Statistical Analysis Plan (V3): I7W-MC-UDAA(c)

A Randomized, Double-blind, Placebo-controlled, Clinical Trial of LY3127804 in Patients who are Hospitalized with Pneumonia and Presumed or Confirmed COVID-19

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A Randomized, Double-blind, Placebo-controlled, Clinical Trial of LY3127804 in Patients who are Hospitalized with Pneumonia and Presumed or Confirmed COVID-19

I7W-MC-UDAA

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1. Revision History

SAP Version 1.0 approved on May 8, 2020 prior to unblinding.

SAP Version 2.0 prepared after the decision of study discontinuation due to futility.

SAP Version 3.0 released before database lock/unblinding.

2. Study Objectives

2.1 Primary Objective

The primary objective is to evaluate ventilator free days during treatment with LY3127804. This is defined as the number of days from Day 1 to Day 28 on which a patient breathes without assistance, if the period of unassisted breathing lasted at least 24 consecutive hours and the patient did not die within 28 days from first dose of study drug. If the patient died within 28 days, then this end point will be set equal to -1.

2.2 Secondary Objectives

Objectives	Endpoints
• To evaluate clinical status of patients during treatment with LY3127804	• NIAID ordinal assessment
• To evaluate survival without the need for IMV/ECMO	• Complete response is the proportion of patients who are alive and respiratory failure free (i.e. never having required mechanical ventilatory support) by Day 28
• To evaluate mortality rate during treatment with LY3127804	• Death within 28 days from first dose of study drug
• To evaluate reduction in hospital stay during treatment with LY3127804	• Length of hospitalization
• To evaluate safety of LY3127804	• AEs and SAEs

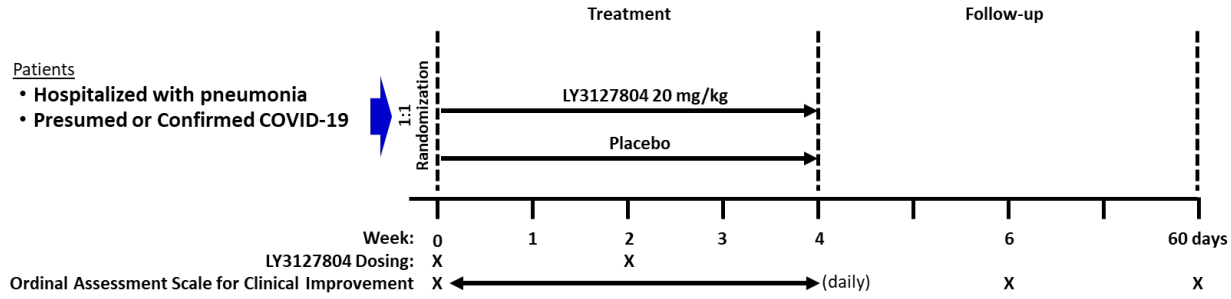
Abbreviations: AE = adverse event; NIAID = National Institute of Allergy and Infectious Diseases; SAE = serious adverse event; SpO_2 = oxygen saturation

3. Study Design

3.1 Summary of Study Design

Study I7W-MC-UDAA is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 2 study in patients who are hospitalized with a pneumonia and presumed or confirmed COVID-19.

Figure 1.0. Illustration of study design for Clinical Protocol I7W-MC-UDAA.



3.2 Determination of Sample Size

Approximately 210 patients may be enrolled in a 1:1 ratio to LY3127804 or placebo (105 per treatment group) in order that 200 patients complete the study. A sample size of 100 in each group will have 81% power to detect a difference between the placebo group and the LY3127804 group using a Wilcoxon rank-sum test with a 0.05 one-sided significance level. This powering is based on the following assumptions: intermittent mandatory ventilation (IMV) rate of 25% and mortality rate of 12.5% in the placebo group, 50% improvement in IMV rate and mortality rate for the LY3127804 group relative to placebo, and a mean difference (LY3127804 minus placebo) of 3.0 ventilator-free days where patients who die are assigned a value of -1.

3.3 Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be stratified by age group (<65 years and ≥65 years), sex, and site, and then, on Day 1, randomly assigned in a 1:1 ratio within each stratum to receive either LY3127804 or placebo. Treatment assignment will be determined by a computer generated randomization sequence using an interactive web response system (IWRS).

4. A Priori Statistical Methods

4.1 General Considerations

Efficacy analyses will be conducted on the Efficacy Analysis Set; safety analyses will be conducted on the Safety Analysis Set. Analyses to be conducted on both the Efficacy set and the Safety set will not be replicated if the two Analysis sets are the same.

Descriptive statistics will include the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of observations with non-missing values) as the denominator. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If all baseline values are missing for a particular variable, then the change from baseline and percent change (or percent improvement) from baseline will not be calculated.

All confidence intervals (CIs) and statistical tests will be two-sided unless otherwise specified. P-values which are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to three decimal places. All other p-values which are less than 0.001 will be presented as '<0.001', while p-values greater than 0.999 will be presented as '>0.999'. CIs will be presented to one more decimal place than the raw data.

Unless otherwise noted, treatment comparisons of dichotomous variables will be made using Chi-square test. The proportions, difference in proportions, and 90% Wald confidence interval (CI) of the difference in proportions will be reported. Stratification is ignored in the analysis of dichotomous variables.

Unless otherwise noted, treatment comparisons of quantitative variables will be made using a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM). The model will include treatment, age group, sex, and site as fixed categorical effects, and, if applicable, study day as a continuous effect and treatment-by-study day interaction. The covariance structure to model the within-patient errors will be unstructured. If the available data cannot support the covariance structure (e.g., due to missing values), other structures will be attempted. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz (TOEPH) covariance structure, followed by the heterogeneous autoregressive [ARH(1)] covariance structure, followed by the compound symmetry structure will be used. The first structure to yield convergence will be used for inference. The NewtonRaphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger approximation (KR2) will be used to estimate the denominator degrees of freedom and adjust standard errors. Type III tests based on the LS means will be used for the statistical comparison; the 90% CI will also be reported.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.05, unless otherwise stated. No adjustments for multiple comparisons will be made.

All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statisticians.

When implementing parametric methods of analysis, the distribution of analysis variables will be examined to determine if model assumptions are satisfied. Transformations or nonparametric methods of analysis may be added as sensitivity analyses if warranted. Whenever alternative methods of analysis are required, the description of the new method along with the rationale for its use will be documented in the Clinical Study Report (CSR).

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Additional exploratory analyses of the data will be conducted as deemed appropriate.

4.2 Analysis Populations

Population	Description
Enrolled Set	All patients who sign informed consent
Efficacy Analysis Set	All randomized patients who take at least 1 dose of double-blind study treatment. Patients will be included in the treatment group to which they were randomized.
Safety Analysis Set	All randomized patients who take at least 1 dose of double-blind study treatment. Patients will be analyzed according to the treatment they actually received.

If any of the above population definitions result in the same set of patients, then analyses will not be replicated for each population.

4.3 Handling of Dropouts or Missing Data

4.3.1 NIAID Ordinal Scale

Missing values for NIAID ordinal scale during Days 1-28 will be imputed as the worse of the two values recorded before and after the missing value(s), including values after Day 28. If the patient has been discharged, then the imputed value will be, at worst, "7- Not hospitalized, limitation on activities and/or requiring home oxygen." If there is no recorded value after the missing value, then the missing value will not be imputed.

4.3.2 Non-Responder Imputation (NRI)

For categorical efficacy endpoints, non-responder imputation (NRI) will be used when the response status cannot be determined. Patients whose survival status cannot be determined at day 28 will be non-responders in the analyses of Complete Response.

4.3.3 Missing Data Imputation for Adverse Event, Concomitant Medication Dates, and Laboratory Values

If a medication date or AE date is completely or partially missing, the following imputation rules should be utilized in the analysis unless otherwise stated:

- For the start date:
    - If year, month, and day are missing then use the patient's first treatment date.
    - If either month or month and day are missing, then use the same month and day as treatment start.
    - If only day is missing, impute as day of treatment start.
- For the start time: o Impute as 23:59.

- For the end date:
    - If year, month, and day are missing then use the patient's last visit date. o If either month or month and day are missing then use December 31.
    - o If only day is missing then use the last day of the month.
    - The imputed date will not be beyond the patient's last visit date.

The incomplete dates will be imputed only if it is deemed necessary in calculation/determination for analysis purpose. If there is any doubt for the start and end date/times for AEs, the event will be flagged as treatment-emergent. For medications, the medication will be flagged as concomitant.

For determining treatment-emergent status, missing severity in the baseline period will be considered "mild" and missing severity in the post-baseline period will be considered "severe". When reporting TEAEs by severity or causality, "missing" severity or causality will be considered its own category.

Laboratory parameters will be summarized based on the available data at each time point and no imputation is proposed in this document.

4.4 Handling of Deaths in Efficacy Analyses

For the endpoint that does not contain mortality as a component, such as length of hospital stay during Days 1 to 28, they will be assumed in the hospital for 29 days. The median length in such case will be more appropriated to be reported.

Other efficacy endpoints will handle death via similar imputation: patients who die will be assumed to have experienced the worst outcome. These analyses include percentage of patients discharged from hospital at Day 28, percentage of patients who ever received each of the various types of supportive care, and length of the various types of supportive care.

4.5 Multicenter Studies

While study center will be included as a covariate for some analyses, differences between study centers will not be a feature of the statistical analyses for this study. Baseline variables and demographics will be described by site.

ALL sites that have one or no patient in either treatment group will be pooled together as a single site. If there is only one site with one or no patient in either treatment group, it will be pooled with the next smallest site. If more than one sites with the same number of patients as the next smallest site, the one with the patient who enrolled the study last will be chosen for pooling.

4.6 Multiple Comparisons/Multiplicity

There are no planned adjustments for multiple efficacy endpoints or analyses.

4.7 Patient Disposition

The disposition of all enrolled patients will be summarized. The disposition of all randomized patients will be presented by level of stratification factors in randomization, by treatment group and overall. In addition, the reason for study discontinuation will be tabulated using the list of reasons provided in the eCRF. The disposition of randomized patients will be analyzed for the Efficacy population and the Safety population.

4.8 Patient Characteristics

Patient's baseline age, sex, race, height, body weight, body mass index, other baseline efficacy measures including NIAID ordinal assessment, FiO_2, respiratory rate, disease history, and preexisting conditions will be summarized using descriptive statistics by treatment arm, overall, and by study site (unpooled). These summaries will be based on both the Efficacy population and the Safety population. Patients who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.

Patient height and weight will be collected prior to randomization. Both variables will be reported in metric units (height in cm and weight in kg) and will be summarized as continuous variables along with Body Mass Index (in kg/m^2).

No statistical testing will be performed for comparisons of baseline characteristics.

4.9 Medical History

Medical history will be coded according to MedDRA. The number of subjects reporting medical history events will be summarized by treatment and overall, by system organ class, and preferred term. The summary will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall.

4.10 Treatment Compliance

As all study drug doses will be administered at study site, treatment compliance per se will not be reported.

4.11 Concomitant Therapy

Concomitant medications will be defined as medications taken on or after the date of the first dose of study treatment. This includes all medications initially taken prior to the date of first dose of study treatment but with a stop date that is either missing or after the date of first dose of study treatment. Those medications where the stop date is documented as prior to the date of first dose of study treatment will be classified as prior medications. The prior medications will not be included in any summary reports.

Concomitant medications will be summarized and will be presented by anatomical therapeutic chemical drug classes (ATC level 4) using the latest version of the WHO drug dictionary.

4.12 Efficacy Analyses

4.12.1 Primary Outcome and Methodology

The primary outcome variable will be defined as follows:

- For patients who survive through day 28, the value is the number of days free of mechanical ventilation.
- For patients who do not survive through day 28, the value is set to -1.

If a patient is discharged from the hospital before day 28, and if the patient is still alive at day 28, then days between hospital discharge and Day 28 will be considered ventilator free. A table listing the counts of patients with each number of ventilator free days, including patients with -1 values due to death, will be presented by treatment group. The statistical method for this endpoint will be based on the Wilcoxon rank-sum test using the van Elteren test adjusting for the randomization stratification factors (age group, sex, and site).

4.12.2 Additional Analyses of the Primary Outcome

The number of ventilator free days among survivors will also be reported.

4.12.3 Secondary Efficacy Analyses

Secondary end points will be described and compared between treatment groups.

4.12.3.1 Alive and Respiratory Failure Free Complete Response

Complete Response is defined as being alive and never requiring mechanical ventilator support (at any point while on trial) through day 28.

The rates of complete response and non-response will be summarized by treatment group and by the stratification factors. See section 4.1 for details on the methods to be used to test the differences between LY3127804 and placebo.

Ninety percent confidence interval for the difference in proportions (LY3127804 – placebo) will be reported.

Patients for whom complete response status cannot be determined will be considered non-responders. See section 4.3.2 for details on NRI.

4.12.3.2 NIAID Ordinal Assessment

The NIAID will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

NIAID Score	Description
1	Death

2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (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 ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

The lowest value from Day 1 through Day 28 for a patient on the NIAID ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. The number need to treat (NNT) to prevent one patient from progressing to level 2 or 1 will be calculated. Mean values will be calculated and differences in treatment effect estimates at Days 7, 14 and 28 will be analyzed. Mean value by treatment group will be plotted over time.

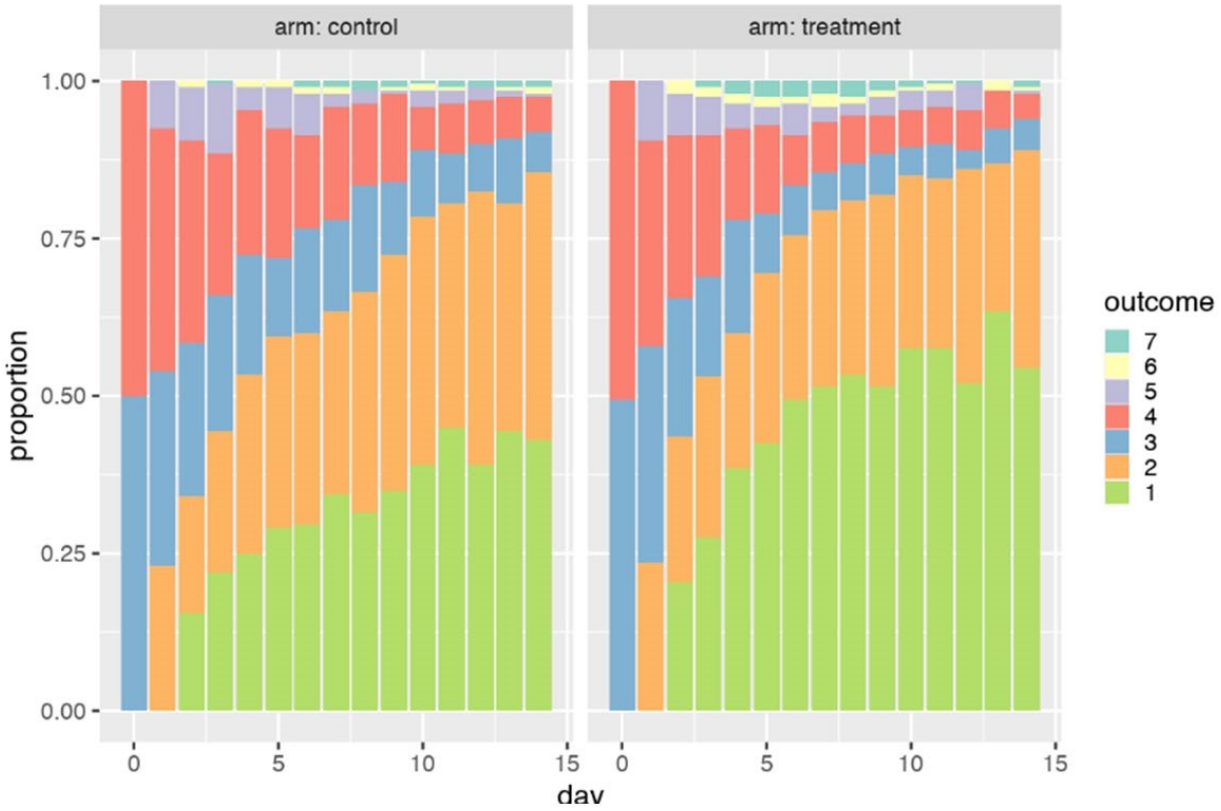
Time to the first 2-point improvement on the NIAID scale will be analyzed between treatment groups. The time for subjects who did not achieve 2-point improvement will be censored at day 28 and stratification will be ignored in this analysis. A Kaplan-Meier plot with log-rank test will be used to compare treatment groups.

The stacked bar plot(s) representing the proportion of subjects in each score by treatment arm over time will be generated with stratification ignored. An example of such plot is as follows. The details of the score will be included in the footnote of the plot.

In addition to the stacked bar plot based on the original NIAID scores, another stacked bar plot that lumps NIAID scores into four categories will be generated. The four new categories are:

a. Death (NIAID score = 1),
b. IMV/ECMO (NIAID score = 2),
c. Requiring O2 or medical care (NIAID scores = 3, 4, 5), and
d. Not requiring O2 nor medical care (NIAID scores = 6, 7, 8).

Figure 2.0 Example of a Stacked Bar Plot:



4.12.3.3 28-day Mortality

Mortality will be defined as 28-day all-cause mortality, defined as 672 hours from the time of randomization. All patients will be classified as either "alive at Study Day 28" or, if dead, "dead at Study Day 28." Patients whose mortality status cannot be determined will be classified as "dead at Study Day 28." The difference between treatment groups will be analyzed.

The 60-day mortality will be analyzed in a similar fashion.

4.12.3.4 Length of Hospital Stay

Length of hospital stay will be defined as the number of days hospitalized for at least 1 hour duration.

The length of hospitalization will be analyzed with the Wilcoxon rank-sum test using the van Elteren test adjusting for the randomization stratification factors and will be evaluated through Day 28. The summary will include the median length of hospital stay for the patients who died before Day 28.

Hospital discharge rates at Day 28 will be reported and compared between treatment groups.

4.12.4 Other Efficacy Analyses

Other efficacy endpoints will be described and compared between treatment groups.

4.12.4.1 Pulmonary Function

Pulmonary function will be reported daily as the range of average lowest value for SpO_2 and the highest value of oxygen flow-rate; the FiO_2 will be derived for non-closed systems. The midpoint of the range of average lowest SpO_2 and derived FiO_2 and respiratory rate for each day will be analyzed via MMRM and plotted over time by treatment group. Mean values will be calculated and differences in treatment effect estimates at Days 7, 14 and 28 will be analyzed.

If any subject has multiple FiO2 records in a day, the maximum of the records of the day will be taken in the analysis; if a subject has multiple respiratory rate records in a day, the mean of the records of the day will be used in the analysis.

However, FiO_2 will only be available for analysis when the patients used the following devices during the study:

- Ventilator (FiO_2 is given directly in the CRF),
- Nasal Cannula (FiO_2 will be calculated using the table listed below),
- Venturi Mask (FiO_2 will be calculated using the table listed below).

FiO_2 (Fraction of Inspired Oxygen) information (from louisville.edu, for reference only):

For all supplemental oxygen delivery devices, the patient is not just breathing the direct oxygen, but rather is breathing a combination of room air plus the oxygen from the supplemental device. Different devices deliver to the patient more or less of a % of what is coming in from the tank.

Fraction of Inspired Oxygen (FiO_2) for a nasal canula and a Venturi mask are given in the tables below. For other oxygen delivery systems, such as masks, tents, there is more oxygen that "blows by" or is lost, therefore higher flow rate setting on the oxygen tank are needed to achieve the same FiO_2. A tracheostomy would require different calculations as well.

Example: with a nasal cannula, we assume that the fraction of oxygen that is inspired (above the normal atmospheric level or 20%) increases by 4% for every additional liter of oxygen flow administered.

For a Nasal Cannula:

Oxygen tank **FLOW RATE** in liters / min	**FiO2** -- Fraction of Inspired Oxygen value
0 (no oxygen, just room air)	.20
1 L / min	.24
2 L / min	.28
3 L / min	.32
4 L / min	.36
5 L / min	.40
6 L / min	.44

For a Venturi Mask:

Oxygen tank **FLOW RATE** in liters / min	**FiO2** – Fraction of Inspired Oxygen Value
0 (no oxygen, just room air)	.20
4 L / min	.26
6 L / min	.31
8 L / min	.375
12 L / min	.447

4.12.4.2 Supportive Care

The following types of supportive care will be analyzed: ECMO, IMV, ECMO or IMV, noninvasive ventilation, and/or high-flow oxygen, any of the previous 4 types of care, proning, tracheostomy, COVID-19 convalescent plasma, and remdesivir use. The percent of patients who ever receive each of these and the number of days each of these is given, during Days 1-28, will be analyzed between treatment groups.

4.13 Safety Analyses

All safety evaluations will be based upon the Safety Analysis Set.

Safety will be assessed by evaluating all reported AEs and changes in laboratory analytes, ECGs, and vital signs (including body weight) in the Safety Analysis Set and summarized by treatment group.

The baseline for computing the change in safety data is the last value collected before the first dose of study drug. The parameters will be listed and summarized with standard descriptive statistics. Change from baseline will also be summarized.

4.13.1 Extent of Exposure

Exposure to therapy will be calculated for each subject as the number of complete infusions delivered.

4.13.2 Adverse Events

Summaries of AEs will include the number of patients with at least one AE for each treatment group. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the screening period will be used as baseline. The treatment period will be included as post-baseline for the analysis.

AEs will be coded according to the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, severity, and relationship to investigational product. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated.

In an overview table, the number and percentage of patients who experienced a TEAE, serious adverse event, adverse event related to study drug, died due to an adverse event, or discontinued from the study due to an adverse event will be summarized by treatment. TEAEs will be reported separately for Days 1-28 while in the hospital and for the post-hospitalization follow-up period.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) include all adverse events that emerge or worsen after taking the first dose of study drug. TEAEs will be summarized for each treatment group by SOC and PT, and by PT in order of decreasing frequency of preferred term.

Serious Adverse Events

Treatment-Emergent SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.

Treatment-Emergent Adverse Events Resulting in Death

If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.

Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation
TEAEs for which the action taken with medication is 'Drug Withdrawal' will be identified as TEAEs that lead to study drug discontinuation. The TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the Safety population.

Treatment-Related Treatment-Emergent Adverse Events
Every AE will be assessed by the investigator for its relationship to the randomly assigned study medication. The subset of TEAEs considered by the investigator as either possibly, probably, or definitely related to study treatment will be summarized as drug-related TEAEs by SOC and PT.

Treatment-Emergent Adverse Events by Maximal Severity
Every AE will be graded by the CTCAE criteria, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.

4.13.3 Clinical Laboratory Evaluation

Blood samples for hematology and clinical chemistry will be collected. Profiles for the hematology, clinical chemistry will be summarized, and patients with values outside the normal range during the on-treatment period during the study will be summarized.

Change from baseline for each of the hematology, clinical chemistry will be derived for each of the post-dose time points using the pre-dose measurement as the baseline. Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each postdose time point will be tabulated.

Laboratory results recorded as "< x" or "≤ x" will be imputed as x; results recorded as "> x" or "≥ x" will be imputed as x and a footnote will be added to indicate the number of patients and visits that were above the limit.

Each laboratory parameter will be classified as low, normal or high relative to the central laboratory's normal range. For each treatment group shift tables will be generated from the predose category to the category post-dose for each laboratory parameter. The shift tables will present the number (percent) of patients who started in a category (low, normal, high) at baseline and ended in a category at each scheduled visit before the end of the study. A missing category will be included for both pre-dose and post-dose, so that all patients in the Safety population will be represented in the table. The missing category includes the cases where the normal range is partially or completely missing, the unit of measurement is missing, and/or the laboratory result itself is missing. The percentages will be calculated using number of patients in the Safety population who have measurements at pre-dose and post-dose.

Shift tables comparing pre-dose to the other time points in the study may be generated if warranted after data review.

4.13.4 Vital Signs

Extreme vital signs will be determined using the following criteria:

- Heart rate either < 50 bpm or > 100 bpm,
- Systolic blood pressure either ≤ 90 mmHg or ≥ 160 mmHg,
- Diastolic blood pressure either ≤ 50 mmHg or ≥ 100 mmHg.

The number (percent) of patients having extreme vital signs will be tabulated by treatment group at each scheduled visit. The percentage will be calculated using the number of patients in the Safety population with data at each visit as the denominator. The number (percent) of patients having extreme vital signs post-baseline (including unscheduled assessments) will be calculated.

Change from baseline statistics will also be defined for the measurements of blood pressure, heart rate and temperature using the pre-dose values as baseline. Descriptive statistics for the measurement of temperature will also be provided by treatment group.

All patients who have an extreme vital sign value will be documented in a by-patient listing. The listing will include all of the vital sign measurements from the study for the patient, and the extreme values will be flagged.

4.13.5 Electrocardiograms

The number (percent) of patients who had an abnormal ("Abnormal, CS" or "Abnormal, NCS") ECG at any time while on-treatment will be tabulated by treatment group. All on-treatment ECGs, including unscheduled assessments, will be considered.

4.14 Subgroup Analyses

The primary end point will be analyzed for the following subgroups:

- Patients who are confirmed SARS-CoV-2 positive and otherwise o age group < 65 and ≥ 65 o sex o BMI < 30 and ≥ 30 o Patients that receive one dose and two doses of study drug o Patients who reach NIAID ordinal scale score = 2 within day 4 and those who do not o Patients with baseline NIAID ordinal scale score of 3, and those with baseline score of 4 or 5
- Patients who received remdesivir and those who do not.

For endpoints which do not consider mortality, subgroup analyses of survivors only may be conducted if appropriate.

4.15 Protocol Violations

A list of major protocol violations that could potentially impact the analysis of the study will be determined during the conduct of the study by study team members who are blinded to study treatment being received. These will be presented in a listing.

4.16 Interim Analyses and Data Monitoring

An independent DMC will review unblinded safety data on an ongoing basis (Protocol Section 9.4.5). These will consist of the following:

- Listing of individual SAEs o Table of SAEs by treatment group o Table of TEAEs by treatment group o Table of NIAID ordinal scale assessment – worst value per patient by treatment group o Table of demographics by treatment group
- Table of Baseline disease characteristics by treatment group

If the DMC requests and the sponsor agrees to conducting a futility analysis, the conditional power for the primary efficacy analysis will be assessed via simulations, using the data collected so far to predict the remaining data to be collected.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study by the sponsor using blinded data.

4.16.1 Interim Analysis

After approximately 100 randomized patients have 28 day data available, an analysis was conducted to assess study futility. An unblinded snapshot of the eCRF database was used for this interim analysis. In addition to the safety data regularly provided to the DMC for their review, efficacy data consisting of ventilation status, hospital discharge, and mortality during days 1-28 as well as the calculation of ventilator free days (VFD) were provided for evaluation.

The conditional power for the primary efficacy analysis was calculated by the DMC Statistician, using the data collected as of the interim analysis to predict the data to be collected after the interim analysis. If this conditional power is less than 10%, then the DMC should recommend that the study be stopped: no new patients should be randomized, and no new doses of study drug given, but ongoing patients should be allowed to complete other protocol procedures and be followed to collect their full data.

4.17 Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and ‘Other’ Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered ‘Serious’ whether or not it is a treatment emergent adverse event (TEAE).

- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - The number of participants at risk of an event
    - The number of participants who experienced each event term
    - The number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

5. List of TLFs

The numbering of the TLFs will be left for the medical writers to assign. The sequential numbers are provided below just for clarity. These numbers should be excluded from the TLFs.

5.1 List of Tables

	Title
1	Demographics and Baseline Characteristics (Safety Population)
2	Demographics and Baseline Characteristics by Site (Safety Population)
3	Analysis Populations
4	Patient Disposition by Treatment Group and Overall
5	Drug Exposure (Safety Population)
6	Concomitant Medications By Drug Class And Name (Safety Population)
7	Medical History (Safety Population)
8	Overview of Adverse Events (Safety Population)
9	Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
10	Number and Percentage of Subjects with Study Drug Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
11	Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity (Safety Population)
12	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
13	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Population)
14	Treatment Emergent Adverse Events that Result in Death by System Organ Class and Preferred Term (Safety Population)
15	Hematology Lab Results by Study Day and Change from Baseline (Safety Population)
16	Chemistry Lab Results by Study Day and Change From Baseline (Safety Population)
17	Hematology Shift from Baseline (Safety Population)
18	Chemistry Labs Shift from Baseline (Safety Population)
19	Subjects with Abnormal Hematology Results (Safety Population)
20	Subjects with Abnormal Chemistry Results (Safety Population)
21	Pregnancy Status (Safety Population)
22	Vital Signs and Change from Baseline by Study Day (Safety Population)
23	Subjects with Extreme Vital Signs (Safety Population)

24	Number and Percentage of Subjects with Abnormal ECGs (Safety Population)
25	COVID-19, Influenza, RSV, and Respiratory Viral Panels (Safety Population)
26	(Primary Objective) Ventilator Free Days (Efficacy Population)
27	Ventilator Free Days by SARS-Cov-2 Status (Efficacy Population)
28	Ventilator Free Days by Age Group (Efficacy Population)
29	Ventilator Free Days by Sex (Efficacy Population)
30	Ventilator Free Days by BMI Group (Efficacy Population)
31	Ventilator Free Days by Number Of Doses (Efficacy Population)
32	Ventilator Free Days by NIAID = 2 within Day 4 (Efficacy Population)
33	Ventilator Free Days by NIAID = 3 vs. NIAID = 4 or 5 (Efficacy Population)
34	Ventilator Free Days by Remdesivir Use (Efficacy Population)
35	(Secondary Objective) Alive and Respiratory Failure Free Complete Response (Efficacy Population)
36	(Secondary Objective) NIAID Ordinal Assessments (Efficacy Population)
37	(Secondary Objective) Time to 2-Point Improvement on NIAID (Efficacy Population)
38	(Secondary Objective) Mortality Rate within 28 Days from Randomization (Efficacy Population)
39	(Secondary Objective) Mortality Rate within 60 Days from Randomization (Efficacy Population)
40	(Secondary Objective) Length of Hospitalization Stay (Efficacy Population)
41	(Secondary Objective) Hospital Discharge Rate at Day 28 (Efficacy Population)
42	(Other Objective) Pulmonary Function by Study Day (Efficacy Population)
43	(Other Objective) Supportive Pulmonary Care (Efficacy Population)

5.2 List of Data Listings

	Title
1	Analysis Populations (including exclusion reason from efficacy population)
2	Protocol Deviations
3	Demographics and Baseline
4	Patient Disposition
5	Drug Exposure
6	Concomitant Medications by Drug Class and Name
7	Medical History

8	Adverse Events
9	Serious TEAEs
10	All Deaths
11	Related TEAEs
12	Hematology Lab Results
13	Abnormal Hematology Lab Results
14	Chemistry Lab Results
15	Abnormal Chemistry Lab Results
16	Pregnancy Test Results
17	Vital Signs
18	Extreme Vital Signs
19	ECGs
20	Abnormal ECGs
21	Physical Exams
22	COVID-19, Influenza, RSV, and Respiratory Viral Panels
23	Thyroid Panels
24	Ventilator Free Days
25	Mortality and Respiratory Failure Status
26	NIAID Ordinal Assessments
27	Pulmonary Function
28	Hospitalizations
29	Supportive Pulmonary Care

5.3 List of Figures

	Title
1	NIAID Mean Score over Time by Treatment Group
2	NIAID Category over Time by Treatment Group (Stacked Bar Plot)
3	NIAID Category over Time by Treatment Group (Stacked Bar Plot) where Categories 3-5 are Combined and 6-8 are Combined
4	Time to 2-Point Improvement on NIAID (Kaplan-Meier Plot)
5	Pulmonary Function over Time by Treatment Group