CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0013
Study Title:
A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults: ACTIV-5
APPENDIX 6 BET-B:
Lenzilumab/Remdesivir vs. Placebo/Remdesivir

NCT04583969

Version 3.0

DATE: 23-MAY-2022

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0013**
Development Phase:	Phase 2/3
Products:	Lenzilumab + Remdesivir IV Placebo + Remdesivir
Form/Route:	IV
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
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Version Number:	3.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BET	Big Effect Trial
BLOQ	Below the Limit of Quantitation
CI	Confidence Interval
Cm	Centimeters
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CP	Conditional Power
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
HLT	High-Level Term
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
eGRF	Estimated Glomerular Filtration Rate
Hgb	Hemoglobin
INR	International Normalized Ratio
ITT	Intent-to-Treat
JAK	Janus kinase
Kg	Kilograms
KM	Kaplan Meier
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N	Number (typically refers to subjects)
NAAT	Nucleic Acid Amplification Test
NEWS	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases

List of Abbreviations *(continued)*

NIH	National Institutes of Health
OP	Oropharyngeal
OR	Odds Ratio
PAP	Pulmonary Alveolar Proteinosis
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic
PLT	Platelet
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SpO2	Blood Oxygen Saturation
TEAE	Treatment-Emergent Adverse Events
TFL	Tables, Figures, and Listings
TMLE	Targeted Maximum Likelihood Estimate
TNF	Tumor Necrosis Factor
ULOQ	Upper Limit of Quantification
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

Refer to the master SAP.

2. INTRODUCTION

2.1. Purpose of the Analyses

This Statistical Analysis Plan (SAP) encompasses all analyses for primary and key secondary endpoints that are specific to the BET-B study only. Details of the rest of the secondary and some exploratory endpoints are covered in the master SAP. Details regarding PK and virology exploratory endpoints will be covered in separate SAPs.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Concurrent with the implementation and enrollment of BET-B under the objectives described in Section 5 of the master SAP, the lenzilumab manufacturer, Humanigen, sponsored the LIVE-AIR, a phase 3 randomized, double-blind, placebo-controlled trial in hospitalized patients with COVID-19 with survival without ventilation as the primary endpoint. Based on the results from the LIVE-AIR trial (and with no knowledge of unblinded interim results from this trial), consideration was made to expanding BET-B from a phase 2 to a phase 2/3 trial to serve as a confirmatory pivotal trial. This could be accomplished with a larger sample size. These changes were implemented in version 5.0 of the protocol.

3.1.1. Primary Objectives

The primary objective for BET-B is to evaluate the clinical efficacy of lenzilumab as assessed by survival without invasive mechanical ventilation or ECMO through Day 29 in subjects who are < 85 years old with a baseline ordinal score 5 or 6 and a baseline CRP<150 mg/L.

3.1.2. Secondary Objectives

3.1.2.1. Key Secondary Objectives

1. To evaluate the clinical efficacy of lenzilumab as assessed by time to mechanical ventilation or death through Day 29 in subjects < 85 years old with baseline clinical ordinal scores 5 or 6 and baseline CRP<150 mg/L.
2. To evaluate the clinical efficacy of lenzilumab as assessed by time to sustained recovery in subjects who are < 85 years old with a baseline ordinal score 5 or 6 and a baseline CRP<150 mg/L.
3. To evaluate the clinical efficacy of lenzilumab as assessed by survival without mechanical ventilation through Day 29.
4. To evaluate the clinical efficacy of lenzilumab as assessed by time to sustained recovery.

3.1.2.2. Other Secondary and Exploratory Objective(s)

See the other secondary objectives listed in Section 3.1.2 and exploratory objectives listed in Section 3.1.3 of the master SAP.

3.1.2.3. Stage Specific Objective(s)

1. To evaluate lenzilumab pharmacokinetics (PK) in subjects with COVID-19.
    a. Measures: Serum samples for PK (at pre-dose, Day 5, Day 15, and Day 29).

Details regarding this exploratory PK endpoint will be covered in a separate SAP addendum.

3.2. Endpoints

3.2.1. Primary Endpoint

The primary endpoint for stage BET-B is whether the subject did not satisfy one of the following two categories from the ordinal scale up to and including Study Day 29:

- Hospitalized, on invasive mechanical ventilation or ECMO (ordinal score 7); or

- Death (ordinal score 8).

The analysis will only include subjects < 85 years old with a baseline ordinal score of 5 or 6 and baseline CRP < 150.

3.2.2. Secondary Endpoints

1. Time to mechanical ventilation or death up to and including Study Day 29 for subjects < 85 years old with baseline ordinal score of 5 or 6 and baseline CRP <150mg/L. That is time to a clinical status of:
   - Hospitalized, on invasive mechanical ventilation or ECMO (ordinal score 7); or
   - Death (ordinal score 8).
2. Time to sustained recovery as defined as the first day on which the subject who is < 85 years old with baseline ordinal score of 5 or 6 and baseline CRP < 150 mg/L satisfies 1 of the following 3 categories from the clinical status ordinal scale (and does not return to a score of ≥ 4 up to and including Study Day 60):
   - Not hospitalized, no new or increased limitations on activities (ordinal score 1);
   - Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen, CPAP, or BiPAP (ordinal score 2);
   - Hospitalized, not requiring new or increased supplemental oxygen - no longer requires ongoing medical care (ordinal score 3).
3. Proportion of subjects at Day 29 that did not satisfy the following criteria up to and including Study Day 29:
   - For subject with baseline clinical status of 5 or 6:
     - Hospitalized, on invasive mechanical ventilation or ECMO (ordinal score 7);
     - Death (ordinal score 8); or
   - For subjects with baseline clinical status of 7:
     - Death (ordinal score 8).

     This is similar to the primary endpoint but will be analyzed including all subjects randomized to BET-B including any shared controls from other stages.
4. Time to sustained recovery will be analyzed including all subjects randomized to BET-B including any shared controls from other stages.

3.3. Study Definitions and Derived Variables

Refer to the master SAP for the definition of study day, analysis visit windows, and laboratory sample collection study day windows.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

See Section 4.1 of the master SAP.

4.2. Discussion of Study Design, Including the Choice of Control Groups

See Section 4.2 of the master SAP.

4.3. Selection of Study Population

Approximately 550 (275 Lenzilumab + RDV and 275 shared placebo) male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to 70 domestic sites and 5 international sites. The target population should reflect the community at large. The estimated time from screening (Day -1 or Day 1) to end of study for an individual subject is approximately 60 days.

4.4. Treatments

4.4.1. Treatments Administered

All subjects will receive remdesivir as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100-mg once-daily IV maintenance dose during hospitalization up to a maximum of 10 total doses (i.e., loading + maintenance doses received during study and pre-study if applicable). The duration of dosing may be adjusted by the site similar to what is described in the product label and based on a subject's clinical course and ultimate disease severity.

In addition to receiving remdesivir, subjects in the BET-B trial will be randomized to receive lenzilumab or placebo as follows:

- Lenzilumab 600-mg IV infusion starting on Day 1 for a total of 3 doses.
- Placebo will be given at an equal volume at the same schedule.

4.4.2. Identity of Investigational Product(s)

Refer to Section 6.1.1 of the Appendix B - BET-B protocol.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

See Section 4.4.3 of the master SAP.

4.4.4. Selection of Doses in the Study

The dose of remdesivir used in this stage will be the same dose shown to be efficacious in the ACTT-1 clinical trial and are the US FDA approved doses. The duration of dosing may be adjusted by the site according to clinical severity. The maximum number of doses to be given during hospitalization is ten doses.

This includes the loading dose and all maintenance doses given during the study and pre-study if applicable.

For lenzilumab, the dosing strategy of 600 mg every 8 hours for three doses will be used. Previous studies using this dosing regimen have shown this regimen to maintain adequate lung tissue levels of lenzilumab for

at least seven days and did not show any evidence of an increase in infections or development of pulmonary alveolar proteinosis (PAP).

4.4.5. Selection and Timing of Dose for Each Subject

Remdesivir will be administered as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100-mg once-daily IV maintenance dose during hospitalization up to a maximum of 10 total doses.

Lenzilumab will be administered as a 600-mg IV infusion starting on Day 1 for a total of 3 doses.

4.4.6. Blinding

See Section 4.4.6 of the master SAP.

4.4.7. Prior and Concomitant Therapy

Steroids and other concomitant therapies intended as specific treatment of COVID-19, as well as all biologics, will be assessed from 7 days prior to enrollment to Day 29. All other concomitant medications will be assessed from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first.

4.4.8. Treatment Compliance

Each dose of study product will be administered by a blinded member of the clinical research team who is qualified and licensed to administer the study product. Administration date and time, and whether any doses were slowed, halted or missed will be entered into the case report form (CRF).

4.5. Efficacy and Safety Variables

See Table 3 for schedule of study procedures. See Section 4.5 of the master SAP for additional details regarding efficacy and safety variables.

5. SAMPLE SIZE CONSIDERATIONS

The LIVE-AIR trial estimated a HR of about 1.5 in its overall population, and a HR of above 3 in the identified subgroup. The corresponding relative risks for the primary endpoint were in the 2.5 or 2.6 range, and the corresponding odds ratios were around 3. Because the treatment effect in the post hoc subgroup may be overly optimistic, the BET-B updated sample size assumes an intermediate odds ratio of 2.5 for the subgroup. The LIVE-AIR trial also observed a 21% event rate in the placebo group in the subgroup, which is likely higher than expected in this trial.

A sample size of 400 in the subgroup will yield 80% power if the control event rate is 16% and 89% power if the control rate is 21%, if the odds ratio is 2.5 and a two-sided alpha=.049. (An odds ratio of 2.5 is defined such that if the control event rate is 16%, the treated rate would be 7%.) At most 550 participants (that is, subjects randomized into BET-B and relevant shared controls) will be randomized. Based on early BET baseline estimates, roughly 75% of subjects are expected to fall in the primary analysis subgroup at baseline (CRP<150mg/L, age<85, and baseline ordinal score < 7). The trial will enroll subjects until 400 are randomized in the subgroup or 550 overall, whatever comes first. These calculations are not inflated for missing data, as little missing data are expected.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Several statistical features were modified at the time BET-B was changed to a Phase 2/3 design including an increase in sample size, change to the primary endpoint, and new futility analysis. Refer to Section 6.1 of the master SAP for additional details of general principles applied in this study. Some of the deviations from the main SAP are noted below:

- The Day 8 ordinal score will be analyzed without multiple imputation.
- The primary endpoint of progression to mechanical ventilation or death will be analyzed using multiple imputation for missing event using the pseudocode provided in Section 6.5. After imputation, odds ratio and risk difference can be obtained using the following pseudocode:

6.2. Timing of Analyses

See Section 6.2.1 of the master SAP. An additional futility analysis will take place after approximately 280 subjects eligible for the primary analysis subgroup have been enrolled and randomized.

6.3. Analysis Populations

The primary analysis will be based on the intention-to-treat (ITT) population, including all subjects who were randomized and will use randomized arm. The primary analysis and key secondary endpoints will be repeated using the mITT analysis population which includes all randomized subjects who received at least one dose of study product and is analyzed as randomized. Safety analyses will be based on the safety population and will use actual treatment received. An enrolled population will include all consented participants and will be used to compute disposition, baseline characteristics, and similar summaries based on randomized treatment group. For all populations, actual ordinal score at baseline will be used to classify subjects into baseline ordinal score category.

See Section 6.3.1 through Section 6.3.4 of the master SAP for full definitions of analyses populations to be used for this stage.

6.4. Covariates and Subgroups

The primary analysis of survival without mechanical ventilation uses baseline ordinal score, baseline CRP, age, and baseline dexamethasone use as covariates in the logistic regression model. This primary analysis will be repeated for the following subgroups: severity of disease, baseline steroid use, baseline use of emerging COVID-19 treatments, duration of symptoms, race, comorbidities (binary 2+ vs less than or equal to 1), age, baseline CRP, and sex. Table 1 provides details of covariates to be used for all analyses of primary, secondary or exploratory endpoints.

Table 1: Covariates and Subgroup Analyses for Each Endpoint

Endpoint	Analysis	Covariates/Subgroups
Primary Endpoint		
Survival without mechanical ventilation in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L. [Note: baseline CRP must be available for inclusion in this analysis.]	Primary and main sensitivity analysis	1. Adjust for the following covariates in the ITT Population • Baseline dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous)
	Additional sensitivity	1. Repeat primary analysis with the following covariates in the ITT Population: • Baseline dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (categorical) • Geographical regions 2. Repeat primary analysis on mITT population using actual baseline ordinal score and adjusting for the following covariates: • Baseline dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous) 3. Repeat primary analysis on mITT population adjusting for the following covariates: • Baseline dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (categorical) • Geographical regions
	Subgroup	Repeat the primary analysis for this endpoint within each of the following subgroups using the ITT population: • Actual baseline ordinal score • Baseline steroid use • Baseline use of emerging COVID-19 treatments • Duration of symptoms prior to enrollment • Race • Ethnicity • Comorbidities • Age (categorical) • Sex • Baseline CRP (≤ median, >median) • Baseline CRP (<150, ≥150) Baseline dexamethasone use, baseline CRP (continuous), age (continuous), and baseline ordinal score will be included in the subgroup analysis as covariates unless the covariate is the subgroup.

Endpoint	Analysis	Covariates/Subgroups
Key Secondary Endpoints **[Note: All key secondary endpoint analyses in the ITT population will be repeated in the mITT population.]**		
1. Time to mechanical ventilation or death up to and including Day 29 in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L. [Note: baseline CRP must be available for inclusion in this analysis.]	Primary	1. Adjust for the following covariates using ITT population: • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous)
	Subgroup	Repeat the primary analysis for this endpoint within each of the following subgroups using the ITT population: • Actual baseline ordinal score • Baseline use of emerging COVID-19 treatments • Duration of symptoms prior to enrollment • Race • Ethnicity • Comorbidities • Age (categorical) • Sex • Baseline CRP (≤ median, >median) • Baseline CRP (<150, ≥150) Baseline dexamethasone use, baseline CRP (continuous), age (continuous), and baseline ordinal score will be included in the subgroup analysis as covariates unless the covariate is the subgroup.
2. Time to Sustained Recovery up to Day 60 in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L.	Primary	1. Adjust for the following covariates using ITT population: • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous)
	Supplementary	1. Adjust for the following covariates using ITT population: • Baseline Dexamethasone use • Actual baseline ordinal score • Age (continuous) • Duration of symptoms prior to enrollment (continuous)
	Subgroup	Repeat the primary analysis for this endpoint within each of the following subgroups: • Actual baseline ordinal score • Baseline steroid use • Baseline use of emerging COVID-19 treatments • Duration of symptoms prior to enrollment • Race • Ethnicity • Comorbidities • Age (categorical) • Sex • Baseline CRP (≤ median, >median) • Baseline CRP (<150, ≥150)

Endpoint	Analysis	Covariates/Subgroups
		Baseline dexamethasone use, and baseline ordinal score, baseline CRP, and age will be included in the subgroup analysis as covariates unless the covariate is the subgroup.
3. Survival without invasive mechanical ventilation/ECMO for all subjects in ITT population	Primary	1.Adjust for the following covariates • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous)
	Sensitivity	1. Repeat primary analysis with the following covariates: • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (categorical) • Geographic regions (categorical)
	Subgroup	Repeat the primary analysis for this endpoint within each of the following subgroups using the ITT population: • Actual baseline ordinal score • Baseline use of emerging COVID-19 treatments • Duration of symptoms prior to enrollment • Race • Ethnicity • Comorbidities • Age (categorical) • Sex • Baseline CRP (≤ median, >median) • Baseline CRP (<150, ≥150) Baseline dexamethasone use, baseline CRP (continuous), age (continuous), and baseline ordinal score will be included in the subgroup analysis as covariates unless the covariate is the subgroup.
4. Time to Sustained Recovery up to Day 60 for all subjects in ITT population	Primary	Adjust for the following covariates using ITT population: • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous)
	Supplementary	Repeat the primary analysis adjusting for the following covariates: • Baseline Dexamethasone use • Actual baseline ordinal score • Baseline CRP (continuous) • Age (continuous) • Duration of symptoms prior to enrollment (continuous)
	Subgroup	Repeat the primary analysis for this endpoint within each of the following subgroups: • Actual baseline ordinal score • Baseline steroid use • Baseline use of emerging COVID-19 treatments • Duration of symptoms prior to enrollment

Endpoint	Analysis	Covariates/Subgroups
		• Race • Ethnicity • Comorbidities • Age (categorical) • Sex • Baseline CRP (≤ median, >median) • Baseline CRP (<150, ≥150) Baseline dexamethasone use, baseline ordinal score, baseline CRP (continuous), and age (continuous) will be included in the subgroup analysis as covariates unless the covariate is the subgroup.
Other Secondary Endpoints and Exploratory Endpoints		
The analysis described for the other secondary efficacy and safety endpoints and exploratory endpoints in the Master SAP will be followed. Refer to Table 6 in the master SAP for addition details regarding covariates and subgroups to be used for those endpoints.		

6.5. Missing Data

For the primary endpoint of incidence of mechanical ventilation or death, subjects who are lost to follow-up before Day 29 prior to having an event and have their last assessment within window for Day 29 (i.e., Day 26, 27, 28) will be considered as non-events by Day 29 regardless of their discharge status at that time. Remaining missing data for subjects lost to follow-up after discharge, while still hospitalized, or with no post baseline data will be imputed using multiple imputation. The main sensitivity analysis will consider subjects missing data while discharged as non-events and use a similar multiple imputation as the primary analysis for remaining missingness. Additional sensitivity analyses of the primary endpoint will use the same imputation approach as the primary analysis on different analysis populations and using different covariates in the final model.

Two secondary analyses of the primary endpoint will be conducted: the first is based on targeted maximum likelihood estimation (TMLE), and the second is a multiple imputation approach that uses TMLE for analysis of each imputed dataset. These approaches are described in Section 6.5.2.

Analysis of time to event endpoints (i.e., sustained recovery, time to improvement, time to mechanical ventilation or death) will be based on observed ordinal score along with discharge and death information. Refer to Table 2 for additional details regarding censoring and handling of missing data for all endpoints.

Some analyses of ordinal score such as ordinal scores over time described in Section 6.5.1 of the master SAP will be performed based on the complete dataset of ordinal score created using the following steps:

- All planned timepoints after death are assigned a score of 8
- Intermittent missingness:
  - Impute the intermittent missing ordinal score as 1 if the scores reported before and after the missing value are both 1 and no change in oxygen use or hospitalization status after discharge to a location other than hospice, long term acute care or other hospital.
  - Impute the intermittent missing ordinal score as 2 after discharge to a location other than hospice, long term acute care or other hospital if the subject doesn't fall into the category above and subject is not hospitalized at the time point.
  - Remaining intermittently missing data imputed using last observation carried forward.

- All remaining missing ordinal scores after last assessment imputed using last observation carried forward.

6.5.1. Multiple Imputation

The multiple imputation approach will classify subjects with missing event into 3 categories as listed below and will apply different imputation models for each as detailed in this section.

6.5.1.1. Imputation Strategy for Subjects Lost to Follow-up with no Post-Baseline Data

This group includes subjects randomized but who withdrew from the study soon after randomization without any post-baseline data. Missing incidence of mechanical ventilation or death data for these subjects will be imputed using multiple imputation model implemented using PROC MI procedure in SAS based on the monotone logistic regression model. The imputation model will include the following covariates: Randomized treatment group (trtvar), baseline dexamethasone use (basedexafl), actual baseline ordinal score (baseordscorevar), age, indicator for black or Hispanic ethnicity (blackhispfl), presence of 2 or more comorbidities (comorb2fl), and baseline CRP (basecrp).

Since missing data in any of these baseline characteristics may cause issues with the monotone missing data patterns, the following methods will be used to fill in missing baseline covariates data:

- For continuous baseline covariates (age, CRP), mean imputation will be used to replace missing values with the overall mean value from all randomized subjects for the given covariate. Note that there will not be any missing data for age and baseline CRP for subjects in the primary subgroup, but there will be some missingness in either of these variables for some of the subjects in the full ITT population.
- For indicator variables of baseline dexamethasone use, black or Hispanic ethnicity, presence or two or more comorbidities, subjects with missing values will be given the value with the greatest number of subjects among all randomized subjects.
- We do not anticipate any missing data for actual baseline ordinal score.

In the case that more than 1% of subjects have missing baseline covariates and the overall p-value for the primary endpoint is < 0.1, a sensitivity analysis will be performed that uses a fully conditional specification (FCS) to impute missing baseline covariates. This is implemented by replacing the `monotone logistic` line in the PROC MI pseudocode shown below with the following line:

```
fcs logistic(eventD29= trtvar baseordscorevar basedexausevar age blackhispfl comorb2fl
basecrp );
```

For most of the modeling, the reference group for categorical variables will be ‘No’ for indicator variables, ‘Placebo + RDV’ for treatment group, and ‘6 or 7’ for actual baseline ordinal score. As an exception, analyses based on the primary subgroup will use ordinal score '6' as the reference group for actual baseline ordinal score.

Pseudocode:

- DEFINE `eventD29` as the binary variable for death or progression to mechanical ventilation or death by Day 29 (1=Yes, 0=No, .=Missing)
- DEFINE input1 as the full analysis dataset containing all baseline covariates and event indicator for complete data subjects as well as subjects with no post-baseline data with missing event indicator to be imputed.

- DEFINE imp_out1 as the output dataset containing the 20 imputed datasets

```
proc mi data=input1  out= imp_out1 nimpute=20 seed = 837405 noprint;
class trtvar baseordscorevar basedexausefl blackhispfl comorb2fl eventD29;
var trtvar baseordscorevar basedexausefl age blackhispfl comorb2fl basecrp eventD29;
monotone logistic(eventD29= trtvar baseordscorevar basedexausevar age blackhispfl
comorb2fl basecrp );
run;
```

The above procedure will output imp_out1 dataset which contains 20 replicates for each subject. Update the dataset to remove subjects with complete data and only keep the 20 imputed datasets for subjects with no post-baseline data.

6.5.1.2. Imputation Strategy for Subjects Lost to Follow-up while Discharged

This group includes subjects with post-baseline data available who were lost to follow-up or terminated early from the study prior to Day 29 and prior to death or progression to mechanical ventilation and were discharged to a location other than LTAC, hospice care or other hospital at the time of their last assessment.

Imputation Approach if Less than 10 Events are Observed

If, as expected, less than 10 post-discharge events are observed in the discharged group, missing incidence of mechanical ventilation or death data for these subjects will be imputed from a simple binomial distribution with the event rate calculated as the proportion of discharged subjects with known outcome (i.e., discharged to a location other than LTAC, hospice care or other hospital) who died or progressed to mechanical ventilation after discharge, without adjusting for any covariates in this group.

If no event is observed in a given analysis such as in subgroup analyses, the event rate of 0.5/total number of discharged subjects with outcome in the subgroup will be used instead of 0.

Pseudocode:

- DEFINE `eventD29` as the binary variable for death or progression to mechanical ventilation or death by Day 29 (1=Yes, 0=No, .=Missing)
- DEFINE input2 as the analysis dataset containing discharged subjects with missing event.
- Define evntrate as the event rate among subjects discharged to a location other than LTAC, hospice care or other hospital who have known outcome.
- DEFINE imp_out2 as the output dataset containing the 20 imputed datasets

```
 data imp_out2;
      set input2;
      subid=input(substr(usubjid,5,4),best12.);
      seed=3849+subid;
      call streaminit(seed);
      p=&evntrate;
      do i=1 to 20;
            _imputation_ = i;
                  eventd29=rand("Binomial",p,1);
            output;
      end;
      drop p i;
run;
```

imp_out2 contains 20 imputed values for each subject discharged to a location other than LTAC, hospice care or other hospital who had missing event.

Imputation Approach if 10 Events or More are Observed

In the case that 10 post-discharge events or more are observed in this group of discharged subjects, missing events will be imputed using PROC MI adjusting for baseline ordinal score as shown in the below pseudocode.

Pseudocode:

- DEFINE input2 as the analysis dataset containing all discharged subjects including those with missing event to be imputed and those with known outcome.

```
proc mi data=input2 out= imp_out2 nimpute=20 seed = 748485 noprint;
class baseordscorevar eventD29;
var eventD29;
monotone logistic(eventD29= baseordscorevar);
run;
```

6.5.1.3. Imputation Strategy for Subjects Lost to Follow-up while Hospitalized or Transferred

This group includes subjects with post-baseline data available who were lost to follow-up or terminated early from the study prior to Day 29 and prior to death or progression to mechanical ventilation and were still hospitalized or discharged to LTAC, hospice care or other hospital at the time of their last assessment. Missing incidence of mechanical ventilation or death data for these subjects will be imputed using the algorithm described below that takes into account each subject's baseline covariates and time of last assessment. For each of these subjects with missing event, the first step will be to estimate the probability of having an event between their last assessment date and Day 29 which will be estimated from a Cox model as described below:

Step 1: Define a dataset including all subjects regardless of missingness except those that have no post baseline data. For all subjects who terminated early without event, consider them as non-events and censor them at the time of last assessment.

Step 2: Fit a Cox proportional hazards model for all subjects in step 1 using the following covariates: randomized treatment group (trtvar), baseline dexamethasone use (basedexavar), baseline actual ordinal score (baseordscorevar), age, indicator for black or Hispanic ethnicity (blackhispfl), presence of 2 or more comorbidities(comorb2fl), and baseline CRP (basecrp). The resulting Cox proportional hazards model will be of this form:

$$h(t) = h_0(t)\exp\left(b_1X_1 + b_2X_2 + \cdots + b_pX_p\right)$$

where

$h(t)$: Expected hazard at time t.

$h_0(t)$: Baseline hazard function and represent the hazard when all the covariates are zero.

$X_1, X_2, \ldots, X_p$: Covariates in the cox model

$b_1, b_2, \ldots, b_p$: Model coefficients.

Pseudocode:

- aval: time variable. All subjects except those with no post-baseline data are included. Subjects missing endpoint are censored at their last assessment day in this cox model.
- cnsr: Event indicator variable (1=No event, 0=event). Subjects with missing outcome are censored.
- Subjects_miss: Dataset with subjects lost to follow-up while discharged or transferred whose endpoint needs to be imputed.
- Outset: Output dataset containing survival estimates for all subjects in subject_miss dataset given their covariates for all timepoints specified in timelist.

```
proc phreg data = analysis;
class trtvar (ref = "Placebo + RDV") basedexavar(ref="No"); baseordscorevar (ref="5")
blackhispfl(ref="No") comorb2fl(ref="No");
model aval * cnsr(1) = trtvar basedexavar baseordscorevar blackhispfl comorb2fl basecrp
age / ties=efron;
baseline out = outset survival = survival covariates=subjects_miss timelist=1 to 29 by 1
/ method = emp;

run;
```

Step 3: For each subject to be imputed (i.e., those lost to follow-up while hospitalized/transferred), estimate the survival probability at their last assessment (SL) and the survival probability at Day 29 (S29). Then, the probability that this subject will have an event between their last assessment day and Day 29 is given by:

Pe = Prob (Event by Day 29|no event through last assessment) = 1 – S29/SL

Step 4: For each subject lost to follow-up while discharged or transferred to another hospital, impute the event from a binomial distribution using the event probability calculated in Step 3.

Pseudocode:

- DEFINE `eventD29` as the binary variable for death or progression to mechanical ventilation or death by Day 29 (1=Yes, 0=No, .=Missing)
- DEFINE input3 as the analysis dataset containing subjects lost to follow-up while hospitalized or transferred with missing event. Add the variable for the probability of an event between last assessment and Day 29 (**pe)** calculated in step 3 to the dataset for subjects with missing data to be imputed.
- DEFINE imp_out2 as the output dataset containing the 20 imputed datasets

```
data imp_out3;
      set input3;
      subid=input(substr(usubjid,5,4),best12.);
      seed=7564+subid;
      call streaminit(seed);
      p=&pe.;
      do i=1 to 20;
            _imputation_ = i;
                  eventd29=rand("Binomial",p,1);
            output;
      end;
      drop p I ;
run;
```

imp_out3 will have 20 imputed values for each subject who was lost to follow-up while hospitalized or transferred and had missing event.

Combine the 3 output datasets from the three different imputations.

```
data imp_out_all;
      set imp_out1 imp_out2 imp_out3;
run;
```

Create 20 replicates for each subject with non-missing event:

```
 data complete_all;
      set complete;
      do i=1 to 20;
            _imputation_ = i;
            output;
      end;
      drop  i;
run;
```

The final dataset to be used for analysis will be created by combined imputed data and complete data:

```
data imp_out;
      set imp_out_all complete;
      proc sort; by subject_imputation_;
run;
```

Using this imp_out dataset, calculate odds ratio follow:

Odds ratios from logistic regression using multiple imputation:

```
proc logistic data=imp_out out=imp_parms;
      by _imputation_;
      class baseordscorevar (param=ref ref=5) basedexausevar (param=ref ref=no steroid
use) trtvar (param=ref ref=placebolabel);
       model eventd29 (eventd29='1') = trtvar baseordscorevar basedexausevar age
baseCRP;
ods output oddsratioswald = orest parameterestimates=pars;
run;

*Keep only estimates for the treatment variable;
data pars1;set pars;where Variable='Treatment variable';run;
*Combine estimates;
PROC MIANALYZE DATA=pars1;
      ODS OUTPUT PARAMETERESTIMATES= logor;
      MODELEFFECTS estimate ;
      STDERR stderr ;
RUN;
*Transform estimates from the log(OR) scale to the OR scale;
data OR;
      SET logor;
      OR_estimate = EXP(ESTIMATE);
```

```
      OR_LCL_95 =OR_estimate*EXP(-1.96*STDERR);
      OR_UCL_95 =OR_estimate*EXP(+1.96*STDERR);
      OR_LCL_80 =OR_estimate*EXP(-1.28*STDERR);
      OR_UCL_80 =OR_estimate*EXP(+1.28*STDERR);

RUN;run;
```

To estimate risk differences from logistic regression, the approach from Ge et. al [1] as described below:

```
proc logistic data = dataset outmodel=pout;
      class trtvar ;
      model surv(event='1') = trtvar othercovariates  ;
run;

*Create dataset tempa to contain all subjects and assign them the active Lenzilumab +
RDV and dataset tempp which include all subjects assigned the placebo treatment;

proc logistic inmodel=pout;
  score data = tempa out=preda(keep=id P_a rename= (P_1=P_a))) ;
run;

proc logistic inmodel=pout;
  score data = tempp out=predp(keep=id P_1 rename= (P_1=P_p)) ;
run;

proc sort data=preda;by subjectid;run;
proc sort data=predp;by subjectid;run;

*Combine to obtain risk differences in probabilities for each subject;

data comb;
      merge predp preda;
      by subjectid;
      diff=P_a-P_p;
run;

proc means data=comb; var diff; run;
```

To obtain the CI for the risk difference, use bootstrap with the following steps:

1. Sample with replacement from the dataset.
2. Obtain risk difference estimate for each bootstrap sample.
3. Repeat this step the above step 1000 times and use the 2.5th and 97.5th percentiles of the risk estimates as the limits for the 95% CI for the risk difference. The risk difference from bootstrap should be equal to the risk difference obtained prior to performing bootstrap.

To generate bootstrap CI for risk difference using multiple imputation, repeat steps 1 and 2 for each imputed dataset. The final risk difference will be calculated as the mean risk difference across all imputed datasets, and the 95% CI will be obtained as the 2.5th and 97.5th percentile of risk difference estimates across all imputed datasets and bootstrap samples [2].

6.5.2. Targeted Maximum Likelihood Method (TMLE)

Missingness in the outcome is easily accounted for in the estimation procedure of TMLE using the missing indicator as shown in the below pseudocode provided that only baseline covariate and treatment information is used in the adjustment for missing data. Because of this requirement, we consider two approaches:

First approach:

The first approach uses TMLE with only baseline covariates to adjust for missing data and does not make use of discharge or transfer data for this adjustment. All subjects missing outcome data due to being terminated early from the study or being lost to follow-up before having an event and before Day 29 will be considered as having a missing outcome data and be imputed using the missing indicator in TMLE.

Second approach:

The second uses a multiple imputation approach that, as in the multiple imputation analyses described in Section 6.5.1, does make use of the discharge and transfer data. TMLE is used to analyze the individual imputed data sets. Standard methods are then used to combine across results across the imputed data sets. We note that this approach cannot be considered formally to be a TMLE analysis. The reason for the second approach is to assess the impact of not using the post-baseline data in the first approach.

Assumptions for the second approach:

- Discharged subjects missing event will be considered non-events.
- For participants who are censored while hospitalized or after transfer, the multiple imputation approach described in Section 6.5.1.3 will be used.
- Event for subjects with no post-baseline data will be missing and handled using TMLE

Each imputed dataset will be analyzed using TMLE. For patients with no post-baseline follow-up, no imputation is required. We will use the feature in TMLE that permits use of baseline data as part of adjustment for these patients.

The estimates of treatment effects , $\widehat{\theta}$, are obtained by taking the mean of risk difference estimates across imputations. The variance of these estimates is estimated by the sum of the average variances of estimates within each imputation and (m+1)/m multiplied by the empirical variance across of the estimates of interest across imputations, where m is the number of imputations.

The within imputation variance, V_W, is the average variance of risk difference estimates within each imputation and is calculated as:$V_W = \frac{1}{m} \sum_{i=1}^{m} SE^2$

The between imputation variance, V_B, reflects the extra variance due to imputation and is obtained by taking the variance of risk difference over imputed datasetsis the average variance of risk difference estimates within each imputation and is calculated as: $V_B = \frac{1}{m-1} \sum_{i=1}^{m} (\hat{\theta} - \theta_i)^2$ where

$\hat{\theta}$ is the overall mean estimate for risk difference

θ_i is the risk difference estimate for each imputed dataset.

The total variance, $\boldsymbol{V_B}$, is then calculated as: $V_T = V_W + \frac{(m+1)}{m} V_B$

The 95% CI for risk difference can then be obtained by ($\hat{\theta} - 1.96\sqrt{V_T}$, $\hat{\theta} - 1.96\sqrt{V_T}$)

The same approach will be followed for combining odds ratio estimates from TMLE version with MI and their 95% CI. First, odds ratio will first be transformed on the log scale before calculating the mean log-OR (mlog_OR) and total variance for for log (OR) ($VlogOR_T$). The final OR estimate is then obtained as

$OR = \exp(mlog_{OR})$ and the 95% CI is obtained as $(OR * \exp(-1.96 * \sqrt{\text{VlogOR}_\text{T}}\ , OR * \exp(1.96 * \sqrt{\text{VlogOR}_\text{T}})$

These estimates can also be obtained in SAS for risk difference and ORs as shown below:

Pseudocode in SAS:

Risk difference calculation in SAS after TMLE:

1. Combine transformed estimates from multiple imputed datasets;
   - **rd_t** is a dataset that has columns for imputation number, risk difference estimates and standard error for risk difference calculated from each imputation dataset
   - **comb_rd_t** contains the final combined estimates and standard errors for risk difference

```
PROC MIANALYZE DATA=rd_t;
     ODS OUTPUT PARAMETERESTIMATES= comb_rd_t;
     MODELEFFECTS rd_value ; #risk difference estimates;
     STDERR rd_se; ; #risk difference standard error;
RUN;
```

2. Back-transform combined values to obtain final estimate and 95% CI;

```
DATA comb_rd_bt;
     SET comb_rd_t;
     RD_Estimate = ESTIMATE; *Pooled risk difference;
     RD_LCL =ESTIMATE -1.96*STDERR; *Pooled lower limit;
      RD_UCL =ESTIMATE +1.96*STDERR; *Pooled upper limit;
RUN;
```

Odds ratio calculation in SAS after TMLE:

3. Combine transformed estimates from multiple imputed datasets;
   - **logsodds_t** is a dataset that has columns for imputation number, log(OR) estimates and standard error for log(OR) calculated from each imputation dataset
   - **comb_logsodds_t** contains the final combined estimates and standard errors for log (OR)

```
PROC MIANALYZE DATA=logsodds_t;
     ODS OUTPUT PARAMETERESTIMATES= comb_logsodds_t;
     MODELEFFECTS log_or_value ; #log_OR estimates;
     STDERR log_or_se; ; #log_OR standard error;
RUN;
```

4. Back-transform combined values to obtain final estimate for OR and its 95% CI;

```
DATA comb_lgsodds_bt;
     SET comb_logsodds_t;
     OR_estimate = EXP(ESTIMATE); *Pooled odds ratio;
     OR_LCL =OR_estimate*EXP(-1.96*STDERR); *Pooled lower limit;
```

```
        OR_UCL =OR_estimate*EXP(+1.96*STDERR); *Pooled upper limit;
    RUN;
```

For both of these approaches, TMLE will be implemented using the tmle R package (https://cran.r-project.org/web/packages/tmle/index.html). For the second approach of TMLE that includes MI, final estimates will be combined across the different imputation datasets using either SAS pseudocode provided above or using formulas provides in either R or SAS.

Pseudo code:

```
Y = binary outcome variable (that can include missing values)
trt = treatment information coded as 0, 1
BaselineCov = Dataframe of baseline covariates (numerical) of each
patient.
MissingIndicator = Vector with 1 indicating that outcome was missing, 0
otherwise
SL.library = c("SL.glm", "SL.gam", "SL.glmnet")

tmResult = tmle(Y = Y, A = trt, Delta = MissingIndicator, W =
BaselineCov, family = "binomial", Q.SL.library  = SL.library,
g.SL.library = SL.library, Delta.SL.library = SL.library)
```

Table 2: Imputation Method for Each Endpoint and Analysis Type

Endpoint	Analysis	Imputation/Censoring Method
Primary Endpoint		
Survival without mechanical ventilation in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L.	Primary, additional sensitivity and subgroup	• Subjects who complete follow-up without mechanical ventilation or death or who have the event after Day 29 will be considered non-events. • Subjects who die or progress to mechanical ventilation after Day 29 will be considered non-events. • Subjects whose last assessment in the study is before Day 29 and before experiencing death or progression to mechanical ventilation will have missing event data for this endpoint and multiple imputation will be used to impute the missing data. See Section 6.5 for details. • Subjects whose last assessment in the study is before Day 29 but within window for Day 29 (i.e., Day 26, 27, 28) and before experiencing death or progression to mechanical ventilation will be considered non-events regardless of their discharge status.
	Sensitivity 1	• Subjects who complete follow-up without mechanical ventilation or death or who have the event after Day 29 will be considered non-events. • Subjects who die or progress to mechanical ventilation after Day 29 will be considered non-events. • Subjects whose last assessment in the study is before Day 29 and before experiencing death or progression to mechanical ventilation and were discharged to a location other than LTAC, hospice care, or other hospital will be considered non-events. • Subjects whose last assessment in the study is before Day 29 and before experiencing death or progression to mechanical ventilation and either had no post-baseline data or were still hospitalized or were discharged to LTAC, hospice care, or other hospital will have missing event data for this endpoint and multiple imputation will be used to impute the missing data. See Section 6.5 for details. • Subjects whose last assessment in the study is before Day 29 but within window for Day 29 (i.e., Day 26, 27, 28) and before experiencing death or progression to mechanical ventilation will be considered non-events regardless of their discharge status.
	Sensitivity 2	• Subjects who complete follow-up without mechanical ventilation or death or who have the event after Day 29 will be considered non-events. • Subjects who die or progress to mechanical ventilation after Day 29 will be considered non-events. • Subjects whose last assessment in the study is before Day 29 and before experiencing death or progression to mechanical ventilation will have missing event data for this endpoint and multiple imputation will be used to impute the missing data. See Section 6.5 for details. • Subjects whose last assessment in the study is before Day 29 but within window for Day 29 (i.e., Day 26, 27, 28) and before experiencing death or progression to mechanical ventilation will be considered missing and imputed using multiple imputation as described in Section 6.5.
Key Secondary Endpoints		
Time to mechanical ventilation or death up to and including Day 29 in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150	Primary and subgroup	• Use the complete data for ordinal score to define survival without mechanical ventilation. • All subjects whose last assessment in the study is before Day 29 and before progression to mechanical ventilation or death will be considered non-events and censored at the date of their last observed assessment. • Subjects who complete follow-up without mechanical ventilation or death will be censored at the expected study Day 29.

Endpoint	Analysis	Imputation/Censoring Method
mg/L.	Sensitivity	• Use the complete data for ordinal score to define survival without respiratory failure. • Subjects whose last assessment in the study is before Day 29 and were discharged to a location other than LTAC, hospice care or other hospital, or progressed to mechanical ventilation or death after Day 29 will be considered non-events and censored at Day 29. • Subjects whose last assessment in the study is before Day 29 and before progression to mechanical ventilation or death and without being discharged to a location other than LTAC, hospice care or other hospital at their last assessment will be considered non-events and censored at the date of their last observed assessment. • Subjects who complete follow-up without mechanical ventilation or death will be censored at the expected study Day 29.
Time to Sustained Recovery up to Day 60 in subjects who are < 85 years old, have baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L.	Primary and subgroup	• Use the complete data for ordinal score to derive sustained recovery. • Subjects whose last assessment in the study is prior to Day 60 prior to recovery will be considered not recovered and censored at the date of last follow-up. • Death prior to recovery will be considered not recovered and censored at expected study Day 60.
	Sensitivity	• Use the complete data for ordinal score to derive sustained recovery. • Subjects whose last assessment in the study is prior to Day 60 after discharge from the hospital to a location other than LTAC, hospice care or other hospital will be treated as recovered by Day 60. Their time to recovery will be the day the time of their first observed/imputed recovery score (i.e; 1, 2, 3) or the day of discharge, whichever comes first. • Subjects whose last assessment in the study is prior to Day 60 without being discharged from the hospital to a location other than LTAC, Hospice care or other hospital at their last assessment will be considered not recovered and censored at the date of last follow-up. • Death prior to recovery will be considered not recovered and censored at expected study Day 60.
Survival without mechanical ventilation for all subjects in ITT population	Primary, sensitivity, and subgroup	• Use the same imputation methods as those used for the primary endpoint of BET-B
Time to Sustained Recovery up to Day 60 for all subjects in ITT population	Primary, sensitivity, and subgroup	• Use the same imputation methods as those used for the analysis of time to recovery endpoint based on the primary subgroup of BET-B
Other Secondary Endpoints and Exploratory Endpoints		
The analysis described for the other secondary efficacy and safety endpoints along with exploratory endpoints in the Master SAP will be followed. Refer to Table 7 in the master SAP for addition details regarding imputation methods to be used for those endpoints.		

6.6. Interim Analyses and Data Monitoring

Refer to Section 6.6 of the master SAP for details of interim analyses. The details of the futility analysis are provided below. If enrollment is nearing completion at the timepoint of interim futility analysis (study enrollment projected to be completed within weeks), the below futility analysis will not be completed.

A futility analysis will take place after approximately 280 subjects eligible for the primary analysis subgroup have been enrolled and randomized. If protocol version 6.0 is implemented after the 280th subject is randomized, then the futility analysis will be based on data observed by the implementation date. Subjects discharged to locations other than LTAC, Hospice care or other hospital, and with no other follow-up data

indicating death or mechanical ventilation will be treated as non-events and censored at Day 29 for futility analysis. Subjects that are lost to follow-up or terminated early before Day 29 prior mechanical ventilation or death but were hospitalized at their last assessment will be considered non-events and censored at the date of their last observed assessment. Subjects that are lost to follow-up or terminated early after discharge or after Day 29 prior mechanical ventilation or death will be considered non-events and censored at Day 29. Subjects who complete follow-up without mechanical ventilation or death will be considered non-events and censored at Day 29. Mechanical ventilation or death that occur after Day 29 are considered non-events and censored at Day 29. No other imputation methods will be applied for the futility analysis.

For the futility analysis, the conditional power (the probability of rejecting the hypothesis that the proportion who survive without mechanical ventilation is the same between subjects who received active treatment versus those subjects who received placebo given the data observed) will be computed for the randomized subjects eligible for the primary analysis subgroup. The conditional power will be computed under the hypothesized treatment effect (a relative risk of 2.2). If the conditional power under the hypothesized treatment effect is less than 20%, the DSMB could recommend stopping the study for futility.

To consider all accumulated data properly, the interim Z value for the conditional power calculation will be based on a test of difference in the Kaplan-Meier (KM) estimates at Day 29, as some subjects will be in the middle of their follow-up. The alpha used in the conditional power calculation will be 0.049 to account for the spending of alpha= 0.001 during the first interim analysis. The hypothesized drift parameter will be updated by the lumped event rate and will be based on the overall interim event rate and the assumed relative risk rather than the interim relative risk. The unconditional power will be updated for a z-test (unpooled variance) of the difference in KM estimates using the current overall event rate and the hypothesized relative risk of 2.2. Based on these assumptions the following formula will be used to calculate conditional power (CP):

$$CP = \frac{t\hat{\theta}_t + \theta_F(1-t) - Z_{1-\alpha/2}}{\sqrt{1-t}}$$

where $\hat{\theta}_t$ is the estimated drift parameter at information time t. $\hat{\theta}_t$ can be estimated using

$$\hat{\theta}_t = \frac{B_t}{t}, B_t = Z_t\sqrt{t}$$

where Z_t is the interim Z statistic of difference in KM estimates using an unpooled variance estimate. θ_F is the drift parameter at the final time and can be estimated as

$$\theta_F = Z_{1-\alpha/2} + Z_{1-\beta}$$

where Z is the standard normal with α=0.49 and 1-β is the recalculated unconditional power using the pooled event rate, $\bar{p} = \frac{\hat{p}_1+\hat{p}_2}{2}$, at information time, t and $\hat{p}_1$ and $\hat{p}_2$ are the KM estimates of each group. The updated conditional power can be estimated as

$$1-\beta = \Phi\left(z - Z_{1-\frac{\alpha}{2}}\right) + \Phi\left(-z - Z_{1-\frac{\alpha}{2}}\right), z = \frac{p_A - p_B}{\sqrt{\frac{p_A(1-p_A)}{n_A} + \frac{p_B(1-p_B)}{n_B}}}$$

where Φ is the standard normal distribution function and p_A and p_B are the group proportions that are consistent with a relative risk of 2.2 and $\bar{p}$ at information t. p_A and p_B can be calculated as

$$p_B = \frac{2\bar{p}}{3.2}, p_A = 2.2p_B$$

Finally, information time, t, can be estimated as

$$t = \frac{E}{400\bar{p}}$$

where E is the total number of events at the time of the futility analysis.

6.7. Multicenter Studies

Refer to Section 6.7 of the master SAP.

6.8. Multiple Comparisons/Multiplicity

This protocol contains four key secondary endpoints. The key secondary endpoints will be tested in the order presented in the endpoint section using the following hierarchical hypothesis testing: If the primary analysis is significant at .049, then the first key secondary endpoint can be tested at .049. If this is significant, then the second key secondary endpoint can be tested at .049, and so forth. There is no hierarchical testing for other (non-key) secondary endpoints.

The supplementary analyses (e.g., Westfall-Young and Hochberg) in Section 6.8 of the master SAP were intended for the proof-of-concept trials and thus will not be conducted for the BET-B study.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Refer to Section 7.1 of the master SAP.

7.2. Protocol Deviations

Refer to Section 7.2 of the master SAP.

8. EFFICACY EVALUATION

For this phase 2/3 double-blind placebo controlled randomized trial two-sided p-value < 0.049 will be considered statistically significant at the final analysis. That is, an interim efficacy analysis done with alpha=.001, leads to alpha=.049 at the final test, using a Bonferroni approach to yield an overall .05 type I error rate. It is noted that since the endpoint and population are different between the interim test and final test, common interim analysis testing approaches such as O'Brien-Fleming would not apply, hence the use of Bonferroni which will be slightly conservative.

8.1. Primary Efficacy Analysis

8.1.1. Primary Analysis for the Primary Endpoint

All efficacy analyses will be summarized and performed on the ITT and mITT population for both the primary subgroup and all subjects in the analysis population by treatment group and baseline ordinal score.

The primary analysis of the primary endpoint, whether the subject did not satisfy one of the following two categories from the ordinal scale up to and including Study Day 29:

7. Hospitalized, on invasive mechanical ventilation or ECMO or

8. Death,

will be analyzed as a logistic regression model to estimate adjusted odds ratios and adjusted risk differences adjusting for baseline dexamethasone use, baseline ordinal score, baseline CRP, age (continuous) for the pre-specified subgroup (age < 85 years old, baseline clinical status of 5 or 6, and baseline CRP < 150 mg/L) in the ITT population.

The null hypothesis is:

H_0: Odds ratio (treatment vs. placebo) = 1,

and the alternative hypothesis is:

H_A: Odds ratio (treatment vs. placebo) ≠ 1

where:

Odds ratio (treatment vs. placebo) = Odds ratio comparing the odds of patients with treatment vs. placebo in terms of who survived without mechanical ventilation up to and including Study Day 29.

The primary logistic model is defined as follow:

$$logit\,(P(Y=1)) = \beta_0 + \beta_1\, treat + \beta_2 baseordscorevar + \beta_3 basedexafl + \beta_3 baseCRP + \beta_5\, age$$

Where Y is the indicator for whether the subject progressed to mechanical ventilation or death.

Missing data for the primary analysis will be imputed using multiple imputation. Details of the multiple imputation are provided in Section 6.5.1.

Adjusted odds ratios, corresponding 95% CIs, and a p-value from an adjusted logistic regression [1] will be presented in Table 4 for subjects in the primary subgroup. Adjusted risk differences and corresponding 95% CI calculated using bootstrap will also be calculated.

8.1.2. Sensitivity Analysis for the Primary Endpoint

The main sensitivity analysis for the primary endpoint will consider as non-events subjects who were missing event due to loss to follow-up but were discharged to a location other than LTAC, hospice care, or other hospital, and use same multiple imputation approach described in Section 6.5.1.1 and Section 6.5.1.3 for remaining missingness. The second sensitivity analysis will be added if the p-value from the primary analysis is less than <0.1 and will use the same imputation as the primary model but consider all subjects whose last assessment is in window for Day 29 but before Day 29 (Day 26, Day 27, Day 28) as censored on the actual day of the last assessment. Additional sensitivity analyses will use the same multiple imputation approach and functional form of the final model as the primary analysis with the addition of more covariates well as repeating the primary analysis on other analysis populations as listed in Table 1. Details of the multiple imputation are provided in Section 6.5.1.

8.1.3. Secondary Analysis for the Primary Endpoint

A secondary analysis of the primary endpoint will be performed using a targeted maximum likelihood estimate (TMLE) method for binary outcomes that estimates the average treatment effect among the entire population in terms of an odds ratio with corresponding p-value will be used. The test decision for this secondary analysis will be based on the p-value of the marginal odds ratio.

For the underlying estimation of the binary outcome variable in each treatment arm, the following baseline covariates will be utilized:

- Actual baseline ordinal score
- Age (continuous)
- Sex
- Race and Ethnicity (Black or Hispanic indicator)
- Baseline CRP
- Baseline lymphocyte count
- Baseline D-dimer
- Baseline creatinine
- Use of dexamethasone
- Chronic respiratory disease
- Chronic kidney disease
- Cardiovascular disease
- Comorbidities (Indicator for 2 or more comorbidities)

The following super learner libraries with logistic link functions will be applied:

- SL.glm (generalized linear model)
- SL.gam (general additive model using smoothing splines of degree 2 for continuous variables)
- SL.glmnet (generalized linear model with Lasso regularization, deviance as loss function and applying the lamba with minimal deviance for the prediction).

Categorical covariates with 90% of the subjects in one category will be dropped from the TMLE analysis. Mean imputation will be used for subjects missing values for continuous baseline variables. Missing values for categorical variables will be given a value of 'No'. No missing data is expected for baseline ordinal score

Odds ratio (treatment vs. placebo) = marginal odds ratio comparing the odds of patients with treatment vs. placebo in terms of who survived without ventilation up to and including Study Day 29.

Marginal odds ratios, corresponding 95% CIs, and a p-value from an TMLE will be presented. Additionally, marginal risk differences with corresponding 95% CI will be presented.

Missingness in the outcome is accounted for in the estimation procedure of TMLE using the missing indicator as shown in the below pseudocode. The TMLE approach will be implemented using the tmle R package (https://cran.r-project.org/web/packages/tmle/index.html).

Pseudo code:

```
Y = binary outcome variable (that can include missing values)
trt = treatment information coded as 0, 1
BaselineCov = Dataframe of baseline covariates (numerical) of each
patient.
MissingIndicator = Vector with 1 indicating that outcome was missing, 0
otherwise
SL.library = c("SL.glm", "SL.gam", "SL.glmnet")

tmResult = tmle(Y = Y, A = trt, Delta = MissingIndicator, W =
BaselineCov, family = "binomial", Q.SL.library  = SL.library,
g.SL.library = SL.library, Delta.SL.library = SL.library)
```

As a secondary analysis of the primary endpoint, marginal odds ratios, risk differences, and p-value calculated using TMLE will also be provided. If results from the primary analysis substantially differ between the logistic regression and TMLE, an assessment of the logistic regression model fit will be explored (including testing the model fit based on Nattino et al. [3]).

The proportion of subjects with baseline ordinal score 5 or 6, who survived without mechanical ventilation including Study Day 29 will be presented by Lenzilumab + RDV long with 95% CIs obtained from logistic regression with bootstrap as described in Section 6.1 for the logistic regression rows or using TMLE for the TMLE row.

Results of the sensitivity, secondary, and subgroup analyses for this endpoint will also be presented in Table 4 for subjects in the primary subgroup.

Refer to Table 1 for a list of covariates and subgroup analyses for this endpoint. Refer to Table 2 for imputation methods to be applied to this endpoint.

A tipping point analysis that systematically and comprehensively varies assumptions about the missing outcomes on the two treatment arms will be performed. This tipping point analysis will vary assumptions about the missing outcomes on the two arms independently. The goal is to explore the plausibility of missing data assumptions under which the conclusions regarding efficacy change. Different scenarios will be explored that vary the assumed event rate among missing data to take values 1, 5, 10, 15, 20, 40% for the active treatment group (P_T) and for the placebo group (P_P). For each scenario, draws from the binomial distribution with parameter P_T for subjects in the active treatment group with missing outcome and draws from the binomial distribution with parameter P_P will be done for subjects in the placebo group missing outcome. This

process will be repeated 20 times to obtain 20 imputed datasets. For each scenario, the odds ratio and corresponding 95% CI will be obtained by fitting the same logistic regression model as the primary analysis for each imputation dataset and combining the estimates using PROC MIANALYZE in similar manner as was done for the primary analysis. The odds ratio and 95% CI will be presented in Table 17 for the primary subgroup and Table 18 for the ITT population. P-values from the tipping point analysis calculated using the same logistic regression described above are also provided in Figure 9 and Figure 10. Color shading will be used to show areas of the graph that show statistical significance. If significant shifts in conclusions regarding efficacy are observed in the tipping point analyses, additional tipping point analyses will be performed where additional assumptions regarding the event rate among discharged subjects will be explored. For example, scenarios where event rate in placebo missing discharged subjects are 1%, 2%, or 3% and event rate for the treated arm missing discharged subjects is the same as placebo or 3 times higher. Remaining missingness from non-discharged subjects will then be imputed in a similar manner as the main tipping point analysis.

Pseudocode for Tipping Point analysis:

- Define input dataset as the dataset of all subjects with a missing outcome.
- Define P_T as the proportion of subjects imputed as Event in the Lenzilumab + RDV. P_T will take values 1, 5, 10, 15, 20, 40%
- Define P_P as the proportion of subjects imputed as Event in the Placebo + RDV. P_P will take values 1, 5, 10, 15, 20, 40%
- For each combination of P_T and P_P, follow the below pseudocode to impute missing data and fit the final model to obtain odds ratio and its 95% CI along with the p-value.

```
Data imp_tipping_&pp._&pt.;
      set input;
      subid=input(substr(usubjid,5,4),best12.);
      seed=645+subid;
      call streaminit(seed);
      pP= &pP.;
      pT= &pT.;
      do i=1 to 20;
            _imputation_ = i;
            If TRTVAR='Placebo + RDV' then      eventd29=rand("Binomial",pP,1);
            Else if TRTVAR='Lenzilumab + RDV'  then   eventd29=rand("Binomial",pT,1);
            output;
      end;
      drop p i;
run;
```

For each of the 20 imputed datasets, combine `imp_tipping_&pp._&pt.` with the dataset of all subjects with complete outcome data to obtain the final dataset `imp_tipping_final_&pp._&pt.`

Odds ratios from logistic regression using multiple imputation for each scenario:

```
proc logistic data= imp_tipping_final_&pp._&pt. out=imp_parms_&pp._&pt.;
      by _imputation_;
      class baseordscorevar (param=ref ref=5) basedexausevar (param=ref ref=no steroid
use) trtvar (param=ref ref=placebolabel);
       model eventd29 (event='1') = trtvar baseordscorevar basedexausevar age baseCRP;
```

```
run;

proc mianalyze data=parms_&pp._&pt.;
      class baseordscorevar (param=ref ref=5) basedexausevar (param=ref ref=no steroid
use) trtvar (param=ref ref=placebolabel);
      modeleffects trtvar baseordscorevar basedexausevar age baseCRP;
      ods output parameterestimates=mianalyze_parms_&pp._&pt.;
run;


data OR_&pp._&pt.;
set mianalyze_parms_&pp._&pt.;
      OR=exp(estimate);
      LCL_OR=exp(LCLMean);
      UCL_OR=exp(UCLMean);
run;
```

Repeat the above process for all combinations of P_T and P_P to obtain estimates and p-values for each scenario.

8.2. Key Secondary Efficacy Analyses

All analyses of key secondary endpoints on the ITT population outlined in Section 8.2.1, Section 8.2.2, Section 8.2.3 and Section 8.2.4 will be repeated for the mITT analysis population. For brevity, only the ITT analyses are described in the text and presented in output shells. The mITT analyses and their output will follow exactly what is provided for their ITT counterparts.

8.2.1. Time to Mechanical Ventilation or Death Up to and Including Day 29 for Primary Endpoint Subgroup and All Subjects in ITT Population

The time to mechanical ventilation or death up to and including Day 29 will be defined as the elapsed time (in days) from Study Day 1 to date of invasive mechanical ventilation/ECMO or death. For the primary analysis of this endpoint, all subjects lost to follow-up or terminated early prior to death or progression to invasive mechanical ventilation will be considered non-events and censored at the date of their last observed assessment. As sensitivity analysis of this endpoint, any subjects that are lost to follow-up or terminated early prior to death or progression to mechanical ventilation and were discharged to a location other than LTAC, hospice care or other hospital, or progress to invasive mechanical ventilation/ECMO or death after Day 29 will be considered non-events and censored at Day 29 while subjects that are lost to follow-up or terminated early before Day 29 and before progression to invasive mechanical ventilation/ECMO or death and were either still hospitalized or discharged to LTAC, hospice care or other hospital at their last assessment will be considered non-events and censored at the date of their last observed assessment. If it is learned that a subject who terminated early had subsequently received ventilation or died prior to Day 29, then the subject will be classified as having the event. Subjects who complete follow-up without an event will be censored at the date of their expected Study Day 29 visit. Events that occur after Day 29 will be censored at the expected Study Day 29 date.

Table 7 will present median time to event along with corresponding 95% confidence intervals for each Lenzilumab + RDV long with the hazard ratio estimate and p-value from a Cox proportional hazards model for subjects in the primary subgroup. Restricted mean survival time estimates (RMST) which do not rely on the proportionality assumption will be provided for each treatment group and actual baseline ordinal score stratum as well as the difference in restricted mean recovery time between treatment groups within each of the

baseline ordinal score strata for the primary subgroup (Table 9). For both the Cox proportional hazards model and the RMST method, tied event times will be handled using the Efron method.

Kaplan-Meier curves for each Lenzilumab + RDV will be presented and supplemented with the hazard ratio estimate, p-value, and the number of subjects at risk in each Lenzilumab + RDV Study Day (not necessarily actual Study Days 1, 3, 5, 8, 11, 15, 22, 29) (Figure 1). A forest plot will be generated to display 95% CIs for hazard ratios from each of the subgroup analyses (Figure 5). These analyses will also be repeated for all subjects in the ITT population and results will be reported in Table 8, Figure 2, and Figure 6.

Refer to Table 1 for a list of covariates and subgroup analyses for this endpoint. Refer to Table 2 for imputation methods to be applied to this endpoint.

8.2.2. Time to Sustained Recovery Up to and Including Day 60 for Primary Endpoint Subgroup in the ITT Population

Recovery will be defined as having a value of 1, 2, or 3 on the clinical status 8-point ordinal scale or discharge from the hospital to a location other than LTAC, hospice care, or other hospital. The time to sustained recovery will be defined as the elapsed time (in days) from Study Day 1 to the day prior to the earliest recorded day at which a subject reaches recovery and doesn't worsen (ordinal score > 3) up to and including Study Day 60. This analysis will be conducted on the ITT population for those subjects who at baseline have a clinical status score of 5 or 6, CRP<150 mg/L, and age<85 years. For the primary analysis of this endpoint, all subjects lost to follow-up or terminated early prior recovery will be considered not recovered and censored at the date of their last observed assessment, regardless of their discharge status. As sensitivity analysis of this endpoint, any subjects that are lost to follow-up or terminated early prior to recovery and were discharged to a location other than LTAC, hospice care or other hospital will be considered recovered by study Day 60 with a time to recovery of time of discharge or time of first score of 1, 2, or 3, whichever comes first, while subjects that are lost to follow-up or terminated early before Day 60 before recovery, were still hospitalized or were discharged to LTAC, hospice care or other hospital at their last assessment will be considered not recovered and censored at the date of their last observed assessment.

Refer to Table 1 for a list of covariates and subgroup analyses for this endpoint. Refer to Table 2 for imputation methods to be applied to this endpoint.

The primary analysis time to sustained recovery up to and including Study Day 60 conducts a score test to compare treatment to control up to and including Study Day 60. The treatment median survival time, confidence intervals and p-value from the score test will be presented (Table 10). Restricted mean recovery time estimates will be provided for each treatment group and actual baseline ordinal score stratum as well as the difference in restricted mean recovery time between treatment groups within each of the baseline ordinal score strata (Table 12).

Kaplan-Meier curves for each Lenzilumab + RDV will be presented and supplemented with the hazard ratio estimate, p-value, and the number of subjects at risk in each Lenzilumab + RDV Study Day (not necessarily actual Study Days 1, 3, 5, 8, 11, 15, 22, 29, and 60) (Figure 3).

Each subgroup from Table 1 will be considered separately, and the tabular and graphical summaries described above will be replicated for each subgroup (Table 10). A forest plot will be generated to display 95% CIs for hazard ratios from each of the subgroup analyses (Figure 7).

8.2.3. Survival without Mechanical Ventilation up to and Including Day 29 for All Subjects in the ITT and mITT Populations

The analysis for survival without mechanical ventilation for the primary endpoint described in Section 8.1 will be repeated for all subjects in the ITT population without the restrictions in Table 5 and all subjects in mITT population in Table 6.

8.2.4. Time to Sustained Recovery up to and including Day 60 for ITT Population

The analysis for the time to sustained recovery for the primary endpoint subgroup described in Section 8.2.1 will be repeated for all subjects in the ITT population without the restrictions. Results will be reported in Table 11, Table 12, Figure 4, and Figure 8.

8.3. Other Secondary Efficacy Analyses

The analysis described for the other secondary efficacy and safety endpoints in the Master SAP will be followed. However, analysis of secondary endpoints will be conducted for all subjects in the ITT Population and only 95% confidence intervals will be reported for efficacy and safety analyses. For the time to death and mortality endpoints, additional tables for the primary subgroup and full ITT population will be provided in Table 13 and Table 14, respectively. Results for time to death and mortality using subjects with baseline ordinal score of 5 or 6, CRP≥150 mg/L, and age<85 years are provided in Table 15. Results from analysis of time to death using a restricted mean survival approach are provided in Table 16.

9. SAFETY EVALUATION

Safety evaluation for this study will be similar to that provided in the master SAP. However, additional safety summaries by baseline CRP<150 and CRP≥150 will be provided.

9.1. Demographic and Other Baseline Characteristics

Refer to Section 9.1 of the master SAP.

9.2. Measurements of Treatment Compliance

Refer to Section 9.2 of the master SAP.

9.3. Adverse Events

Refer to Section 9.3 of the master SAP.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

Refer to Section 9.4 of the master SAP.

9.5. Pregnancies

Refer to Section 9.5 of the master SAP.

9.6. Clinical Laboratory Evaluations

Refer to Section 9.6 of the master SAP.

9.7. Vital Signs and Physical Evaluations

Refer to Section 9.7 of the master SAP.

9.8. Concomitant Medications

Refer to Section 9.8 of the master SAP.

9.9. Other Safety Measures

No additional safety analyses are planned.

10. PHARMACOKINETICS

Details for PK analysis will be provided in a separate SAP.

11. IMMUNOGENICITY

Not Applicable.

12. OTHER ANALYSES

Not Applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "<0.001" and p-values greater than 0.9995 will be reported as ">0.999".

The mean, confidence intervals, median, IQR, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than 0.5% but < 1% will be presented as "<1"; values greater than 99.5% but less than 100% will be reported as ">99".

For all other estimators, the NEJM statistical reporting guidelines will be followed: results will be presented with no more precision than is of scientific value and is meaningful. For example, measures of association, such as odds ratios, will be reported to two or three significant digits. Results derived from models will be limited to the appropriate number of significant digits.

14. TECHNICAL DETAILS

SAS version 9.4 or above, or R language and environment for statistical computing 3.6.1 or above, will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

15.1. Changes from v1.0 to v2.0 of the BET-B SAP

- Change of the multiple imputation approach for the primary endpoint from a subject-specific imputation to an imputation method that imputes missing data depending on the discharge status of the subject at their last assessment or whether they have any post-baseline results or not.
- A tipping point analysis for the primary endpoint was added.
- Added a subgroup analysis of baseline CRP (< 150 vs ≥150) to the primary analysis using the ITT analysis population.
- Change in the definition for censoring time for time to death or progression to mechanical ventilation. The original model considered subjects discharged missing outcome as non-events and censored at Day 29. The update analysis censors these subjects at last assessment and provides a sensitivity analysis that censors these subjects at Day 29. Similar updates were made to time to sustained recovery.
- Analysis of time to death based on restricted mean survival time was added.

15.2. Changes from v2.0 to v3.0 of the BET-B SAP

- The tipping point analysis was updated to use the same methodology as the primary analysis.
- A possible sensitivity analysis that considers as missing subjects without event whose last assessment is on Day 26, 27, or 28 was added and will be performed only if the p-value from the primary analysis is less than 0.1.
- A possible sensitivity analysis using the fully conditional specification (FCS) logistic approach to impute missing data will be added if more than 1% of subjects have missing data in the baseline covariates used in the multiple imputation model and if the p-value from the primary analysis is <0.1.
- The imputation procedure for discharged subjects was updated to estimate the event rate from the logistic regression model with baseline ordinal score as a covariate only if 10 or more events (after discharge) are observed in this group of discharged subjects with outcome. If less than 10 events are observed, the event rate will be estimated as the proportion of events among discharged subjects with outcome. Additionally, if 0 events are observed in a subgroup, the event rate will be calculated as 0.5/total number of discharged subjects with outcome in that subgroup.

16. REFERENCES

1. M. Ge, L. K. Durham, R. D. Meyer, W. Xie and N. Thomas, "Covariate-Adjusted difference in proportions from clincal trials using logistic regression and weighted risk differences.," *Ther Innov Regul Sci,* vol. 45, pp. 481-493, 2011.
2. Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Stat Med*. 2018;37(14):2252-2266. doi:10.1002/sim.7654
3. Nattino G, Pennell ML, Lemeshow S. Assessing the goodness of fit of logistic regression models in large samples: A modification of the Hosmer-Lemeshow test. *Biometrics*. 2020 Jun;76(2):549-560. doi: 10.1111/biom.13249. Epub 2020 Apr 6. PMID: 32134502.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

The tables and figures listed below are those that are specific to BET-B study. The rest of the tables will come from the master SAP. For endpoints such as time to sustained recovery and time to mechanical ventilation or death that have TFLs in both master and BET-B SAPs, the TFLs in BET-B will be used for analysis. In all TFLs, Treatment A will be replaced by Lenzilumab + RDV and Treatment B will be replaced by Placebo + RDV. Only 95% CIs will be reported for BET-B.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 3: Schedule of Study Procedures

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*				
Day +/- Window	**−1 or 1**	**1[16]**	**Daily until hospital discharge (up to Day 29)**	**8[11] ± 2**	**15[6] ± 2**	**22[11] ± 3**	**29[6] ± 3**	**60[11] ± 3**
ELIGIBILITY								
Informed consent	X							
Demographics & Medical History	X							
Targeted physical exam	X							
Review SARS-CoV-2 results	X							
STUDY INTERVENTION								
Randomization		X						
Administration of investigational agent		• Lenzilumab or placebo: 3 infusions starting on Day 1[10] • Remdesivir: IV daily for 5-10 days or until discharge.						
STUDY PROCEDURES								
Vital signs and NEWS score [1, 15]		X[3]						
Clinical data collection[1]		X[3]	Daily until discharge	X	X	X	X	X[14]
Adverse event evaluation		X[3]	Daily until discharge	X	X	X	X	X
Concomitant medication review[13]		X[3]	Day -7 until discharge	X	X	X	X	
SAFETY LABORATORY								
Safety hematology, chemistry, and liver tests[4,9]	X[2]	X[3]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5]		X		X	
Pregnancy test for females of childbearing potential	X[2]							
RESEARCH LABORATORY[17]								
Oropharyngeal swab[7]		X[3]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		X		X	
Blood draw for serum and plasma. Specific testing is as follows:		X[3]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		X		X	
PCR SARS-CoV-2		*X[3]*	*Day 3, 5, 8, 11 (all ± 1 day) if hospitalized*					
proteomic analysis (including specifically for lenzilumab GM-CSF, MCP-1, IP-10, IL-6, IL-1, TNF-a, G-CSF and MIPa*)*		*X[3]*	*Day 3, 8, (all ± 1 day) if hospitalized*		*X*		*X*	
lenzilumab pharmacokinetics[12]		*X[8]*	*Day 5 (± 1 day) if hospitalized*		*X*		*X*	
Serum for secondary research		*X[3]*	*Day 3, 5, 8, 11 (all ± 1 day) if hospitalized*		*X*		*X*	
Blood for RNA		X[3]	Day 3, 8 (all ± 1 day) if hospitalized		X		X	
Blood for PBMC[12]		X[3]	Day 3, 8 (all ± 1 day) if hospitalized		X		X	

Notes:
[1] Refer to Section 8.1 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.
[2] Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR) the formula used is determined by the sites, but should be consistent throughout the study), and urine or serum pregnancy test for females of child-bearing potential. Laboratory tests performed as part of routine clinical care in the 48 hours prior to enrollment will be accepted for determination of eligibility.
[3] Baseline assessments should be performed prior to first infusion. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests if obtained in the 24 hours prior to first dose.
[4] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, INR.
[5] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.
[6] In-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone.

- *If still hospitalized at Day 15 and 29 or returns to the site for an in-person visit: assess adverse events, collect clinical data, vital signs, safety laboratory tests, and research laboratory samples (OP swab and blood) as able.*
- *If phone call only on Days 15 and 29 and all Day 22 and Day 60 visits: assess adverse events, clinical status (ordinal score), readmission to a hospital, and mortality only.*

[7] Oropharyngeal swabs are preferred, but if these are not obtainable, saliva or nasopharyngeal or nasal swabs may be substituted.
[8] Pre-dose serum sample collections for PK.
[9] To include markers of inflammation and coagulation: CRP, ferritin, fibrinogen, d-dimer, and LDH.
[10] Approximately 1 hour prior to lenzilumab/placebo infusion, premedication with acetaminophen 500 to 1000 mg PO or IV, or 650 mg PR and diphenhydramine 12.5 to 25 mg IV, or 25 mg PO or equivalent is required.
[11] Day 8, 22 and 60 visits performed by phone or home visit if discharged from the site hospital: assess adverse events, clinical status (ordinal score), readmission to a hospital, and mortality only.
[12] Only collected at selected sites capable of processing.
[13] Steroids and other concomitant therapies intended as specific treatment of COVID-19, as well as all biologics, will be assessed from 7 days prior to enrollment to Day 29. All other concomitant medications will be assessed from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first.
[14] Ordinal score only.
[15] Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. In addition, height and weight are obtained only at baseline (height can be self-reported). Vital signs collected as part of standard care may be used.
[16] Day 1 is defined as the calendar day of randomization.
[17] Blood draws for research labs may be omitted on any given study day if inappropriate for a subject's clinical status per site investigator judgment.

Table 4: Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

[Implementation note: Sensitivity analysis 2 will be performed only if the p-value for the initial model of the primary endpoint is <0.1.

Sensitivity analysis 4 that uses FCS logistic for multiple imputation will be performed only if more than 1% of subjects have missing baseline covariates and the overall p-value for the primary endpoint is < 0.1.]

Analysis/Subgroup	Category	Lenzilumab + RDV (N=x)		Placebo + RDV (N=x)		Odds Ratio		Risk Difference[j]		P-value[k]
		n	% (95%CI)[i]	n	% (95%CI)[i]	Estimate	95% CI	Estimate	95% CI	
Initial model, Baseline dexamethasone, Baseline OS, CRP, age (cont.), MI[a]	-	x	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Sensitivity										
Sensitivity analysis 1: Baseline dexamethasone, Baseline OS, CRP, age (cont.), MI[b]	-	x	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Sensitivity analysis 2: Baseline dexamethasone, Baseline OS, CRP, age (cont.), MI[c]	-	x	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Sensitivity analysis 3: Baseline dexamethasone, Baseline OS, CRP, age (cat.), Geographical regions, MI[d]	-	x	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Sensitivity analysis 4: Baseline dexamethasone, Baseline OS, CRP, age (cont.), FCS MI[e]	-	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx	x
Secondary										
TMLE-Approach 1[f]	-	x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
TMLE-Approach 2: MI combining TMLE analysis in imputed datasets[g]	-	x	x.x, x.x	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Subgroup Analyses[h]										
Baseline Ordinal Score	5	x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	6	x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	7	x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	5 or 6	x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	P-value for interaction[i]									0.xxx
Repeat for all subgroups from Table 1		x	x.x (x.x, x.x)	x	x.x (x.x, x.x)	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx

Analysis/Subgroup	Category	Lenzilumab + RDV (N=x)		Placebo + RDV (N=x)		Odds Ratio		Risk Difference[j]		P-value[k]
		n	% (95%CI)[i]	n	% (95%CI)[i]	Estimate	95% CI	Estimate	95% CI	

CI=Confidence Internals. OR=Odds Ratios. NA=Not applicable. MI=Multiple Imputation.

N=Number of subjects in the ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years . n=Number of subjects without mechanical ventilation or death through Day 29.

[a] Odds Ratios of Active treatment vs Placebo calculated from the logistic regression model adjusted for baseline dexamethasone use, baseline OS, age (continuous), and baseline CRP. Missing data imputed using the 3-stage imputation procedure described in Section 6.5.

[b] Sensitivity Analysis 1: Odds Ratios of Active treatment vs Placebo calculated from the logistic regression model adjusted for baseline dexamethasone use, baseline OS, age (continuous), and baseline CRP. Missing outcomes for subjects with a good discharge at last assessment are considered non-events for this analysis.

[c] Sensitivity Analysis 2: Odds Ratios of Active treatment vs Placebo calculated from the logistic regression model adjusted for baseline dexamethasone use, baseline OS, age (continuous), and baseline CRP. Subjects without event whose last assessment is in window for Day 29 (Day 26, 27, 28) are considered missing. Missing data imputed using the 3-stage imputation procedure described in Section 6.5.

[d] Sensitivity Analysis 3: Same imputation as initial model in [a]. The final model also includes categorical age and geographical regions as covariates.

[e] Sensitivity Analysis 4: PROC MI part of the imputation model uses FCS logistic instead of monotone logistic. The rest of the imputation procedure and final covariates are similar to those in the initial model in [a].

[f] TMLE Approach 1: Estimates marginal ORs and risk differences using TMLE and adjusts for all missing data using the missing indicator functionality of TMLE.

[g] TMLE Approach 2: Estimates marginal ORs and risk differences using MI combining TMLE analysis in imputed datasets. Missing events for discharged subjects are considered non-events, missing events for subjects with no post baseline data are handled using the missing indicator in TMLE, while a similar MI procedure as the primary analysis is used to impute missing event for subjects who were hospitalized or transferred to another hospital at their last assessment.

[h] For the subgroup analyses, the model described in [a] was performed for each level of the subgroup without multiple imputation. P-value from the interaction between the subgroup variable and treatment group is also reported.

[i] Estimate and 95% CI for the proportion are estimated using either logistic regression or TMLE.

[j] Risk Differences calculated using the approach described in Ge.et al [1] or TMLE. CIs calculated using bootstrap or TMLE.

[k] P-value from the logistic regression model or TMLE. For the interaction, P-value from interaction Type III test in subgroup analysis where the interaction between subgroup and treatment is being added to the logistic regression model.

Tables with similar format:

Table 5: Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population

[*Implementation note: Add subgroup analysis for baseline CRP < 150 mg/L vs baseline CRP ≥ 150 mg/L. Add footnote that analysis for this subgroup analysis will only include subjects in the ITT population with baseline ordinal score of 5 or 6 and age<85years.]*

Table 6: Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — mITT Population

Table 7: Time to Mechanical Ventilation or Death through Day 29 — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

Analysis/Subgroup	Treatment	Number of Subjects to Mechanical Ventilation or Death[d]		Median Time Until Event		Hazard Ratio		P-value[e]
		n	%	Estimate	95% CI	Estimate	95% CI	
Initial Model[a]	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Sensitivity[b]	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Subgroup Analyses[c] **Baseline Ordinal Score**								
5	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
6	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
5 or 6	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							x.xxx
Repeat for the rest of the subgroups in Table 1.								

CI=Confidence Intervals.
N= Number of subjects in ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years. n= Number of unique subjects who progressed to mechanical ventilation or death that satisfies the row criteria.
[a] Hazard Ratio (HR) is the hazard ratio calculated from the Cox Proportional Hazard Model comparing Active treatment vs Placebo and adjusting for the baseline dexamethasone use (yes, no), Baseline Ordinal Score (5, 6 or 7), age, and baseline CRP as covariates. All subjects whose last assessment was before Day 29 and were missing the event were censored at the date of last assessment.
[b] Same analysis as the initial model but subjects missing event and whose last assessment is before Day 29 are non-events for good discharges and censored at Day 29 or at last assessment for subjects still hospitalized or discharged to LTAC, hospice care, or other hospital.
[c] For the subgroup analyses, the model described in [a] was performed for each level of the subgroup.
[d] Number of subjects who progressed to a clinical status of 7 or 8 through Day 29.
[e] P-value is based on the adjusted cox model or P-value from interaction Type III test in subgroup analysis where the interaction between subgroup and treatment is being added to the Cox Proportional Hazard Model.

Table with similar format:

Table 8: Time to Mechanical Ventilation or Death through Day 29 — ITT Population

[Implementation note: Add subgroup analysis for baseline CRP < 150 mg/L vs baseline CRP ≥ 150 mg/L. Add footnote that analysis for this subgroup analysis will only include subjects in the ITT population with baseline ordinal score of 5 or 6 and age<85years.]

Table 9: Time to Mechanical Ventilation or Death through Day 29 by Treatment Group, Actual Baseline Ordinal Score, and Analysis Population: Restricted Mean Survival Time Analysis

Analysis Population	Treatment Group	Actual Baseline Ordinal Score	n	Tau[a]	Restricted Mean Time (Days)		Difference	
					Estimate	95% CI	Estimate	95% CI
ITT with BOS 5 or 6, CRP<150 mg/L, and age<85 years	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
ITT	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	7	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		

N= Number of subjects in the specified treatment group, actual baseline ordinal score, and analysis population.
n = Number of subjects who experiences a clinical status of 7 or 8 through Day 29.
Difference is the difference in the restricted mean recovery time between active treatment to placebo. All subjects lost to follow-up before Day 29 and missing event were censored at last assessment.
[a] Tau is the truncation time point for the Restricted Mean Survival Time analysis and is equal to the minimum of the largest observed times in each group.
[b] There were X additional subjects with an Actual Baseline Ordinal Score of 4 that are included in the 'Any BOS' summaries.

Programming

Within an actual baseline ordinal score stratum:

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
by stratum;
time evntday * Censor(1);
strata trtcode /diff=all;
ods output  rmst=rmst;
run;
```

Table 10: Time to Sustained Recovery through Day 60 — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

Analysis/Subgroup	Treatment	Number of Recovered Subjects		Median Time Until Recovery		Hazard Ratio		P-value[e]
		n	%	Estimate	95% CI	Estimate	95% CI	
Initial Model[a]	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x, x.x			
Sensitivity Analyses								
Sensitivity Analysis 1: Imputation for good discharges[b]	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x, x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x, x.x			
Supplemental Analysis 1: Impact of age and duration of symptoms[c]	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x, x.x			
Subgroup Analyses[d]								
Baseline Ordinal Score								
5	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x, x.x			
6	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
7	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Baseline Steroid Use								
Yes	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
No	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Baseline Use of Emerging Covid-19 Treatments								
Yes	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			

Analysis/Subgroup	Treatment	Number of Recovered Subjects		Median Time Until Recovery		Hazard Ratio		P-value[e]
		n	%	Estimate	95% CI	Estimate	95% CI	
No	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Duration of Symptoms Prior to Enrollment Group 1								
≤ Median	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
> Median	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Duration of Symptoms Prior to Enrollment Group 2								
< 25th percentile	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
25 ≤ 75th percentile	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
≥ 75th percentile	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]	x	x.x					0.xxx
Race								
White	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Black/African American	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Asian	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Other	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx

Analysis/Subgroup	Treatment	Number of Recovered Subjects		Median Time Until Recovery		Hazard Ratio		P-value[e]
		n	%	Estimate	95% CI	Estimate	95% CI	
Ethnicity								
Hispanic or Latino	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Not Hispanic or Latino	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Comorbidities Group 1								
None	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Any	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Comorbidities Group 2								
One	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Two or More	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							
Comorbidities Group 3								
Obese	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Non-obese	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Age								
< 40	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			

Analysis/Subgroup	Treatment	Number of Recovered Subjects		Median Time Until Recovery		Hazard Ratio		P-value[e]
		n	%	Estimate	95% CI	Estimate	95% CI	
41-64	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
65 and older	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Sex								
Male	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
Female	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx
Baseline CRP								
<= Median	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
>Median	Lenzilumab + RDV (N=X)	x	x.x	x.x	x.x,x.x	x.x	x.x,x.x	0.xxx
	Placebo + RDV (N=X)	x	x.x	x.x	x.x,x.x			
	P-value for interaction[e]							0.xxx

CI=Confidence Intervals. N=Number of subjects in the ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years. n= Number of unique recovered subjects that satisfies the row criteria.

[a] Hazard Ratio (HR) is the hazard ratio calculated from the Cox Proportional Hazard Model comparing Active treatment vs Placebo. All subjects lost to follow-up before recovery are censored at last assessment date.

[b] Sensitivity Analysis 1: Subjects discharged to a location other than LTAC, hospice care, or other hospital are considered recovered and censored at Day 60. The rest of lost to follow-up subjects are censored at last assessment date. Model [a] was fit to estimate the HR, 95% CI and p-values.

[c] Supplemental Analysis 1 (age and duration of symptoms prior to enrollment): In addition to the variable included in the model described in [a], age and duration of symptoms prior to enrollment as additional covariates were added to the model when estimating the HR, 95% CI and p-values. Same censoring as in model [a].

[d] For the subgroup analyses, the model described in [a] was performed for each level of the subgroup.

[e] P-value is based on the Cox adjusted model or P-value from interaction Type III test in subgroup analysis where the interaction between subgroup and treatment is being added to the Cox Proportional Hazard Model.

Table with similar format:

Table 11: Time to Sustained Recovery through Day 60 — ITT Population

[Implementation note: Add subgroup analysis for baseline CRP < 150 mg/L vs baseline CRP ≥ 150 mg/L. Add footnote that analysis for this subgroup analysis will only include subjects in the ITT population with baseline ordinal score of 5 or 6 and age<85years.]

Table 12: Time to Sustained Recovery through Day 60 by Treatment Group, Actual Baseline Ordinal Score, and Analysis Population: Restricted Mean Survival Time Analysis

Analysis Population	Treatment Group	Actual Baseline Ordinal Score	n	Tau[a]	Restricted Mean Recovery Time (Days)		Difference	
					Estimate	95% CI	Estimate	95% CI
ITT with BOS 5 or 6, CRP<150 mg/L, and age<85 years	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
ITT	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	7	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		

N= Number of subjects in the specified treatment group, actual baseline ordinal score, and analysis population.
n = Number of recovered subjects.
Difference is the difference in the restricted mean recovery time between active treatment to placebo.
[a] Tau is the truncation time point for the Restricted Mean Survival Time analysis and is equal to the minimum of the largest observed times in each group.
[b] There were X additional subjects with an Actual Baseline Ordinal Score of 4 that are included in the 'Any BOS' summaries.

Programming notes:

Within an actual baseline ordinal score stratum:

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
by stratum;
time evntday * Censor(1);
strata trtcode /diff=all;
ods output  rmst=rmst;
run;
```

Table 13: Mortality Rates — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

Analysis Type	Baseline Ordinal Score	Treatment Group	Number of Deaths		Mortality Rate (CI)[c]			Difference in Mortality Rates at the Specified Time Point[d]			HR[e]			P-value[f]
			n	%	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	
Time to Death by Day 15														
Primary[a]	5	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
Primary with Sensitivity Imputation[b]	5	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							

Analysis Type	Baseline Ordinal Score	Treatment Group	Number of Deaths		Mortality Rate (CI)[c]			Difference in Mortality Rates at the Specified Time Point[d]			HR[e]			P-value[f]
			n	%	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
Time to Death by Day 29														
Primary[a]	5	Lenzilumab + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
Primary with Sensitivity Imputation[b]	5	Lenzilumab + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx

Analysis Type	Baseline Ordinal Score	Treatment Group	Number of Deaths		Mortality Rate (CI)[c]			Difference in Mortality Rates at the Specified Time Point[d]			HR[e]			P-value[f]
			n	%	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
Time to Death by Day 60														
Primary[a]	5	Lenzilumab + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
Primary with Sensitivity Imputation[b]	5	Lenzilumab + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	6	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							

Analysis Type	Baseline Ordinal Score	Treatment Group	Number of Deaths		Mortality Rate (CI)[c]			Difference in Mortality Rates at the Specified Time Point[d]			HR[e]			P-value[f]
			n	%	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	Estimate	80% CI	95% CI	
	7	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							
	Any BOS	Lenzilumab + RDV (N=X)	X	x.x	x.x	x.x, x.x	x.xxx	x.x	x.x, x.x	x.x, x.x	x.x	x.x, x.x	x.x, x.x	0.xxx
		Placebo + RDV (N=X)	X	x.x	x.xx	x.x, x.x	x.xxx							

CI= Confidence Intervals. N=Number of subjects in the Safety population. n= Number of unique subjects that satisfies the row criteria.
[a] For the primary endpoint, all subjects whose last assessment was before the corresponding timepoint (Day 15 Visit, Day 29 Visit, Day 60 Visit) and were missing the event were censored at the date of last assessment.
[b] Primary with Sensitivity Imputation: Same analysis as the initial model but subjects missing event and whose last assessment is before the corresponding timepoint (Day 15 Visit, Day 29 Visit, Day 60 Visit) are non-events for good discharges and censored at Day 15, Day 29, Day 60 respectively or at last assessment for subjects still hospitalized or discharged to LTAC, hospice care, or other hospital.
[c] Mortality Rates are the Kaplan-Meier estimates.
[d] Difference in mortality rates (80%, 95% CI) obtained from Kaplan Meier.
[e] HR is the hazard ratio from the Cox Proportional Hazard Model adjusted for baseline ordinal score and baseline steroid use.
[f] P-value is based on the Cox adjusted model.

Tables with similar format:

Table 14: Mortality Rates — ITT Population

Table 15: Mortality Rates — ITT Population with Baseline Ordinal Score of 5 or 6, CRP≥150 mg/L, and age<85 years

Table 16: Time to Death by Treatment Group, Actual Baseline Ordinal Score, and Analysis Population: Restricted Mean Survival Time Analysis

Analysis Population	Treatment Group	Actual Baseline Ordinal Score	n	Tau[a]	Restricted Mean Time to Death (Days)		Difference	
					Estimate	95% CI	Estimate	95% CI
Time to Death through Day 15								
ITT with BOS 5 or 6, CRP<150 mg/L, and age<85 years	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
ITT	Lenzilumab + RDV (N=X)	5	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	6	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	7	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
	Lenzilumab + RDV (N=X)	Any BOS[b]	x	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x	x.x	x.x, x.x		
Time to Death through Day 29								
Time to Death through Day 60								

N= Number of subjects in the specified treatment group, actual baseline ordinal score, and analysis population.
n = Number of subjects who died.
Difference is the difference in the restricted mean time to death between active treatment to placebo.
[a] Tau is the truncation time point for the Restricted Mean Survival Time analysis and is equal to the minimum of the largest observed times in each group.
[b] There were X additional subjects with an Actual Baseline Ordinal Score of 4 that are included in the 'Any BOS' summaries.

Table 17: Summary Results of Tipping Point Analysis for the Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

	Probability of event among nonresponders in Lenzilumab + RDV					
Probability of event among nonresponders in Placebo + RDV	**1%**	**5%**	**10%**	**15%**	**20%**	**40%**
1%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
5%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
10%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
15%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
20%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
40%	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Note: Values presented are odds ratios and their corresponding 95% CI calculated from the logistic regression model adjusting for Baseline dexamethasone, Baseline OS, CRP, and age (cont) with Placebo + RDV as the reference treatment arm.

Table with similar format:

Table 18: Summary Results of Tipping Point Analysis for the Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population

APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Treatment group labeling will be the following will vary by stage. Abbreviations will be used if the treatment group labels need to be abbreviated to improve fit.
- Use the same color for a treatment on the different graphs (SAS standard colors):
  - Lenzilumab + RDV = Blue
  - Placebo + RDV = Red
- For severity graphs (SAS standard colors):
  - 5 = green
  - 6 = blue
  - 7 = red
  - Death = black

LIST OF FIGURES

Figure 1: Kaplan-Meier Plot for Time to Mechanical Ventilation or Death through Day 29 - ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

[Implementation note: For time to mechanical ventilation or death, create individual figures 8A through 8F for all baseline dexamethasone use=Yes, No and Baseline ordinal score=5,6]

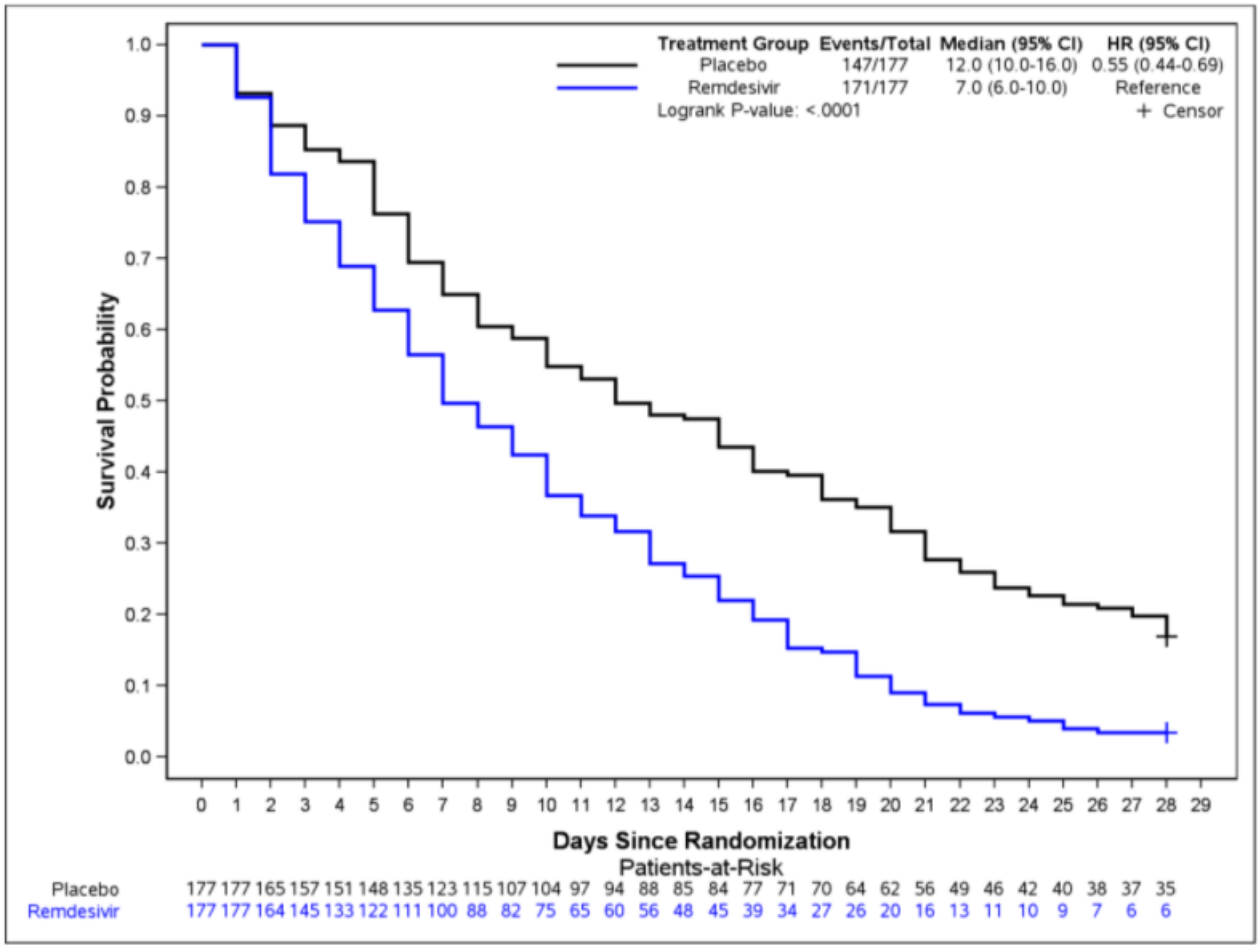


Figure with Similar Format:

Figure 2: Kaplan-Meier Plot for Time to Mechanical Ventilation or Death through Day 29 - ITT Population

Figure 3: Kaplan-Meier Plot for Time to Sustained Recovery through Day 60 defined by 8-point Ordinal Scale - ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

[Implementation note: For time to sustained recovery, create individual figures 8A through 8F for all subjects, baseline steroid use=Yes, No and baseline ordinals score=5,6]

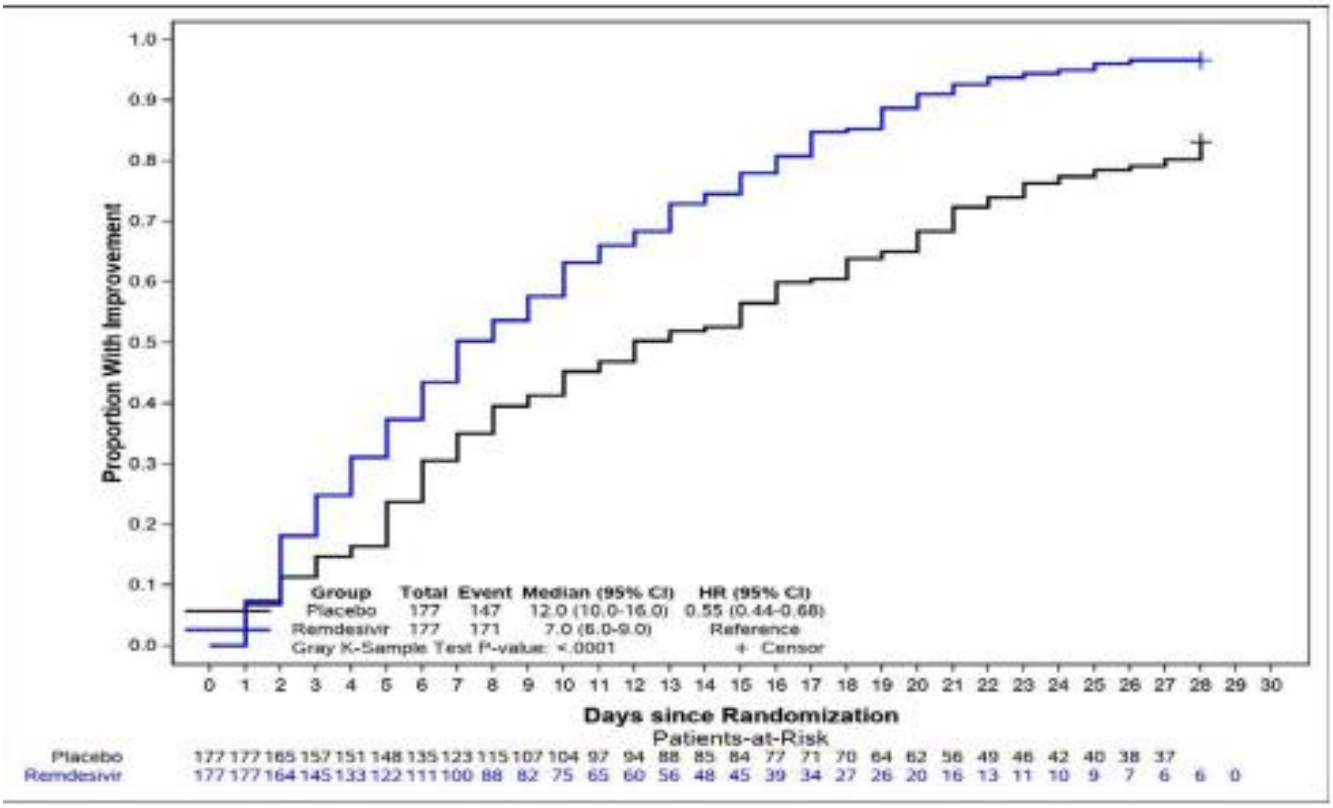
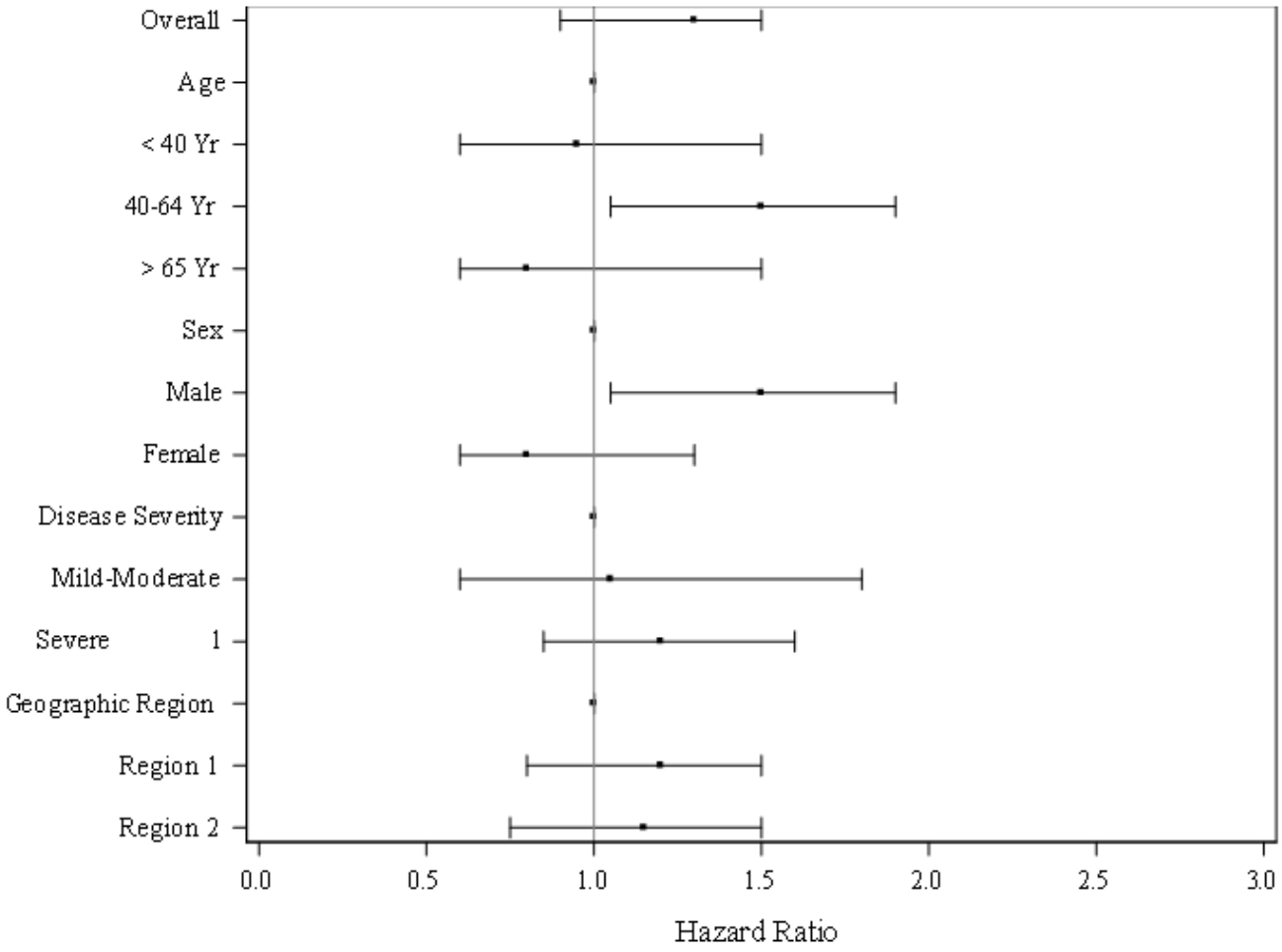


Figure with Similar Format:

Figure 4: Kaplan-Meier Plot for Time to Sustained Recovery through Day 60 defined by 8-point Ordinal Scale - ITT Population

Figure 5: Adjusted Hazard Ratios and 95% Confidence Intervals of Time to Mechanical Ventilation or Death through Study Visit Day 29 Using a Cox Proportional Hazard Model Overall and for each Subgroup - ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

[Implementation note: The figure below is a shell. The final figure will include all subgroups from Table 1.]



Figures with Similar Format:

Figure 6: Adjusted Hazard Ratios and 95% Confidence Interval of Time to Mechanical Ventilation or Death through Study Visit Day 29 Using a Cox Proportional Hazard Model Overall and for each Subgroup – ITT Population

Figure 7: Adjusted Hazard Ratios and 95% Confidence Interval of Time to Sustained Recovery through Study Visit Day 60 Using a Cox Proportional Hazard Model Overall and for each Subgroup – ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

Figure 8: Adjusted Hazard Ratios and 95% Confidence Interval of Time to Sustained Recovery through Study Visit Day 60 Using a Cox Proportional Hazard Model Overall and for each Subgroup – ITT Population

Figure 9: P-values from Tipping Point Analysis for the Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population with Baseline Ordinal Score of 5 or 6, CRP<150 mg/L, and age<85 years

[Implementation note: Use the 'TippingPoint' R package to generate this figure following the example saved here: https://mran.microsoft.com/snapshot/2016-07-08/web/packages/TippingPoint/vignettes/TippingPoint.html

R code from this package will be updated to present p-values from logistic regressiont. Color shading will be added to illustrate which areas of the graph show significant statistical difference. The x and y axes will be added to present proportion of events among nonresponders instead of number of events.

Update the x-axis label to be 'Probability of event among nonresponders in Lenzilumab + RDV group'.

Update the y-axis label to be 'Probability of event among nonresponders in Placebo + RDV group'.]

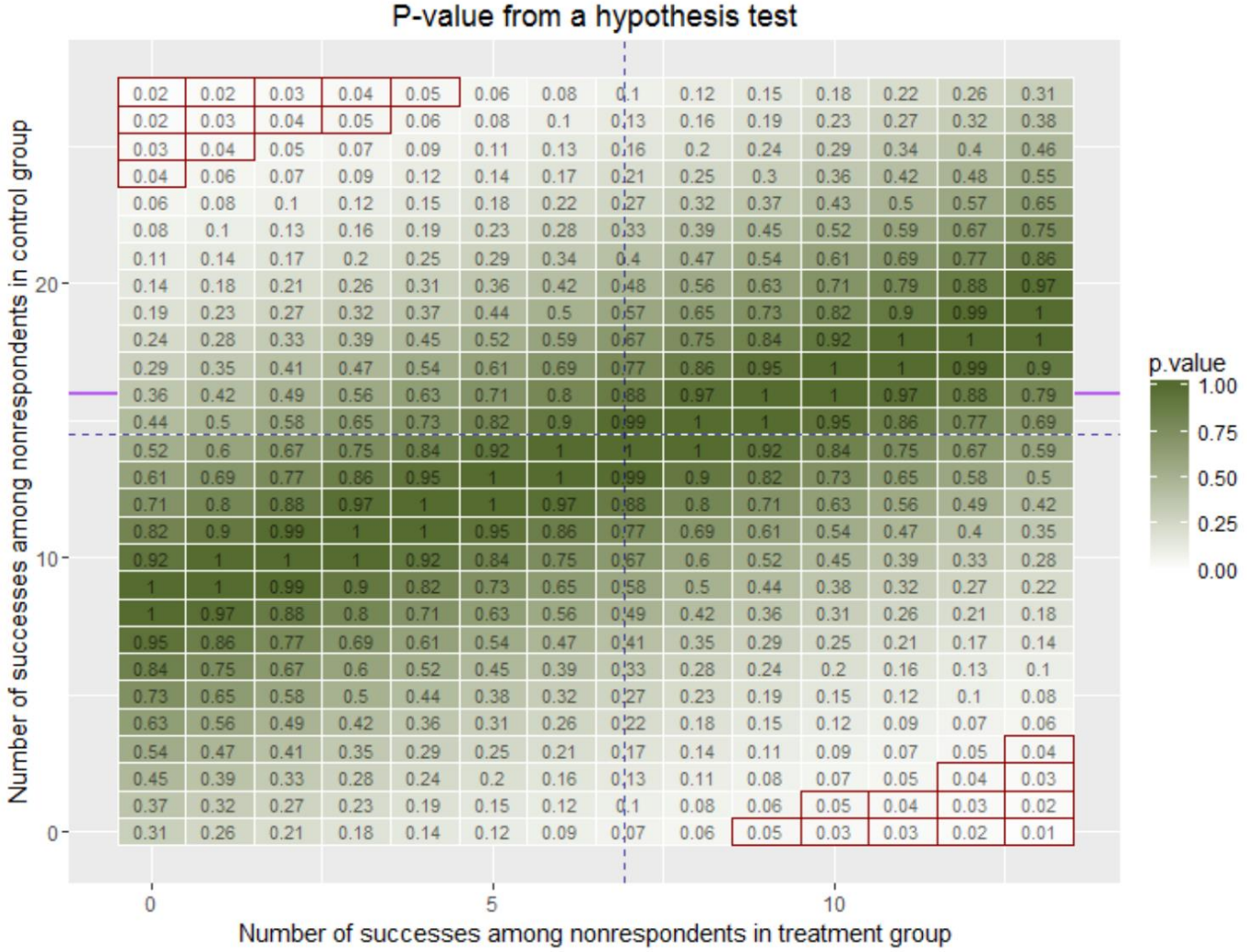


Figure with same format:

Figure 10: P-values from Tipping Point Analysis for the Proportion of Subjects Alive and Without Mechanical Ventilation through Day 29 — ITT Population