MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose Escalation and Proof-of-Concept Study to Evaluate the Safety and Efficacy of Razuprotafib in Hospitalized Subjects With Moderate to Severe Coronavirus Disease 2019 (COVID-19) (RESCUE Study)
Protocol Number:	AKB-9778-CI-6001
Protocol Version/Date:	Version 3.0 / 10 December 2020
Investigational Product:	AKB-9778 (razuprotafib)
Sponsor:	Aerpio Pharmaceuticals, Inc. 9987 Carver Road, Suite 420 Cincinnati, OH 45242 United States Telephone: 513-985-1920 Fax: 513-985-0999
SAP Version/Date:	Version 1.0 / 16 February 2021

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
1.0	16 February 2021	Original version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANOVA	Analysis of Variance
ATC	Anatomical therapeutic chemical
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
DRC	Data Review Committee
FiO2	Fractional inspired oxygen
ECMO	Extracorporeal membrane oxygenation
FA	Full Analysis
GCP	Good Clinical Practice
HMGB-1	High mobility group box 1
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NIAID	National Institute of Allergy and Infectious Diseases
PaO2	Partial pressure of oxygen
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
Q8H	Every 8 hours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SpO2	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	Three times daily
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number AKB-9778-CI-6001. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of this study are to assess the safety and efficacy of razuprotafib in subjects with moderate to severe COVID-19.

2.1.2 Secondary Objectives

The secondary objectives of this study are to examine the effects of razuprotafib on biomarkers of inflammation and coagulopathy (ie, C-reactive protein [CRP] and D-dimer) in the plasma of subjects with moderate to severe COVID-19 and to characterize exposure of razuprotafib based on plasma concentrations for the samples collected on Day 1 and Day 6.

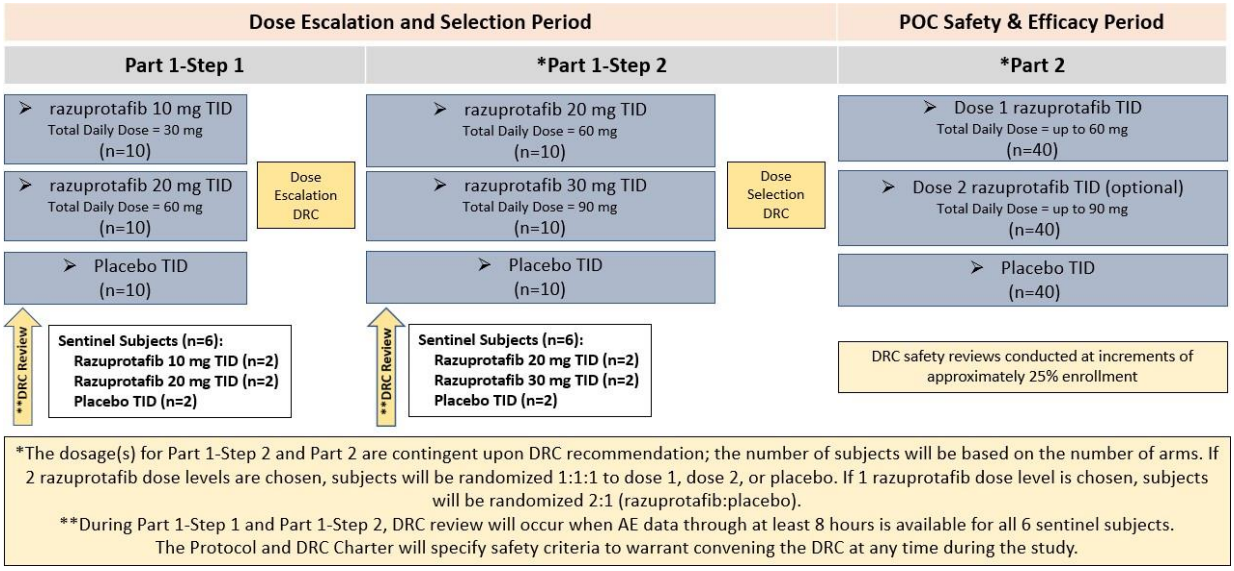
2.1.3 Exploratory Objectives

The exploratory objective of this study is to examine the effects of razuprotafib on biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, tumor necrosis factor alpha [TNFα], and high mobility group box 1 [HMGB-1]) in the plasma of subjects with moderate to severe COVID-19.

2.2 Study Design

2.2.1 Overview

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose escalation and proof-of-concept study to evaluate the safety and efficacy of razuprotafib, administered three times daily (TID) (every 8 hours [Q8H]), in hospitalized subjects with moderate to severe COVID-19 receiving standard of care therapy. The study design is summarized in the figure below.



2.2.2 Randomization and Blinding

After eligibility is determined, 30 subjects (6 sentinel subjects) will be randomized in a 1:1:1 ratio to 1 of the treatment groups in Part 1, Step 1:

- Razuprotafib 10 mg TID;
- Razuprotafib 20 mg TID; or
- Placebo TID.

If the Data Review Committee (DRC) recommends that Part 1, Step 2 should proceed as planned, then another 30 subjects (6 sentinel subjects) will be randomized in a 1:1:1 ratio (or a 2:1 ratio if only 1 razuprotafib dose level is chosen) to 1 of the treatment groups in Part 1, Step 2:

- Razuprotafib 20 mg TID;
- Razuprotafib 30 mg TID; or
- Placebo TID (the placebo volume will match the active volume for each treatment group).

Note: The planned dosing for Part 1, Step 2 may be changed after the DRC reviews the safety and PK data from Part 1, Step 1.

Based on the DRC's review of the available safety and PK data from Part 1, Step 1 and Part 1, Step 2, the study will proceed to Part 2. In Part 2, 120 subjects will be randomized to 1 of the treatment groups (dose 1 razuprotafib TID, dose 2 razuprotafib TID [optional], or placebo TID) in a 1:1:1 ratio (or a 2:1 ratio [razuprotafib:placebo] if only 2 treatment groups). The dosage(s) for Part 1, Step 2 and Part 2 are contingent upon DRC recommendation.

Subjects will be randomized using the centralized randomization system, according to a computer-generated randomization list, and stratified by disease severity. Sentinel subject

randomization will not be stratified by disease severity. Treatment group assignment will be blinded to subjects, clinicians, Sponsor study team, Contract Research Organization (CRO) study team, and Investigators. Specific individuals from the bioanalytical CRO and Sponsor's PK group will have access to the randomization code to allow for ongoing analysis of bioanalytical samples from the subjects treated with razuprotafib and to provide PK analysis results for the DRC reviews.

2.2.3 Study Drug

The drug product formulation contains AKB-9778-sodium salt ready to dose, preservative free, isotonic, sterile solution (20 mg/mL or 40 mg/mL) in a 3 mL borosilicate vial fitted with a 13 mm septum and aluminum flip top seal. Placebo for razuprotafib (sterile normal saline) will be sourced locally by the site as a parenteral formulation ready to dose.

Razuprotafib will be provided in an open-label format that is compliant with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. The placebo will be sourced locally and provided with the commercially available product label.

A volume of 0.50 mL or 0.75 mL of study drug will be administered TID (Q8H) by SC injection to the abdomen. Subjects will be dosed for 7 days or until discharge from the hospital (or death), whichever occurs first. The first study drug administration must occur within 12 hours after randomization. Study drug should be administered at the same nominal times (±1 hour) for each Q8H dose throughout the Treatment Period. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days.

2.2.4 Sample Size Determination

Part 1 will include approximately 60 subjects. In Part 1, Step 1, approximately 30 subjects (including the 6 sentinel subjects) will be enrolled. In Part 1, Step 2, approximately 30 subjects (including the 6 sentinel subjects) are planned to be enrolled. Part 2 will include approximately 120 subjects. No formal statistical assessment for sample size determination has been performed for Part 1 or Part 2. The sample size is considered adequate to provide the necessary data to evaluate the objectives for Part 1 or Part 2.

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

The efficacy endpoints include the following:

- Proportion of subjects alive and free of respiratory failure at Day 28;
- Proportion of subjects alive and free of respiratory failure at Day 7;
- Proportion of subjects alive and not requiring invasive mechanical ventilation at any time through Day 28;
- Time to reach grade 6, 7 or 8 on the NIAID 8-point ordinal scale;
- Change in PaO2:FiO2 ratio from baseline to Day 7 (or discharge) and baseline to Day 28 (or discharge);

- Length of hospitalization and not requiring invasive mechanical ventilation from baseline to Day 7 and baseline to Day 28 or death;
- Length of hospitalization from baseline to Day 7 and baseline to Day 28 or death;
- Proportion of subjects who improve by ≥2 categories on the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- Proportion of subjects who worsen by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- All-cause mortality at Day 7 and Day 28;
- Number of subjects in each category of the NIAID 8-point ordinal scale at Day 7 and Day 28;
- Time to return to prehospitalization oxygen requirement; and
- Proportion of subjects who were discharged and remained free of respiratory failure prior to Day 7 and Day 28.

The NIAID 8-point ordinal scale includes the following grades:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO);
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplementation 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; and
8. Not hospitalized, no limitations on activities.

2.3.2 Pharmacodynamic (PD) and Pharmacokinetic (PK) endpoints

The PD and PK endpoints include in the following:

- Change from baseline in CRP and D-dimer;
- Change from baseline in systemic biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, TNFα, and HMGB-1);
- Summary of plasma concentrations of biomarkers at each sampling time point for each treatment group; and

- Summary of plasma razuprotafib concentrations for the samples collected on Day 1 and Day 6.

2.3.3 Safety Endpoints

The safety endpoints include the following:

- Number of subjects with any serious adverse event (SAE); and
- Number of subjects with any treatment-emergent AE.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug.

3.1.3 Visit Windows

No analysis visit windows will be defined for this study, i.e., the nominal visits /time-points will be used for all statistical summaries/analyses.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

Summaries of change from baseline variables will include only patients who have both a baseline value and corresponding value at the post-baseline time point of interest.

3.1.5 Hypothesis Testing

All statistical comparisons will be made using two-sided tests at $\alpha = 0.05$. All null hypotheses will be of no treatment difference, and all alternative hypotheses will be two-sided. Confidence intervals will be two-sided, unless stated otherwise.

3.1.6 Handling of Dropouts and Missing Data

For all efficacy endpoints that do not include death as a possible outcome, data from subjects who die prior to Day 28 will be imputed at Day 28 based on the worst outcome. Other missing data for selected endpoints will be imputed using the methods as described in Section 3.4.

In cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing,

will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population is defined as all subjects randomized. Subjects in this population will be analyzed according to the treatment group to which they were assigned at randomization.

3.2.2 Full Analysis (FA) Population

The Full Analysis (FA) Population is a subset of the ITT Population and will include subjects receive at least one dose of study drug and have at least 1 post-dose efficacy evaluation.

3.2.3 Per-Protocol (PP) Population

The Per-Protocol (PP) Population is a subset of the FA Population and will include subjects that have at least 1 post-dose efficacy evaluation and do not have major protocol deviations.

3.2.4 Safety Population

The Safety Population is defined as all randomized subjects who received at least 1 dose of study drug. Subjects in this population will be analyzed according to the study drug they actually received.

3.2.5 Pharmacokinetic (PK) Population

The Pharmacokinetic (PK) Population is defined as all randomized subjects who received at least one dose of study drug and had least one PK sample with plasma concentration.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The number and percentage of subjects in each of the following categories will be presented by the treatment group and overall for all screened subjects:

- screened,
- randomized,
- treated,
- randomized but not treated,
- completed the Treatment Period, and
- completed the study.

Primary reasons for discontinuation of study treatment and primary reasons for early withdrawal from the study will be tabulated.

3.3.2 Protocol Deviations

Any major protocol deviation will be documented as described in the protocol deviation plan, and its impact on inclusion in each analysis population for any subject will be specified. The final list of protocol deviations impacting the analysis populations will be reviewed prior to database lock. Counts and percentages of subjects with major protocol deviations by deviation category will be summarized for all randomized subjects.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race
- Ethnicity
- COVID-19 severity (moderate or severe)
- NIAID Assessment
- PaO_2:FiO_2 ratio
- Pre-hospitalization oxygen requirement (None, Low-flow or High-flow Nasal cannula or CPAP mask)
- Concomitant medication to treat COVID-19 at baseline
- Comorbid conditions (diabetes, obesity, hypertension, heart failure, chronic kidney disease)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment group and overall for each Analysis Population.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment group and overall.

Counts and percentages of subjects with COVID-19 symptoms will be summarized by treatment group and overall.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization Drug Dictionary (WHO Drug Global B3, March 2020).

Prior medications will include medications which started prior to the first dose of study drug.

Concomitant medications will include medications taken on and after the first dose of study drug.

Medications that started prior to the first dose of study drug but continued into treatment are considered as both prior and concomitant.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and overall based on the ITT Population.

Any novel therapies for COVID-19 will be summarized based on the ITT Population.

3.3.7 Study Drug Exposure

Exposure to study treatment will be described in terms of duration of treatment and number of doses administered. Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. The number of doses administered for each subject will be summarized with counts and percentages in total.

3.4 Efficacy Assessment

All efficacy analysis will be performed using the ITT Population. Selected endpoints will be repeated on the FA and PP Populations. In addition, the efficacy analyses will be analyzed for pooled razuprotafib doses and placebo.

Additional analyses to understand safety and efficacy variables further may be carried out and will be labeled as post-hoc analyses.

3.4.1 Efficacy Endpoints

The following parameters will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by disease severity:

- Proportion of subjects alive and free of respiratory failure at Day 28;
- Proportion of subjects alive and free of respiratory failure at Day 7;

All results will be summarized descriptively by treatment arm and expressed as proportions, along with corresponding 95% CI of the difference between response rates, and p-values. The 95% CI will be constructed using the normal approximation method.

Additional Analysis may be considered by incorporating other covariate adjustments into the analysis.

Respiratory failure will be defined as subjects who are on invasive mechanical ventilation; are receiving oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) noninvasive positive pressure ventilation or extracorporeal membrane oxygenation; or have a

clinical diagnosis of respiratory failure (ie, clinical need for 1 of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation).Subject who die prior to the study timepoint (Day 7 or Day 28) will be imputed based on the worst outcome. Other missing responses will be imputed using a multiple imputation (MI) method under the assumption of missing at random (MAR).

Sensitivity Analysis

- All missing responses will be considered as non-responders and which will be imputed taking the worst case approach.
- The analysis will be repeated on FA and PP Populations.

The following parameters will be analyzed using the CMH test as stated above:

- Proportion of subjects alive and not requiring invasive mechanical ventilation at any time through Day 28;
- Proportion of subjects who improve by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- Proportion of subjects who worsen by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- All-cause mortality at Day 7 and Day 28; and
- Proportion of subjects who were discharged and remained free of respiratory failure prior to Day 7 and Day 28.

The following parameters will be analyzed using an analysis of variance (ANOVA) model with effects for treatment, baseline value and disease severity as factors:

- Change in PaO2:FiO2 ratio from baseline to Day 7 (or discharge) and baseline to Day 28 (or discharge),
- Length of hospitalization and not requiring invasive mechanical ventilation from baseline to Day 7 and baseline to Day 28 or death,
- Length of hospitalization from baseline to Day 7 and baseline to Day 28 or death,

Missing responses will be imputed using a multiple imputation (MI) method under the assumption of missing at random (MAR).

All results will be summarized descriptively by treatment group, along with corresponding 95% CI of the difference between razuprotafib groups vs. placebo, and p-value.

The length of hospitalization will include all days that the subject is admitted to the hospital. For subjects who are discharged and readmitted to the hospital, the length of hospitalization will include the days after readmission.

Hospitalization days will be counted in 24-hour periods; any partial days will be counted as a whole day.

Days that subjects are on the ventilator will be counted as days of respiratory failure. Days that subjects are of respiratory failure based on the definition will be counted as days of respiratory failure. For subjects receiving high flow oxygen by a nasal cannula or noninvasive positive

pressure ventilation when enrolled, the length of respiratory failure will include all the days of respiratory failure from baseline.

The time-to-event endpoint of time to reach grade 6, 7 or 8 on the NIAID 8-point ordinal scale will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate of the median time as well as the 2-sided 95% confidence interval will be presented by treatment group.

The endpoint of number of subjects in each category of the NIAID 8-point ordinal scale at Day 7 and Day 28 will be summarized by treatment group and timepoint using descriptive statistics.

The endpoint of time to return to prehospitalization oxygen requirement will be summarized by treatment group using descriptive statistics.

3.5 Pharmacodynamic and Pharmacokinetic Assessment

The PD and PK endpoints include the following:

- Change and percentage change from baseline in CRP and D-dimer;
- Change and percentage change from baseline in systemic biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, TNFα, and HMGB-1);
- Summary of plasma concentrations of biomarkers at each sampling time point for each treatment group; and
- Summary of plasma razuprotafib concentrations for the samples collected on Day 1 and Day 6.

PD and PK endpoints will be summarized descriptively by treatment group using ITT population and PK population.

3.6 Safety Assessment

Safety data will be summarized based on the Safety Population. Safety will be determined by evaluating clinical laboratory findings (blood chemistry, hematology, and coagulation), vital signs (blood pressure, heart rate, SpO2 [for non-ventilated subjects only], and respiratory rate), 12-lead electrocardiograms, and AEs reported during the study.

3.6.1 Adverse Events (AEs)

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of the first dose of study drug until Day 28. All AEs will be coded to system organ class and preferred term using MedDRA version 23.0. Treatment-emergent adverse events (TEAEs) will be defined as an event that occurs on or after the first dose of study drug.

An overview of AEs will be provided including counts and percentages of subjects and event counts with the following:

- Any TEAEs (Overall, by maximum severity)
- Any study drug related TEAEs
- Any treatment-emergent serious AEs (TESAEs)

- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to death

Counts and percentages of subjects and event counts will also be presented by system organ class and preferred term for each of the categories in the overview.

All AEs will be displayed in listings. In addition, listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.6.2 Clinical Laboratory Tests

Values and changes from baseline of clinical laboratory variables for blood chemistry, hematology, and coagulation will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. Clinical Laboratory data will be listed.

3.6.3 Vital Signs

Vital signs will include blood pressure, heart rate, SpO2 (for non-ventilated subjects only), and respiratory rate. Temperature will be measured at Screening only.

Values, changes from baseline, changes from pre-dose for each TID dose of vital signs will be summarized using descriptive statistics by treatment group and time point. Vital signs will be listed.

3.6.4 Electrocardiograms

Values and changes from baseline of electrocardiograms data will be summarized using descriptive statistics by treatment group and time point (baseline and Day 7). The overall interpretation will be summarized by counts and percentages by treatment group and total. 12-lead electrocardiograms data will be listed.

4 DATA REVIEW COMMITTEE

A DRC comprised of members with pertinent expertise will review emerging safety, efficacy, and PK data at appropriate times throughout the study, as described in this protocol and as set forth in the DRC Charter.

The DRC will convene throughout the study to review safety and PK data to recommend if it is safe and appropriate to continue the study as planned. The DRC will convene to recommend if continuation of Part 1, Step 1 and Part 1, Step 2 as planned is acceptable or if dosing modifications are required once AE information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects in both Step 1 and Step 2 of Part 1. Upon both reviews after Part 1, Step 1 and Part 1, Step 2, the DRC will recommend subsequent dosing regimen(s) to be tested in the study. Prior to the initiation of Part 2, the DRC may also make a recommendation to increase the study drug dosing duration to up to 14 days. The highest dose in this study will not exceed 30 mg TID. The DRC can request to unblind efficacy data at any point if deemed necessary to adequately complete their review. Additionally, the DRC may request to unblind efficacy data if an increase in the study drug dosing duration is

under consideration. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

In addition, ad hoc reviews of safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The protocol does not include the following three endpoints: proportion of subjects alive and not requiring invasive mechanical ventilation at any time through Day 28, time to reach grade 6, 7 or 8 on the NIAID 8-point ordinal scale, and length of hospitalization and not requiring invasive mechanical ventilation from baseline to Day 7 and baseline to Day 28 or death, these have been included in the SAP. The following two endpoints have been deleted from SAP: length of ICU stay from baseline to Day 28 or death has been deleted from SAP and length of hospitalized and free of respiratory failure from baseline to Day 7 and baseline to Day 28 or death.

The protocol does not include percentage change for PD endpoints, this has been included in the SAP.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.