO recorded PRI up to Day 14 then:

1- If there is an observed score at Day 14 then the subject will be considered as NO PRI

2- If a subject discontinues without having a PRI observed prior to Day 14, they will be considered as follows:

Primary reason of early study discontinuation	PRI?
Adverse event, Death, Lack of efficacy, Lost to follow up, Non-compliance with study drug, Progressive disease, Met protocol lab criteria for discontinuation	Yes
Recovery, Pregnancy, Protocol deviation, Physician decision, Sponsor Request, Withdrawal by subject, Study terminated by sponsor	No

The assessment of the primary reason for early discontinuation will be collected on the disposition page of the eCRF

3- If a subject completed the study and got discharged from hospital prior to Day 14, they will be considered as NO PRI.

16.1.3. Primary Analysis of Primary Efficacy Endpoint

The primary efficacy goal is to reduce the incidence of PRI by 50% for active-dosed subjects compared to placebo recipients. Number and proportion of subjects with and without PRI during the 14-day primary study period will be provided by treatment group based on the ITT analysis set. The difference between the treatment groups will be presented with corresponding 95% CI. A Cochran-Mantel-Haenszel (CMH) general association test will be used to test for differences in rates between the treatment groups controlling for geographic region (see Section 7.6).

16.1.4. Sensitivity Analyses for Primary Efficacy Endpoint

As sensitivity analyses to inclusion/ Exclusion criteria violation that may affect the primary analysis of the primary

efficacy endpoint, the primary analysis of the primary efficacy endpoint will be repeated:

1. On mITT analysis set.
2. Excluding the subjects with symptoms for more than 5 days prior to screening.

As a third sensitivity analysis, subjects will get imputed as follows:

1- If ≥ 2 increase observed up to and including Day 14 then PRI

2- Else, if there is an observed score at Day 14 without PRI then NO PRI

3- Else, if a subject discontinues the study without having a PRI observed prior to Day 14, then PRI

4- Else, if subject was discharged from hospital prior to Day 14, then NO PRI

As a fourth sensitivity analysis, primary analysis of the primary efficacy endpoint will be repeated updating the imputation as follows:

If a subject discontinues without having a PRI observed prior to Day 14, they will be considered as follows:

Primary reason of early study discontinuation	PRI?
Adverse event, Death, Lack of efficacy, Lost to follow up, Non-compliance with study drug, Progressive disease, Met protocol lab criteria for Discontinuation, Protocol deviation, Physician decision, Sponsor Request, Withdrawal by subject, Study terminated by sponsor	Yes
Recovery, Pregnancy	No

The same CMH test will be performed as for the main analysis.

16.1.5. SUPPLEMENTARY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

The following supplementary analyses will be performed for the primary efficacy endpoint:

- For each subgroup defined in Section 7.7, number and proportion of subjects with and without PRI during the study of 14 days will be provided by treatment group.
- The primary analysis of the primary efficacy endpoint will be repeated to analyze the proportion of subjects

with PRI on or before Days 10, 21, 28 and 63, respectively, instead of the 14-day primary study period.

16.2. SECONDARY EFFICACY

16.2.1. KEY SECONDARY EFFICACY ENDPOINTS

16.2.1.1. Change from Baseline in Quantitative SARS-CoV-2

The first key secondary endpoint is the change from baseline in amount of quantitative SARS-CoV-2 as measured by RT-PCR at the time points required in the protocol schedule of assessments (Days 2, 5, and 14). Quantitative SARS-CoV-2 will be assessed quantitatively via the TaqPath assay, and qualitatively via a separate assay, COBAS.

Analysis will be performed on the mITT analysis set only.

16.2.1.2. Time to Clinical Recovery (days) by Day 14

The second key secondary endpoint is time to clinical recovery in days on or before Day 14, defined as

- Time to clinical recovery by Day 14 (days) = (Date of clinical recovery on or before Day 14 – Date of randomization) +1

Clinical recovery is defined as achieving the NIAID clinical status of level 6 or above, which include subjects who are no longer hospitalized (level 7 or 8) or hospitalized but not requiring supplemental oxygen (level 6). The clinical status and assessment date/time will be reported on the Ordinal Scale for Clinical Severity page of the eCRF.

The date of clinical recovery is based on the date the score is first ≥ 6. Should there be no clinical recovery, then the time to clinical recovery is set to 15 days.

The 8 levels of NIAID are the following:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen

5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)

6. Hospitalized, not requiring supplemental oxygen – no longer requires close medical care for COVID-19 (Note: Examples include recovered subjects needing inpatient quarantining/confinement or needing social services connections for outpatient living).

7. Not hospitalized, but with limitation on activities and needing close outpatient care for COVID-19 manifestations.

8. Not hospitalized, no limitations on activities, no need for continued close medical care.

16.2.1.3. Proportion of Subjects with Respiratory Failure or Death (RFD) by Day 28

The third key secondary endpoint is proportion of subjects with RFD on or before Day 28, which is defined as progression to respiratory support level 5 (requiring intubated mechanical ventilation or ECMO) or 6 (death) (Section 16.1.1). The data will be reported on the Ordinal Scale of Respiratory Support Level and Death Details pages of the eCRF. Proportion of subjects with RFD on or before Days 10, 14, and 63 will also be analyzed. Missing values will be treated as follows:

- If there is no ordinal scale value because the subject discontinued prior to Day 28, then the subject will be assumed as NO RFD.
- If a subject has been discharged prior to Day 28 then they would be assumed as NO RFD.
- If a subject is still on study and in the hospital at Day 28 but with no scale score at Day 28 they will be excluded from the denominator.

16.2.2. SENSITIVITY ANALYSES FOR KEY SECONDARY EFFICACY ENDPOINTS

The analysis of the Key Secondary Efficacy Endpoint of proportion of Subjects with Respiratory Failure or Death (RFD) by Day 28 will be repeated with missing values treated as follows:

- If there is no ordinal scale value because the subject discontinued prior to Day 28, then the subject will be assumed as RFD.
- If a subject has been discharged prior to Day 28 then they would be assumed as NO RFD.

- If a subject is still on study and in the hospital at Day 28 but with no scale score at Day 28 they will be excluded from the denominator.

16.2.3. OTHER SECONDARY EFFICACY ENDPOINTS

16.2.3.1. Proportion of Subjects Improving/Worsening from Baseline in Clinical Status Using the NIAID Ordinal Scale by Day 5 and 14

The endpoint is based on the lowest observed value on the clinical status (NIAID) scale between D1 to D5 and D1 to D14. Subjects will be classified as "improved", "same" or "worsened compared to Baseline.

16.2.3.2. All-cause Mortality

A secondary endpoint is the all-cause mortality i.e., the proportion of subjects who died during the study including the follow-up visits regardless of the cause of death. Death may occur after the 14-day primary study period as some subjects might remain on prolonged ventilation before recovering or dying. Mortality will be assessed at Day 10, 14, 28 and 63. Subjects who are discontinued from the study for a reason other than death, prior to each of Day 10, 14, 28 and 63 will be excluded from the denominator.

16.2.3.3. Duration of Hospitalization for COVID-19 (days)

A secondary endpoint is the duration of hospitalization/confinement in days, defined as the time from start of treatment to either achieving Status 7 or 8 on the NIAID Clinical Status scale or hospital discharge (which ever happens first). Data from the follow-up period after Day 14 will be included. This endpoint will be calculated as follows:

- Duration of Hospitalization for COVID-19 (days) = ((Date of achieving status 7 or 8 OR hospital discharge) – Study Day 1) +1

Subjects who don't achieve status 7 or 8 nor have hospital discharge will be censored at end of study (EOS). Subjects who die will be censored to the latest EOS date available.

16.2.3.4. Time to Sustained Non-detectable SARS-CoV-2 (days)

A secondary endpoint is the time to sustained nondetectable SARS-CoV-2 RNA from randomization in days,

calculated as follows:

- Time to sustained nondetectable SARS-CoV-2 (days) = (Start date of sustained nondetectable SARS-CoV-2 – Date of randomization) +1

The SARS-CoV-2 test results during the study will be captured by the Central Laboratory. The start date of sustained nondetectable SARS-CoV-2 is defined as the earliest date when the test result is negative and remains negative until end of the study or D14 as the test is not required after that day.

Analysis of this endpoint will be performed on the mITT analysis set only. Both COBAS and TaqPath assays report results as detectable or non-detectable. Each method has its own limit of detection. The analyses will be performed separately on results from each assay.

The following algorithm will be followed to determine how a subject which didn't meet the event (i.e., Non-detectable SARS-CoV-2) should be censored:

1. If the subject has no post-baseline SARS-CoV-2 test results, the subject will be censored at the date of first dose of study drug;
2. If the subject's SARS-CoV-2 test remain positive during the study, the subject will be censored at the date of their latest of SARS-CoV-2 test with a non-missing result;
3. If the subject has negative SARS-CoV-2 but not sustained, i.e. the negative result was not confirmed at a later scheduled visit (due to missing data, early discontinuation, study completion, etc.), the subject will be censored at the date of their latest SARS-CoV-2 test date with a non-missing result;
4. If subject has missing baseline SARS-CoV-2 data, but has a post-baseline positive SAS-CoV-2 test result, the subject will be considered SARS-CoV-2 positive at baseline. Otherwise, a subject with missing baseline data will be censored at Day 1.
5. If subject has negative SARS-CoV-2 at baseline, the subject will be censored at Day 1.

16.2.3.5. Time to first SARS-CoV-2 Negative Test

A secondary endpoint is the time to first SARS-CoV-2 negative test in days, calculated as follows:

- Time to first SARS-CoV-2 negative test (days) = (First negative SARS-CoV-2 Date – Date of randomization) +1

The SARS-CoV-2 test results during the study will be captured by the Central Laboratory. The date of first negative SARS-CoV-2 is defined as the earliest date when the test result is negative.

Analysis of this endpoint will be performed on the mITT analysis set only. Analyses will be carried out based on both COBAS and TaqPath results.

The following algorithm will be followed to determine how a subject which didn't meet the event (i.e., Negative SARS-CoV-2) should be censored:

1. If the subject has no post-baseline SARS-CoV-2 test results, the subject will be censored at the date of first dose of study drug;
2. If the subject's SARS-CoV-2 test remain positive during the study, the subject will be censored at the latest day of SARS-CoV-2 test date;

16.2.3.6. Proportion of Subjects SARS-CoV-2 Positive at Each Time Point

The proportion of subjects who are SARS-CoV-2 positive (i.e. detectable) at each scheduled time point will be analyzed as secondary efficacy endpoints. Analyses will be carried out based on both COBAS and TaqPath results. The SARS-CoV-2 test results will be collected by the Central Laboratory. Missing SARS-CoV-2 test results will be treated as positive.

16.2.4. Analysis of Key Secondary Efficacy Endpoints

Method to control the overall type 1 error is described in Section 7.4.

16.2.4.1. Change from Baseline in Quantitative SARS-CoV-2

The first key secondary efficacy goal is to provide greater reduction in quantitative SARS-CoV-2.

The analyses will summarize log10 quantitative SARS-CoV-2 at each required scheduled timepoint. Missing data will not be imputed. Separate summaries will be performed for:

- All subjects who have baseline quantitative SARS-CoV-2 above the limit of quantification.
- All subjects who have baseline quantitative SARS-CoV-2 above the median.

- All subjects who have baseline quantitative SARS-CoV-2 above 4 log10 copies/mL.
- All subjects who have baseline quantitative SARS-CoV-2 above 6 log10 copies/mL.

For each summary, observations reported as below the limit of quantitation (LOQ) by the quantitative TaqPath assay will be assigned a value each of the method below:

- Method 1:
  - Above LOD by TaqPath: TaqPath LOQ-1.
  - Below LOD by TaqPath: TaqPath LOQ/2.
- Method 2:
  - If non detectable by COBAS and below LOD by TaqPath: COBAS limit of detection (LOD) /2
  - If detectable by COBAS: TaqPath LOQ/2

Quantitative laboratory parameters reported as "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries. For samples reported outside the limits of quantification, listings will display "< X" or "> X", as appropriate.

The analyses will compare change from baseline log10 quantitative SARS-CoV-2 at each required scheduled timepoint. Any missing data will not be included in the analyses. Change from baseline quantitative SARS-CoV-2 will be compared between the AT-527 group and the placebo group at each of days 2, 5, and 14 using ANCOVA with treatment as a factor and log10 baseline quantitative SARS-CoV-2 as a covariate. For each time point and LOQ handling method, the least squares mean (LSM) change and its standard error of means (SE) in each group, the differences between two groups in LSM change with corresponding 95% confidence intervals (CIs), and p-values will be presented. Statistical significance at Day 2 and Day 5 will be assessed based on two-sided 0.025 level test to account for 2 comparisons. The formal statistical comparison will be based on Method 1.

The raw and LSMs change from baseline in log10 will also be presented graphically over time.

16.2.4.2. Time to Clinical Recovery (days) by Day 14

Another key secondary efficacy goal is to shorten the median days to clinical recovery (MDCR) by at least 4 days for active-dosed subjects compared to placebo recipients during the 14-day primary study period. The median times

to clinical recovery will be presented for each treatment group as well as the number and percentage of subjects with and without clinical recovery. The Wilcoxon Mann-Whitney test will be used to test that there is no difference between the treatment groups by a one-sided α=0.025 p-value.

As a sensitivity analysis a Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the time to clinical recovery (days). Subjects will be censored as follows:

- If subject dies without clinical recovery, censor at Day 15
- If subject has no post-baseline scale, censor at Day 1
- If no clinical recovery censor at the last day (date of the last non-missing scale score, prior to and including Day 14)

Kaplan-Meier estimates of the time will be provided at the 25th, 50th (median), and 75th percentiles along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates will be derived from the Kaplan-Meier estimates using the log-log transformation.

The p-value associated with the log-rank test statistic will be provided and compared at the one-sided 0.025 alpha level based on a null hypothesis that there is no difference between the two treatment groups and will be presented for descriptive purpose only.

16.2.4.3. Proportion of Subjects with RFD by Day 28

The secondary key efficacy endpoint of proportion of subjects with RFD by Day 28 will be analyzed similarly to the primary efficacy endpoint as described in Section 16.1.3. The one-sided p-value will be calculated to test the null hypothesis that the proportion of subjects with RFD on and before Day 28 is less in the treated group.

16.2.5. Analysis of Other Secondary Efficacy Endpoints

The distribution of subjects improved/the same/worsened from baseline in clinical status will be compared between treatment groups at Day 5 and Day 14 with a Mann-Whitney nonparametric test. The lowest observed value on the clinical status (NIAID) scale during between D1 to D5 and D1 to D14 will be used.

The number and percentage of subjects who have "improved", "same" or "worsened" based on their lowest NIAID ordinal scale between D1 to D5 and D1 to D14 will also be presented.

The proportion of subjects who died during the study regardless of the cause of death will be analyzed in the same manner as the primary efficacy endpoint at Day 10, 14, 28 and 63.

Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the duration of hospitalization for COVID-19 (days), for the time to sustained non-detectable SARS-CoV-2 (days) and the time to first SARS-CoV-2 negative test (Days). Kaplan-Meier estimate of the time will be provided at the 25th, 50th (median), and 75th percentiles along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at each scheduled time point will be derived from the Kaplan-Meier estimates using the log-log transformation.

The p-value associated with the log-rank test statistic will be provided and compared at the two-sided 0.05 alpha level based on a null hypothesis that there is no difference between the two treatment groups and will be presented for descriptive purpose only. For the time to sustained non-detectable SARS-CoV-2 (days) and the time to first SARS-CoV-2 negative test (Days), separate analyses will be performed for:

- All subjects who have baseline quantitative SARS-CoV-2 above the limit of quantification.
- All subjects who have baseline quantitative SARS-CoV-2 above the median.
- All subjects who have baseline quantitative SARS-CoV-2 above 4 log10 copies/mL.
- All subjects who have baseline quantitative SARS-CoV-2 above 6 log10 copies/mL.

Number and proportion of subjects with SARS-CoV-2 positive will be provided by treatment group at each timepoint. The difference between the treatment groups will be presented with corresponding 95% CI. A Cochran-Mantel-Haenszel (CMH) general association test will be used to test for differences in rates between the treatment groups controlling for geographic region. Separate analyses will be performed for:

- All subjects who have baseline quantitative SARS-CoV-2 above the limit of quantification.
- All subjects who have baseline quantitative SARS-CoV-2 above the median.
- All subjects who have baseline quantitative SARS-CoV-2 above 4 log10 copies/mL.
- All subjects who have baseline quantitative SARS-CoV-2 above 6 log10 copies/mL.

16.2.6. OTHER SECONDARY ANALYSES

The following additional secondary analyses will be performed:

- The analysis of the of time to clinical recovery by Day 14 (key secondary efficacy endpoint) will be repeated to analyze time to clinical recovery by Day 28 and 63. The data will be censored at Day 28 and Day 63 respectively instead of Day 14.
- The analysis of the proportion of subjects with RFD by Day 28 will be repeated to analyze proportion of subjects RFD by Day 10, 14, and 63, respectively.
- The secondary analysis of all-cause mortality will be repeated for deaths primarily due to respiratory failure and deaths due to other causes. The primary cause of death will be reported on the Death Details page of the eCRF.
- All-cause mortality at Day 10, 14, 28 and 63 will also be summarized by primary death cause using descriptive statistics.
- The observed NIAID scores and the change from baseline values will be summarized using descriptive statistics at each scheduled day. If a subject dies, the NIAID score of 6 will be carried forward to the later visits.
- The observed respiratory support levels and change from baseline values will be summarized using descriptive statistics at each scheduled day.

16.3. EXPLORATORY EFFICACY

The exploratory efficacy endpoints are:

- Time to a National Early Warning Score (NEWS) score ≤ 2 from Screening (days) for subjects whose Screening NEWS score was >4 (the NEWS score is a subject triaging score developed in Europe);
- Time to COVID-19 symptom resolution;
- Individual COVID-19 symptoms severity over time;
- Level of C-Reactive Protein (CRP) over time (if data available);

- Level of IgG and IgM over time and change from baseline (if data available);
- Level of SARS-CoV-2 infectious virus titer (if data available);
- Serial assessment of the appearance of antibody to SARS-CoV-2 in study subjects' serum samples, when validated antibody tests become more widely available; (this endpoint will be covered in a separate SAP);
- Other relevant COVID-19-specific tests or SARS-CoV-2 tests that may become available (this endpoint will be covered in a separate SAP);
- Proportion of subjects with a ≥ 1-tier increase PRI on or before Day 14;
- Time-weighted average change from baseline in quantitative SARS-CoV-2.

16.3.1. EXPLORATORY EFFICACY ENDPOINTS

16.3.1.1. Time to a NEWS Score ≤ 2 (days)

An exploratory efficacy endpoint is the time to a NEWS score ≤ 2 from Screening, in days, for subjects whose screening NEWS score was > 4.

The NEWS identifies a subject at risk of deterioration and prompts critical care interventions. It is comprised of 7 physiological parameters. Each of these physiological parameters is rated using a 4-point Likert scale (0= no risk to 3 = high risk). The NEWS score is obtained by summing the 7 physiological parameter individual scores and ranges from 0 to 21, with higher score indicating higher risk of deterioration and need for escalation in clinical care, including transfer of the subject to a higher level of care hospital unit. The NEWS score is set to missing if at least one physiological parameter individual score is missing.

For subjects whose screening NEWS score was > 4, the time to a NEWS score ≤ 2 will be calculated as follows:

- Time to a NEWS score ≤ 2 (days) = (Earliest post-baseline assessment date where NEWS score is ≤ 2 – Date of the screening visit)

NEWS score data will be calculated using data from the Vital Signs page and the Level of Consciousness page of the eCRF collected on the same date. See details in Appendix 5.

Missing baseline NEWS scores will be considered as > 4.

Subjects with no post-baseline NEWS scores will be imputed at the first dose of study drug. Subjects who never met the criteria for NEWS scores ≤ 2 will have their time to NEWS score ≤ 2 imputed to one day after the maximum observed time to NEWS score ≤ 2. If a subject dies, their time to NEWS score ≤ 2 will also be imputed to one day after the maximum observed time to NEWS score ≤ 2.

Subjects will be censored as follows:

- If subject dies censor as 1 day after the largest observed time to achieving a NEWS score <= 2.
- If subject has no post-baseline NEWS score, censor at Day 1.
- If no NEWS score ≤ 2 censor at the last non-missing NEWS score.

16.3.1.2. Time to COVID-19 Symptom Resolution

An exploratory efficacy endpoint is the time to all COVID-19 symptoms resolution from randomization, in days.

The time to symptoms resolution will be calculated as follows:

- Time to symptom resolution (days) = (Latest post-baseline assessment symptom end date – Date of randomization)

Time to symptom resolution will be calculated using data from COVID-19 Symptom Duration page the eCRF.

Subjects will be censored as follows:

1. If the subject has no post-baseline date, the subject will be censored at the date of first dose of study drug;
2. If the subject's symptoms are ongoing, i.e. no end date recorded, the subject will be censored at the subject's end of study date.

If subject has no COVID-19 symptom at baseline, the subject will be censored at Day 1

16.3.1.3. COVID-19 Symptoms Severity over Time

An exploratory efficacy endpoint is COVID-19 symptom severity over time according to the COVID-19 Symptom assessment page of the eCRF by symptom and across all symptoms.

Missing and "Unknown" severity will not be taken into account in the percentages.

16.3.1.4. C-Reactive Protein over Time

An exploratory efficacy endpoint is the analysis of the CRP over time.

16.3.1.5. Level of IgG and IgM over Time

An exploratory efficacy endpoint is the level of IgG and IgM over time and change from baseline.

16.3.1.6. Level of SARS-CoV-2 Infectious Virus Titer over Time.

An exploratory efficacy endpoint is the level of SARS-CoV-2 infectious virus titer over time and change from baseline.

16.3.1.7. Proportion of Subjects With a ≥ 1-tier Increase PRI on or Before Day 14

An exploratory efficacy endpoint is the proportion of subjects with a ≥ 1-tier increase PRI on or before Day 14. The PRI is defined as a ≥ 1-tier increase from baseline in respiratory support methods required to maintain satisfactory oxygenation ($SpO_2 \geq 93\%$), using the 6-tier hierarchical scale of Respiratory Support methods.

16.3.1.8. Time-weighted Average Change from Baseline

An exploratory efficacy endpoint is the time-weighted average change from baseline (TWACFB) in quantitative SARS-CoV-2. TWACFB will be calculated as the Area under the ROC Curve (AUC) of the change from baseline in quantitative SARS-CoV-2divided by its total time interval (time of last observation minus time of first observation). In the calculation of area under the curve, the time from first study drug (in days) will be the time component. TWACFB will be calculated to Day 5 ($TWACFB_5$), Day 8 ($TWACFB_8$), Day 10 ($TWACFB_{10}$) and Day 14 ($TWACFB_{14}$), i.e. there will be four TWACFB endpoints for each patient. Each endpoint will include any post non-missing post-baseline data up to and including the reference end day, e.g. $TWACFB_8$ will include all post-baseline observations up-to-and-including Day 8 (i.e. 7 days after first study drug). AUC will be calculated by linear trapezoidal rule on change from baseline on log10 scale.

16.3.2. Analysis of Exploratory Efficacy Endpoints

16.3.2.1. NEWS Score ≤ 2

For the Time to a NEWS score ≤ 2 endpoint, the median times will be presented for each treatment group as well as the number and percentage of subjects who achieve a NEWS score ≤ 2.

A Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the time to a NEWS score ≤ 2 (days).

Kaplan-Meier estimates of the time will be provided at the 25th, 50th (median), and 75th percentiles along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates will be derived from the Kaplan-Meier estimates using the log-log transformation.

The p-value associated with the log-rank test statistic will be provided and compared at the one-sided 0.025 alpha level based on a null hypothesis that there is no difference between the treatment groups and will be presented for descriptive purpose only.

16.3.2.2. COVID-19 Symptom Resolution

Same analysis as for NEWS Score ≤ 2 will be performed for the COVID-19 symptom resolution.

16.3.2.3. COVID-19 Symptom Severity

A shift from baseline to the worst post-baseline observed severity according to the COVID-19 Symptom assessment page of the eCRF by symptom and across all symptoms will be presented.

16.3.2.4. C-Reactive Protein

Change from baseline in CRP will be summarized at the time points required in the schedule of assessments in the protocol. Missing data will not be imputed. CRP will be collected from the central laboratory (if measured).

16.3.2.5. Level of IgG and IgM over Time

Change from baseline and in the level of IgG and IgM will be summarized at the time points required in the

schedule of assessments in the protocol. Missing data will not be imputed.

16.3.2.6. Level of SARS-CoV-2 Infectious Virus Titer over Time

Change from baseline in the level of SARS-CoV-2 Infectious virus titer and percent undetectable will be summarized at the time points required in the schedule of assessments in the protocol. Missing data will not be imputed.

16.3.2.7. Proportion of Subjects with a ≥ 1-tier Increase PRI on or Before Day 14

Same analysis as for the primary efficacy endpoint will be performed.

16.3.2.8. Time-weighted Average Change from Baseline in Quantitative SARS-CoV-2

Summary statistics will be computed for each TWACFB endpoint for all patients with baseline data and at least one post-baseline data value within the time-frame over which AUC is computed and for each baseline quantitative SARS-CoV-2 subgroup:

- All subjects who have baseline quantitative SARS-CoV-2 above the limit of quantification.
- All subjects who have baseline quantitative SARS-CoV-2 above the median.
- All subjects who have baseline quantitative SARS-CoV-2 above 4 log10 copies/mL.
- All subjects who have baseline quantitative SARS-CoV-2 above 6 log10 copies/mL.

17. SAFETY ENDPOINTS

All safety summaries will be presented by treatment group based on the SAF analysis set. There will be no statistical comparisons of the treatment groups for safety data.

17.1. ADVERSE EVENTS

- Prior AEs are defined as any AE that started or worsened in severity on or after the date of signed informed consent but before the first dose of study drug.

- Treatment emergent AEs (TEAEs) are defined as any AE that started or worsened in severity on or after the first dose of study drug but no later than 28 days after the last dose of study drug. Events considered as possibly related to study drug that occur in follow-up more than 28 days after last study drug will also be considered TEAE.

See APPENDIX 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

AEs will be coded using the MedDRA dictionary, version 23.0.

An overall summary of number and percentage of subjects within each of the categories described in the sub-sections below will be provided by treatment group based on the SAF analysis set. Should a subject experience multiple event within a category, the subject will be counted only once for that category.

All AEs (prior and TEAE) will be listed.

17.1.1. ALL TEAEs

Number and percentage of subjects with at least one TEAE will be presented by SOC and PT. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

Number and percentage of subjects with at least one TEAE will be broken down further by maximum severity, relationship to study drug and relationship to non-study drug.

17.1.1.1. Severity

Severity will be classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life-threatening) or grade 5 (death) according to the definitions described in the Division of AIDS (DAIDS) Table and as reported on the AE page of the eCRF. TEAEs starting after the first dose of study drug with a missing severity will be classified as severe (grade 3). Should a subject experience multiple events within a SOC or PT, only the subject's worst severity will be counted for that SOC or PT.

17.1.1.2. Relationship to Study Treatment

Relationship to study treatment, as indicated by the Investigator, will be classified as No Reasonable Possibility or Reasonable Possibility as reported on the AE page of the eCRF.

A "Reasonable Possibility" TEAE is defined as a TEAE with an evidence to suggest a causal relationship between the drug(s) and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure)., while a "No Reasonable Possibility " TEAE is defined as a TEAE with no evidence to suggest a causal relationship between the drug(s) and the AE. TEAEs with a missing relationship to study treatment will be regarded as Reasonable Possibility. Should a subject experience multiple events within a SOC or PT, only the subject's worst relationship will be counted for that SOC or PT.

17.1.1.3. Relationship to Non-Study Treatment

Relationship to non-study treatment, as indicated by the Investigator, will be classified as not related or related (increasing severity of relationship).

A "Related" TEAE is defined as a TEAE with a relationship to non-study treatment of "reasonable possibility", and a "Non-related" TEAE is defined as a TEAE with a relationship to non-study treatment of "no reasonable possibility". TEAEs with a missing relationship to non-study drug will be regarded as related to non-study treatment. Should a subject experience multiple events within a SOC or PT, only the subject's worst relationship will be counted for that SOC or PT.

17.1.2. Adverse Events with an Outcome of Death

TEAEs with an outcome of death are those events which are recorded as "Fatal" on the AE page of the eCRF. A summary of TEAEs with an outcome of death by SOC and PT will be prepared.

A listing of all AEs with an outcome of death will be provided.

17.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the AE page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all SAEs will be provided

17.1.4. TEAEs Leading to Discontinuation from Study Treatment

TEAEs leading to permanent discontinuation from study treatment are those events recorded as "Drug withdrawal" on the AE pages of the eCRF. A summary of TEAEs leading to permanent discontinuation from study treatment by SOC and PT will be prepared. Should a subject experience multiple such events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all TEAEs leading to permanent discontinuation from study treatment will be provided.

17.1.5. TEAEs Leading to Discontinuation from Study

TEAEs leading to discontinuation from study are those events reported as "Yes" for the question "Did the AE cause the subject to discontinue from the study?" on the AE pages of the eCRF. A summary of TEAEs leading to discontinuation of study by SOC and PT will be prepared. Should a subject experience multiple such events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all TEAEs leading to discontinuation from study will be provided.

17.2. Deaths

If any subjects die during the study as recorded on the "Death Details" page of the eCRF, the number and percentage of subjects who died due to COVID-19 as primary cause of death and those who died due to any other primary cause will be summarized by treatment group based on the SAF analysis set. Similarly, the number and percentage of subjects who died due to COVID-19 as secondary cause of death and those who died due to any other secondary cause will be summarized by treatment group based on the SAF analysis set. Death due to COVID-19 will be identified by the study Therapeutic Medical Advisor (TMA) in a blinded fashion before the study DBL.

A listing of all deaths will be provided.

17.3. Laboratory Evaluations (incl. Blood Gas and Coagulation)

A serum pregnancy test will be performed at the screening visit, and urine or serum pregnancy test will be performed on Day 1 prior to the first dose and at hospital discharge or early termination. Chemistry (incl. blood gas,

cardiac related tests), hematology, coagulation and urinalysis will be performed as per the schedule of events (refer to protocol, Section 6.5). A list of laboratory parameters to be included in the outputs is included in APPENDIX 3.

Quantitative laboratory parameters reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. Observed values will then be standardized (refer to Section 17.3.1) before being summarized and changes from baseline will be computed based on the standardized observed values.

The parameters which need clinical assessment will only be listed (Direct Bilirubin).

For hematology, only the following key parameters will be summarized: hemoglobin, hematocrit, RBC, platelets, WBC, neutrophils.

The following summaries will be provided by treatment group based on the SAF analysis set for each of chemistry, hematology, coagulation, and urinalysis laboratory parameters:

- Observed and change from baseline in Standard International (SI) units by visit (for quantitative parameters);
- Number and percentage of subjects in each laboratory parameter category by visit (for categorical parameters);
- Shift from baseline to the worst post-baseline observed value during D1-D14 according to the DAIDS toxicity grades (for quantitative parameters with available DAIDS toxicity grades; refer to Section 17.3.2)
- Listing of subjects with at least one post-baseline laboratory observed value meeting a DAIDS toxicity grade ≥ 3 (for quantitative parameters with available DAIDS toxicity grades; refer to Section 17.3.2)
- Shifts from baseline to the maximum/minimum post-baseline observed value during D1-D14 according to normal range criteria (for quantitative parameters without DAIDS toxicity grades; refer to Section 17.3.3);
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-baseline total bilirubin (TBL) observed value categorized as < 2 x ULN or ≥ 2 x ULN;
- Scatter plots of the maximum post-baseline observed value in ALT value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN;
- Scatter plots of the maximum post-baseline observed value in AST value by the maximum post-baseline

observed value in TBL value, both expressed as multiple of ULN;

- A listing of subjects with at least one post-baseline observed ALT value > 3 x ULN, AST value > 3 x ULN or TBL value ≥ 2 x ULN will be provided.

All laboratory data will be listed.

17.3.1. LABORATORY STANDARDIZATION

As laboratory parameters are collected locally and have different normal ranges in the database, observed values of all subjects will first be standardized to a unique set of normal range using the location-scale standardization formula (Chuang-Stein, 1992):

- $s = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - U_X)}$

where:

- s = standardized observed value;
- x = original observed value;
- L_S = Lower Limit of the normal range chosen to be the standard normal range;
- U_S = Upper Limit of the normal range chosen to be the standard normal range;
- L_X = Lower Limit of the normal range associated with the original observed value;
- U_X = Upper Limit of the normal range associated with the original observed value;

It is to be noted that the choice of the standard normal range is arbitrary.

Standardized values will be used for all analyses and ranges/ DAIDS toxicity grades.

17.3.2. DAIDS TOXICITY GRADES

Quantitative laboratory parameters with available DAIDS toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 4 for each parameter toxicity grade criteria):

- Grade 1 (i.e., mild);

- Grade 2 (i.e., moderate);
- Grade 3 (i.e., severe)
- Grade 4 (i.e., potentially life-threatening)

Although not defined in the DAIDS toxicity grading system, version 2.1, non-missing laboratory parameter results not meeting any of the 4 grades defined in the DAIDS toxicity grading system will be categorized as having a Grade 0 (No Event) for the purpose of the shift from baseline summaries.

17.3.3. Laboratory Normal Ranges

Quantitative laboratory parameters will be compared with the relevant laboratory normal ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory normal range.
- Normal: Within the laboratory normal range (upper and lower limit included).
- High: Above the upper limit of the laboratory normal range.

17.4. Vital Signs

The following vital sign parameters will be collected for this study as per the schedule of events (refer to protocol, Section 6.3 and 6.7):

- Systolic blood pressure (SBP) (mmHg);
- Diastolic blood pressure (DBP) (mmHg);
- Pulse rate (beats per minute [bpm]);
- Oxygen saturation (%);
- Respiratory rate (breaths/min);
- Body temperature (° C);
- Weight (kg);

The following summaries will be provided by treatment group based on the SAF analysis set for each vital sign parameter:

- Observed and change from baseline by visit;
- Number and percentages of subjects with at least one markedly abnormal post-baseline observed value/change from baseline (refer to Section 17.4.1);
- Listing of subjects with at least one markedly abnormal observed value/change from baseline (refer to Section 17.4.1).

All vital sign data will be listed.

17.4.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal vital sign observed values and/or change from baseline will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Oxygen saturation	%	< 93 %	Not applicable
Body temperature	°C	Not applicable	≥ 38.3 °C AND change from baseline ≥ 1.1 °C
Weight	kg	Percent change from baseline ≤ -7.0 %	Percent change from baseline ≥ 7.0 %

17.5. ECG EVALUATIONS

The following electrocardiogram (ECG) parameters will be measured for this study as per the schedule of events (refer to protocol, Section 6.4):

- Heart rate (bpm);
- PR interval (msec);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTc interval (msec);
- QTcF interval (msec);
- QTcB interval (msec);
- Overall ECG interpretation (Investigator's judgment):
    - Normal;
    - Abnormal, not clinically significant (NCS);
    - Abnormal, clinically significant (CS)

The following summaries will be provided by treatment group based on the SAF analysis set for each ECG parameter:

- Observed and change from baseline by visit (for quantitative parameters);
- Number and percentages of subjects with at least one markedly abnormal post-baseline observed value/change from baseline (for quantitative parameters; refer to Section 17.5.2);
- Listing of subjects with at least one markedly abnormal observed value/change from baseline;

- Shift from baseline in overall ECG interpretation to the worst post-baseline assessment;
- Listing of subjects with at least one abnormal overall ECG interpretation, including the finding(s) for each subject

All ECG data will be listed.

17.5.1. ECG Specific Derivations

QTc Bazett's Correction (msec) will be computed as follows:

- $QTcB\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$

17.5.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG parameters will be identified in accordance with the following predefined markedly abnormal criteria:

- Observed values for QTc, QTcF, and QTcB intervals will be classified as:
    - > 450 msec;
    - > 480 msec;
    - > 500 msec
- Change from baseline for QTc, QTcF, and QTcB intervals will be classified as:
    - >30 msec increase from baseline
    - >60 msec increase from baseline

It is to be noted that the previous categories are not mutually exclusive, but cumulative. For example, if a subject worst post-baseline QTc post-baseline observed value is 490 mmHg, then this subject will be reported once under QTc > 450 msec and once under QTc > 480 msec.

17.6. PHYSICAL EXAMINATION

17.6.1. GENERAL PHYSICAL EXAMINATION

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 6.2).

The following summaries will be provided by treatment group based on the SAF analysis set for physical examination data:

- Incidence of abnormalities at screening and each post-screening visit

All physical examination data will be listed.

17.6.2. CHEST IMAGING

Chest imaging will be performed as per the schedule of events (refer to protocol Section 6.8).

Number and percentage of subjects with normal, abnormal NCS, and abnormal CS chest imaging result, as per the Investigator's judgment, will be provided by treatment group and visit based on the SAF analysis set.

All chest imaging data, including findings, will be listed.

18. DATA NOT SUMMARIZED OR PRESENTED

Data that will not be summarized or listed are:

- Comments

These data will not be summarized or listed but will be available in the Study Data Tabulation Model (SDTM) and/or Analysis Dataset Modelling (ADaM) datasets.

19. REFERENCES

Brookmeyer R, Crowley J. A (1982) Confidence Interval for the Median Survival Time. Biometrics 38:29-41.

Chuang-Stein C (1992). Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal 26(1);77-84.

Prytherch DR, Smith GB, Schmidt PE, Featherstone PI (2010). ViEWS – Towards a national early warning score for detecting adult inpatient deterioration. Resuscitation 81(8);932-937

RCP (2017). National Early Warning Score (NEWS) 2. Royal College of Physicians. https://www rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2. Accessed April 7th, 2020

Rubin, DB (1987) Multiple Imputation for Nonresponse in Surveys. Wiley, New York.

Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI (2013). The ability of the National Early Warning Score (NEWS) to discriminate subjects at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 84(4);465-470

APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	END DATE	ACTION
Known	Known/Partial/ Missing	If (AE start date/time < study drug start date/time), then not TEAE; If study drug start date/time ≤ AE start date/time ≤ 28 days after last drug date, then TEAE.
Partial, but known components show that AE started before study drug start date	Known/Partial/ Missing	Not TEAE.
Partial, but known components show that AE started on or after date of first dose of study drug and AE start date ≤ 28 days after last drug date	Known/Partial/ Missing	Assume TEAE.
Missing	Known	If (AE end date/time < study drug start date/time) , then not TEAE; Otherwise, TEAE.
	Partial	If known components of AE end date/time show that AE stopped before study drug start date/time), then not TEAE; Otherwise, TEAE.
	Missing	Assume TEAE.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known or ongoing	If medication stop date < study drug start date, assign as prior; If medication start date < study drug start date and (medication stop date ≥ study drug start date or medication is ongoing at study drug start date), assign as concomitant; If study drug start date ≤ medication start date ≤ study drug end date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before study drug start date, assign as prior; If medication start date < study drug start date and (known components of medication stop date show that medication stopped on or after study drug start date), assign as concomitant; If study drug start date ≤ medication start date ≤ study drug end date, assign as concomitant.
	Missing, not ongoing	If medication stop date is missing, then it can never be assigned as prior only; If medication start date < study drug start date, assign as concomitant; If study drug start date ≤ medication start date ≤ study drug end date, assign as concomitant.

START DATE	STOP DATE	ACTION
Partial	Known or ongoing	If medication stop date < study drug start date, assign as prior; If (known components of medication start date show that medication started before study drug start date) and (medication stop date ≥ study drug start date or medication is ongoing at study drug start date), assign as concomitant; If known components of medication start date show that medication started on or after study drug start date but before or on study drug end date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before study drug start date, assign as prior; If (known components of medication start date show that medication started before study drug start date) and (known components of medication stop date show that medication stopped on or after study drug start date), assign as concomitant; If known components of medication start date show that medication started on or after study drug start date but before or on study drug end date, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before study drug start date, assign as concomitant; If known components of medication start date show that medication started on or after study drug start date but before or on study drug end date, assign as concomitant.
Missing	Known or ongoing	If medication stop date < study drug start date, assign as prior; If medication stop date >= study drug start date or medication is ongoing at study drug start date, assign as concomitant.

START DATE	STOP DATE	ACTION
	Partial	If known components of medication stop date show that medication stopped before study drug start date, assign as prior; If known components of medication stop date show that medication stopped on or after study drug start date, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm:ss.

SPELLING FORMAT

English US.

PAPER SIZE, ORIENTATION, AND MARGINS

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

FONTS

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	Tables and Graphs	Listings
AT-527	1	1
Placebo	2	2
Total [1]	3	n/a
Randomized, Not Treated	n/a	3
Screen Failure	n/a	4

[1] Not applicable for efficacy tables, safety tables and graphs.

PRESENTATION OF NOMINAL VISITS

For outputs, analysis visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scrn
Baseline	Base
Day 2	D02
Day 3	D03
…	…
Day 14	D14
1-week Follow-up	W1FU
2-week Follow-up	W2FU
7-week Follow-up	W7FU

DESCRIPTIVE STATISTICS

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, lower and upper bounds of two-sided 95% CI: N + 1;
- SD and SE: N + 2

PERCENTAGES

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

P-VALUES

p-values will be reported to three decimal places. Rounding will be applied, except for the p-values < 0.001 which will be presented as '< 0.001' and p-values < 1.000 but > 0.999 which will be presented as '> 0.999'.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Randomized treatment group (or treatment received if it's a safety output);
- Subject ID;
- Parameter, when applicable;
- Date/Time, when applicable.
- Timepoint, when applicable

APPENDIX 3. LABORATORY ASSESSMENTS

Chemistry (SI unit)

- Alkaline phosphatase (ALP) (IU/L)
- Alanine transaminase (ALT) (IU/L)
- Aspartate transaminase (AST) (IU/L)
- Total bilirubin (µmol/L)
- Direct bilirubin (µmol/L)
- Indirect bilirubin (µmol/L)
- Amylase (IU/L)
- Lipase (IU/L)
- Albumin (g/L)
- Blood urea nitrogen (BUN) (mmol/L)
- Blood urea
- Creatinine (µmol/L)
- Creatinine Clearance (mL/s)
- Troponin I, Troponin T (ng/L)
- Glucose (mmol/L)
- Total cholesterol (mmol/L)
- Triglycerides (mmol/L)
- Creatine kinase (CK) (IU/L)
- CK MB/MM/BB isoenzyme fraction
- Sodium (mmol/L)
- Potassium (mmol/L)
- Chloride (mmol/L)
- Bicarbonate (mmol/L)
- Calcium (mmol/L)
- Magnesium (mmol/L)
- N-terminal pro b-type natriuretic peptide (NT-proBNP) (ng/L)
- B-type natriuretic peptide (BNP) (ng/L)

Hematology (SI unit)

- Hemoglobin (g/L)
- Hematocrit
- Absolute basophils count (x10E9/L)
- Absolute reticulocyte count (x10E9/L)

- Mean corpuscular volume (MCV) (fL)
- Red blood cells (RBC) (x10E12/L)
- White blood cell (WBC) count total (x10E9/L)
- Absolute neutrophils count (x10E9/L)
- Absolute lymphocyte count (x10E9/L)
- Absolute monocyte count (x10E9/L)
- Absolute eosinophils count (x10E9/L)
- Relative neutrophils count
- Relative lymphocyte count
- Relative monocyte count
- Relative eosinophils count
- Relative basophils count
- Relative reticulocyte count
- Platelet count (x10E9/L)

Coagulation (SI unit)

- Prothrombin time (PT) (s)
- International normalized ratio (INR)
- D-dimer (µg/L DDU)

Urinalysis (SI unit)

Dip stick

- pH
- Specific gravity
- Color
- Appearance
- Blood
- Protein
- Glucose

Microscopy

- White blood cells
- Red blood cells
- Casts
- Bacteria
- Crystals

- Bilirubin
- Ketones
- Nitrite
- Urobilinogen
- Leukocyte esterase

APPENDIX 4. DAIDS TOXICITY GRADE, VERSION 2.1

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017]. Available from:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Chemistry Tests:

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase, High	ALP (IU/L)	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT, High	ALT (IU/L)	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST, High	AST (IU/L)	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Total bilirubin, High	Total bilirubin (µmol/L)	< 1.1 x ULN	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Amylase, High	Amylase (IU/L)	< 1.1 x ULN	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Lipase, High	Lipase (µkat/L)	< 1.1 x ULN	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Albumin, Low	Albumin (g/L)	≥ LLN	30 to < LLN	≥ 20 to < 30	< 20	NA

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine, High	Creatinine (µmol/L)	Criteria for Grade 1 - 4 not met	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance, Low	Creatinine Clearance (mL/s)	Criteria for Grade 2 - 4 not met	NA	< 1.5 to 1 OR 10 to < 30% decrease from participant's baseline	< 1 to 0.5 OR 30 to < 50% decrease from participant's baseline	< 0.5 OR ≥ 50% decrease from participant's baseline or dialysis needed *

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Troponin I, High	Troponin I (ng/L)	Criteria for Grade 4 not met	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory *
Glucose Fasting, High	Glucose (mmol/L)	< 6.11	6.11 to < 6.95	6.95 to < 13.89	13.89 to < 27.75	≥ 27.75
Glucose, Low	Glucose (mmol/L)	≥ 3.55	3.05 to <3.55	2.22 to < 3.05	1.67 to < 2.22	< 1.67
Cholesterol Fasting, High	Total cholesterol (mmol/L)	< 5.18	5.18 to < 6.19	6.19 to < 7.77	≥ 7.77	NA
Triglycerides Fasting, High	Triglycerides (mmol/L)	< 1.71	1.71 to 3.42	>3.42 to 5.7	>5.7 to 11.4	> 11.4
Creatine Kinase, High	Creatine kinase (IU/L)	< 3 x ULN	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, High	Sodium (mmol/L)	< 146	146 to < 150	150 to < 154	154 to < 160	≥ 160
Sodium, Low	Sodium (mmol/L)	≥ 135	130 to < 135	125 to < 130	121 to < 125	≤ 120
Potassium, High	Potassium (mmol/L)	< 5.6	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Potassium, Low	Potassium (mmol/L)	≥ 3.4	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Bicarbonate, Low	Bicarbonate (mmol/L)	≥ LLN	16.0 to < LLN	11.0 to < 16.0	8.0 to < 11.0	< 8.0
Calcium, High	Calcium (mmol/L)	< 2.65	2.65 to < 2.88	2.88 to < 3.13	3.13 to < 3.38	≥ 3.38
Calcium, Low	Calcium (mmol/L)	≥ 2.10	1.95 to < 2.10	1.75 to < 1.95	1.53 to < 1.75	< 1.53
Magnesium, Low	Magnesium (mmol/L)	≥ 0.70	0.60 to < 0.70	0.45 to < 0.60	0.30 to < 0.45	< 0.30

*Will be determined from subject's Adverse Events page and identified by the medical team.

Hematology Tests:

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin, Low	Hemoglobin (g/L)	Male: ≥ 109; Female: ≥ 104	Male: 100 to 109; Female: 95 to 104	Male: 90 to < 100; Female: 85 to < 95	Male: 70 to < 90; Female: 65 to < 85	Male: < 70; Female: < 65
WBC, Decreased	White blood cell count total (x10E9/L)	> 2.499	2.000 to 2.499	1.500 to 1.999	1.000 to 1.499	< 1.000
Absolute Neutrophil Count, Low	Absolute neutrophils count (x10E9/L)	> 1.000	0.800 to 1.000	0.600 to 0.799	0.400 to 0.599	< 0.400
Absolute Lymphocyte Count, Low	Absolute lymphocyte count (x10E9/L)	≥ 0.650	0.600 to < 0.650	0.500 to < 0.600	0.350 to < 0.500	< 0.350
Platelets, Decreased	Platelet count (x10E9/L)	≥ 125.000	100.000 to < 125.000	50.000 to < 100.000	25.000 to < 50.000	< 25.000

Coagulation Tests:

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
PT, High	Prothrombin time (s)	< 1.1 x ULN	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
INR, High	International normalized ratio	< 1.1 x ULN	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN

Urinalysis Tests:

DAIDS Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4
Glycosuria	Glucose	Criteria for Grade 1-3 not met	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Proteinuria	Protein	Criteria for Grade 1-3 not met	1+	2+	3+ or higher	NA

APPENDIX 5. NATIONAL EARLY WARNING SCORE (NEWS)

Physiological parameters	3	2	1	0	1	2	3
Respiration Rate (breaths per minute)	≤8		9–11	12–20		21–24	≥25
S_pO_2 (%)	≤91	92–93	94–95	≥96			
Any supplemental oxygen?		Yes		No			
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	
Systolic BP (mmHg)	≤90	91–100	101–110	111–219			≥220
Heart/pulse rate (beats per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Level of consciousness using the AVPU system				A			V, P or U

Level of consciousness: A = alert; V = responds to voice; P = responds to pain; U = unresponsive. Modified from National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS. Report of a working party. Royal College of Physicians, London, 2012.[12]

Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI (2013). The ability of the National Early Warning Score (NEWS) to discriminate subjects at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 84(4);465-470

[redacted]

Changes to Planned Statistical Analyses Form Page 1 of 3

Customer:	ATEA Pharmaceuticals
Protocol No.:	AT-03A-001
Project Code:	SZA63631
Date (DDMMMYYYY):	16Mar2022

The timing of the change(s) was:

☐ After unblinding (or database lock for an open-label study) but before completion of the final Statistical Report/Clinical Study Report
☐ After completion of the final Statistical Report/Clinical Study Report

Describe the change(s) required:

- Precision on how to handle the subjects having a treatment start date the day after the date of randomization and who have a recovery ON Day 14. They will have time to recovery of 15 days and we will set those without recovery to 15.01 days. (Tables 14.2.3.X)
- Using 65 for age group instead of 70. (Table 14.1.4.1, 14.2.1.3, 14.2.2.3, 14.2.3.3, 14.2.4.3)
- Hypertension co morbidities will use MHTERM=Hypertension instead of baseline diastolic and systolic values. (Tables 14.1.4.1 and 14.1.4.2)
- Updated derivation for symptom resolution: Time to symptom resolution (days) = (Latest post-baseline assessment symptom end date – Date of randomization) +1. (Tables 14.2.4.X)
- We clarified in footnote that we are using both TaqPath and COBAS tests results for mITT population. (See footnotes in tables)
- For titer data we updated AVAL to 1.2 and 0.45 respectively for results <1.5 and <0.75 in summaries:
    - It is as per Atea's virologist request and the logic is (Tables 14.2.5.5 and 14.2.4.6):
        - For "<1.5", we should use 15.8, i.e. [10^1.5]/2, as the untransformed value which is 1.2 on log10 scale.
        - For "<0.75", we'll use 2.8, i.e [10^0.75]/2, as the untransformed value which is 0.45 on the log10 scale.
- Time to Sustained Non-detectable SARS-CoV-2 will be displayed by method (COBAS/ TaqPath). (Table 14.2.5.4)
- Level of SARS-CoV-2 Infectious Titer analysis will use the same approach as for the "Time to sustained non-detectable SARS-CoV-2 (mITT)" output, we will be providing estimates of proportion of subjects with undetectable/negative results, using K-M estimates. (Table 14.2.5.6)
- For all tests except ANCOVA, the 2-sided pvalue will be displayed.
- Childbearing potential and HgbA1c are not included in Demographics and baseline characterics table. (Tables 14.1.4.1 and 14.1.4.2)
- ANCOVA analysis: Present the Change-from-Baseline LSM (SE) for each treatment group. (Table 14.2.5.1)
- Subject level deviations and site level deviations are listed separately.
- Information present in the SAP which are not presented:
    - Subjects with screen failure.
    - Inclusion and exclusion summary.
    - Deviation summary.
    - Medical History summary.
    - Disease history summary.
    - Medication summary.
    - Exposure summary.

Changes to Planned Statistical Analyses Form Page 2 of 3

Customer:	ATEA Pharmaceuticals
Protocol No.:	AT-03A-001
Project Code:	SZA63631
Date (DDMMMYYYY):	16Mar2022

- PRI sensitivity analysis (except on mITT analysis set).
- PRI supplementary analysis (except on subgroups).
- Proportion of subjects with respiratory failure or death (RFD) by Day 28.
- Sensitivity analyses for key secondary efficacy endpoints.
- Proportion of subjects improving/worsening from baseline in clinical status.
- All-cause mortality.
- Duration of hospitalization.
- Time to first SARS-CoV-2 Negative Test.
- Proportion of subjects SARS-CoV-2 positive at each time point.
- Sensitivity analysis for time to clinical recovery by day 14.
- All other secondary efficacy analysis.
- All exploratory analysis except level of SARS-CoV-2 infection virus titer over time and time-weighted average change from baseline in quantitative SARS-CoV-2.
- Treatment emergent adverse events by relationship to study treatment summary.
- Treatment emergent adverse events by relationship to non-study treatment summary.
- Treatment emergent adverse events leading to discontinuation from study summary.
- Death summary.
- Laboratory evaluations summary.
- Vital signs summary.
- ECG summary.
- Physical examination summary.

- The study is conducted in 2 Parts. Part A evaluates an AT-527 dose of 550 mg BID for 5 days and Part B evaluates a dose of 1100 mg BID for 5 days. Part B patients will only be listed.

Describe the process used to decide on the change(s) and who was involved:

While creating the shells and working on the Interim Analysis (IA) outputs it appeared some updates were needed. As the study is terminating early, the IA tables/figures outputs will be used for the final delivery. Atea and [redacted] biostatistical teams were involved.

The group(s) responsible for the change(s) and implications for the study:

[redacted] Biostatistical team will deliver the datasets and outputs according to these updates. The SAP will not be updated.

[redacted]

Changes to Planned Statistical Analyses Form

Customer:	ATEA Pharmaceuticals
Protocol No.:	AT-03A-001
Project Code:	SZA63631
Date (DDMMMYYYY):	16Mar2022

Form completed by:

Title	Name		Date (DDMMMYYYY)
[redacted]	[redacted]	[redacted]	March 21, 2022

Form approved by:

Title	Name		Date (DDMMMYYYY)
[redacted]	[redacted]	[redacted]	March 21, 2022

Form approved by Customer Representative (if applicable):

Title	Name		Date (DDMMMYYYY)
[redacted]	[redacted]	[redacted]	March 21, 2022