A Phase 3 Open-label, Randomized, Controlled Study to Evaluate the Efficacy and Safety of Intravenously Administered Ravulizumab Compared with Best Supportive Care in Patients with COVID-19 Severe Pneumonia, Acute Lung Injury, or Acute Respiratory Distress Syndrome

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-COV-305

A PHASE 3 OPEN-LABEL, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAVENOUSLY ADMINISTERED RAVULIZUMAB COMPARED WITH BEST SUPPORTIVE CARE IN PATIENTS WITH COVID-19 SEVERE PNEUMONIA, ACUTE LUNG INJURY, OR ACUTE RESPIRATORY DISTRESS SYNDROME

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1. APPROVAL SIGNATURES

PPD	Date dd Mmm yyyy
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2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Specialist Term	Explanation
ADA	antidrug antibody
AE	adverse event
AIC	Akaike's information criteria
ANCOVA	analysis of covariance
ARDS	acute respiratory distress syndrome
ATC	Anatomical Therapeutic Class
BSC	best supportive care
C3	complement component 3
C5	complement component 5
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DBP	diastolic blood pressure
ECG	electrocardiogram
EOAP	End of analysis period
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ET	early termination
FiO2	fraction of inspired oxygen
HR	heart rate
HR-QOL	health-related quality of life
ICF	informed consent form
ICU	intensive care unit
IDMC	independent data monitoring committee
IL	interleukin
IV	Intravenous(ly)
ITT	Intent-to-Treat
KM	Kaplan-Meier
MAR	missing at random
MCMC	Markov chain Monte Carlo
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
MMRM	mixed model for repeated measures
MNAR	missing not at random
PaO2	partial pressure of oxygen
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
PR	interval between the onset of the P wave and the start of the QRS complex
PT	Preferred Term
PTAE	pretreatment adverse event
PTSAE	pretreatment serious adverse event
QRS	combination of the Q wave, R wave, and S wave
QT	interval between the start of the Q wave and the end of the T wave
QTcF	corrected QT interval by Fredericia
REML	restricted maximum likelihood
RR	interval between two successive R waves

Abbreviation or Specialist Term	Explanation
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software®
SBP	systolic blood pressure
SD	standard deviation
SF-12	12-item Short Form
SoA	Schedule of Activities
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SpO2	peripheral capillary oxygen saturation
SS	Safety Set
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
VAS	visual analog scale
WHO DD	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

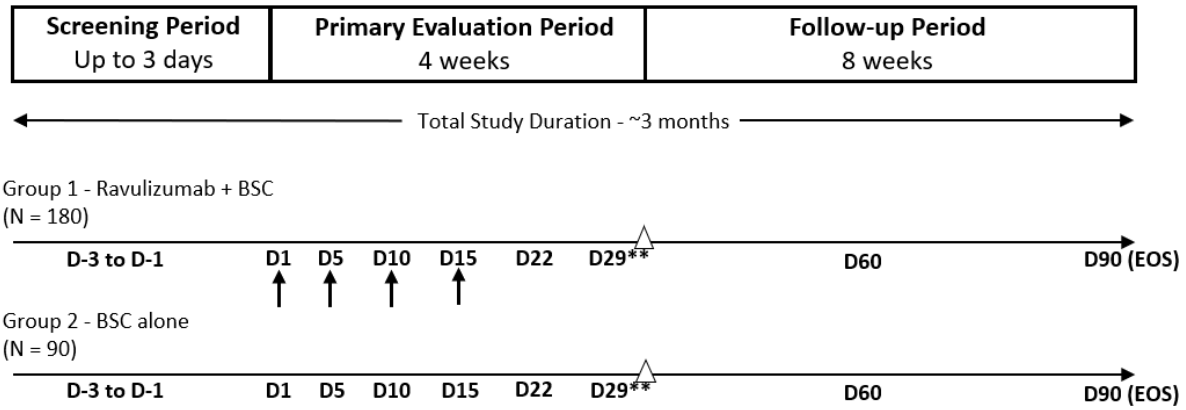
Study ALXN1210-COV-305 is a multicenter Phase 3, open-label, randomized, controlled study designed to evaluate the safety and efficacy of intravenous (IV) ravulizumab + best supportive care (BSC), compared with BSC alone in patients with a confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and a clinical presentation consistent with Coronavirus Disease 2019 (COVID-19) severe pneumonia, acute lung injury, or acute respiratory distress syndrome (ARDS). Patients at least 18 years of age, weighing ≥ 40 kg, and admitted to a designated hospital facility for treatment will be screened for eligibility in this study. Accounting for a 10% nonevaluable rate, approximately 270 patients will be randomized in a 2:1 ratio (180 patients to receive ravulizumab + BSC, 90 patients to receive BSC alone).

Patients randomized to ravulizumab + BSC group will receive a weight-based dose of ravulizumab on Day 1. On Day 5 and Day 10, doses of 600 mg or 900 mg ravulizumab will be administered (according to weight category) and on Day 15 patients will receive 900 mg ravulizumab. Patients in both treatment groups will continue to receive medications, therapies, and interventions per standard hospital treatment protocols for the duration of the study.

The study consists of a Screening Period of up to 3 days, a Primary Evaluation Period of 4 weeks, a final assessment at Day 29, and a Follow up Period of 8 weeks. The 2 follow-up visits will be conducted 4 weeks apart as a telephone call if the patient is discharged from the hospital or an in-person visit if the patient is still hospitalized. The total duration of each patient's participation is anticipated to be approximately 3 months (Figure 1).

Screening and the Day 1 visits can occur on the same day if the patient has met all inclusion and no exclusion criteria.

Figure 1: Study ALXN1210-COV-305 Schematic



A weight-based dose of ravulizumab will be administered on Day 1 as follows: Patients weighing ≥ 40 to < 60 kg: 2400 mg; ≥ 60 to < 100 kg: 2700 mg; or ≥ 100 kg: 3000 mg.
A weight-based dose of ravulizumab will be administered on Day 5 and Day 10 as follows: Patients weighing ≥ 40 to < 60 kg: 600 mg; ≥ 60 to < 100 kg: 900 mg; or ≥ 100 kg: 900 mg.
On Day 15, patients will receive 900 mg ravulizumab.
Day 29 represents the end of the Primary Evaluation Period.
Abbreviations: BSC = best supportive care; D = day; EOS = end of study; N = number of patients.

4.1. Changes from Analyses Specified in the Protocol

The protocol states that the number of days free of mechanical ventilation at Day 29 will be compared between treatment groups using an analysis of covariance (ANCOVA), adjusting for age, and randomization stratification factor, *among survivors*. This has been clarified in Section 7.2.2.1 of this SAP to be the number of days alive and free of mechanical ventilation; this represents a composite strategy for handling the intercurrent event of death.

The same modification applies to the duration of ICU stay at Day 29 *among survivors*, as well duration of hospitalization at Day 29 *among survivors*. These have been clarified in Sections 7.2.2.2, 7.2.2.5, 9.4.5.2 and 9.4.5.3 of this SAP to be the number of days alive and not in the ICU and the number of days alive and not hospitalized, again representing a composite strategy for handling the intercurrent event of death.

Additional changes from the protocol are items 1, 2, and 4 given below in Section 4.2 of this SAP. The analyses as specified in this SAP over-ride the protocol.

4.2. Changes from Analyses Specified in the Previous Version of the SAP

1. The definition of Day 1 has been updated for patients randomized but not dosed with ravulizumab as the later of the date of randomization or the date of the Day 1 visit. This is to allow time for Day 1 assessments to occur on the following calendar day, but within 24 hours of randomization, for patients in the ICU, and to better align with the definition of Day 1 for patients randomized and dosed with ravulizumab (the date of the first infusion of ravulizumab).
2. Missing data sensitivity analyses for the primary endpoint have been added to Section 7.2.1.1 as per feedback from health authorities and will include imputing any missing data assuming death, assuming survival, and performing a tipping point analysis.
3. For the sensitivity analyses of the primary endpoint using a 3-level categorical outcome and a logistic regression model, clarified in Section 7.2.1.1 that the missing data for these analyses will be imputed as for the primary analysis using a multiple imputation approach assuming the data are missing at random (MAR) and using a logistic regression model with covariates for treatment group, the randomization stratification factor, age, sex and presence of a pre-existing condition at baseline.
4. In Section 7.2.2.1, clarified that the number of days free of mechanical ventilation at Day 29 will be summarized by treatment group for all patients and by mortality and added a tipping point sensitivity analysis. These changes also apply to Sections 7.2.2.2 and 7.2.2.5 for the durations of ICU stay and hospitalization.
5. In Sections 7.2.2.3 and 7.2.2.4, added that for patients who die, remaining values up to Day 29 will be imputed as the worst possible value, representing a composite strategy for handling the intercurrent event of death.
6. For the exploratory endpoint of progression to renal failure, explained in Section 7.2.3.1 that deaths will be assumed to be failures (a composite strategy for handling the intercurrent event of death) and that other missing data will be handled as described for the primary analysis of the primary endpoint.

The SAS code in Appendix 9.5.2 has been updated to align with specified analysis methods as described in this SAP. Additional administrative changes have been made for accuracy, clarity and consistency.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint

The primary efficacy endpoint is survival (based on all-cause mortality) at Day 29.

5.1.2. Secondary Endpoints

The secondary efficacy endpoints at Day 29 are:

- Number of days free of mechanical ventilation
- Duration of intensive care unit (ICU) stay
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score
- Change from baseline in SpO2/FiO2
- Duration of hospitalization

An additional secondary endpoint will be assessed beyond Day 29:

- Survival (based on all-cause mortality) at Day 60 and Day 90

5.1.2.1. Mechanical Ventilation

The number of days free of mechanical ventilation is defined as the total number of days from Day 1 to Day 29 without invasive or non-invasive mechanical ventilation.

5.1.2.2. SpO2/FiO2

Oxygenation will be measured using the peripheral capillary oxygen saturation level (SpO2) and the amount of supplemental oxygen as measured by the fraction of inspired oxygen (FiO2) received by taking the ratio of these 2 measures at the same time point.

5.1.2.3. Duration of ICU Stay

The duration of ICU stay is defined as the total number of days from Day 1 to Day 29 that the patient is in the ICU.

5.1.2.4. SOFA Score

Multiple organ failure is a significant indicator of mortality in patients admitted to the ICU. In this study, patients will be evaluated using the SOFA score, an assessment tool that includes a review of 6 organ systems: respiratory, renal, hepatic, cardiac, coagulation, and central nervous system (Vincent, 1998). Each organ system is scored from 0 to 4 points using the worst value observed within the previous 24 hours (Table 2). The total score ranges from 0 to 24, with a higher score indicating a worse condition.

Arterial blood gas may not be drawn on a protocol specified visit day; therefore, the assessment of partial pressure of oxygen (PaO2) is optional and the highly correlated SpO2 will be a surrogate for the respiratory system assessment.

Table 2: Sequential Organ Failure Assessment Scoring

Organ System	Variable (Units)	Score Allocation				
		0	1	2	3	4
Respiratory	PaO2/FiO2 (mmHg)[1]	≥ 400	< 400	< 300	< 200 AND respiratory support (eg, mechanical ventilation)	< 100 AND respiratory support (eg, mechanical ventilation)
	SpO2/FiO2	≥ 302	< 302	< 221	< 142 AND respiratory support (eg, mechanical ventilation)	< 67 AND respiratory support (eg, mechanical ventilation)
Renal	Creatinine (µmol/L)	< 110	110 - 170	171 - 299	300 - 400	> 440
Hepatic	Bilirubin (µmol/L)	< 20	20 - 32	33 - 101	102 - 204	> 204
Cardiac	Inotropes (µg/kg/min)	Mean arterial pressure > 70 mm Hg	Mean arterial pressure < 70 mm Hg	Dopamine ≤ 5 or Dobutamine any dose	Dopamine > 5 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine > 15 or Epinephrine > 0.1 or Norepinephrine > 0.1
Coagulation	Platelets ($\times 10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
CNS	GCS	15	13 - 14	10 - 12	6 - 9	< 6

[1.] As arterial blood gas may not be drawn on a protocol-specified visit day, the PaO2 assessment is optional.
Abbreviations: CNS = central nervous system; GCS = Glasgow Coma Scale; FiO2 = fraction of inspired oxygen; PaO2 = partial pressure of oxygen; SpO2 = peripheral capillary oxygen saturation.
Source: Vincent, 1998; Pandharipande, 2006

5.1.2.5. Duration of Hospitalization

The duration of hospitalization is defined as the total number of days from Day 1 to Day 29 that the patient is in the hospital.

5.1.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- Incidence of progression to renal failure requiring dialysis at Day 29
- Time to clinical improvement (based on a modified 6-point ordinal scale) over 29 days
- SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores at Day 29 (or discharge), Day 60 and Day 90
- EQ-5D-5L scores at Day 29 (or discharge), Day 60 and Day 90

5.1.3.1. Renal Failure

Progression to renal failure will be assessed based on whether a patient required dialysis.

5.1.3.2. Clinical Improvement

Time to clinical improvement will be evaluated during this study and is defined as a live discharge, a decrease from of least 2 points (ie, #5 to #3) from baseline, or both. A modified 6-category ordinal scale (itemized below) will be used to evaluated clinical improvement.

1. Discharged
2. Hospitalized, not requiring supplemental oxygen
3. Hospitalized, requiring supplemental oxygen
4. Hospitalized, requiring noninvasive mechanical ventilation
5. Hospitalized, requiring invasive mechanical ventilation
6. Death

5.1.3.3. 12-item Short Form PCS and MCS Scores

The Short-Form (SF)-12, version 2 (1-week recall period) is a validated health-related quality of life (HR-QOL) instrument that is widely used across a broad spectrum of disease indications. The SF-12 survey contains 12 questions and covers 8 domains. There is a further stratification into 2 summary measures (Physical Component Summary [PCS] and Mental Component Summary [MCS]) as specified below. The summary measures are scored using a norm-based method (ie, mean = 50, SD = 10), where a score of 50 indicates an average score with respect to a healthy population. Higher scores indicate better quality of life.

- PCS: general health (1 item), physical functioning (2 items), role physical (2 items) and body pain (1 item)
- MCS: vitality (1 item), social functioning (1 item), role emotional (2 items) and mental health (2 items)

The survey is anticipated to be completed in several minutes and can be completed by the patient or via an interviewer (in-person or over the telephone).

5.1.3.4. EuroQOL-5 Dimension-5 Level

The EuroQol 5-dimension, 5 severity level (EQ-5D-5L) questionnaire is a brief, validated, HR-QOL instrument that is intended to assess the patient's health status at the time of administration. The questionnaire contains 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which includes 5 response variables (no problems, slight problems, moderate problems, severe problems, and extreme problems). A 5-digit profile based on each of the dimensions can be further converted to a single numerical score called an index. Value sets (a collection of index values) have been derived for multiple countries/regions. Higher index scores indicate better quality of life.

A vertical visual analogue scale (VAS) is included for the patients to indicate a self-rated estimate of their health. The VAS ranges from 100 (best health you can imagine) to 0 (worst health you can imagine).

The EQ-5D-5L questionnaire and VAS are anticipated to be completed in several minutes and can be completed by the patient, via an interviewer (in-person or over the telephone); or via proxy.

5.2. Safety

The safety of ravulizumab will be assessed based on adverse events (AEs), serious adverse events (SAEs), and changes from baseline through study completion in vital signs, routine clinical laboratory tests (eg, chemistry, hematology), physical examination, electrocardiogram results, and pregnancy tests for female patients.

5.2.1. Adverse Events (AEs)

Adverse events are defined in Protocol Section 10.3.

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the last visit at the time points specified in the Schedule of Activities (SoA) (see Protocol Section 1.3).

For the purposes of this SAP, 4 types of AEs will be noted:

- Pre-treatment adverse events and serious adverse events (PTAEs and PTSAEs)
- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)

The PTAEs/PTSAEs are the AEs/SAEs that occur between the signing of informed consent and Day 1. The TEAEs/TESAEs are AEs/SAEs with onset on or after Day 1.

5.2.2. Vital Signs

Temperature (°C or °F), heart rate (HR, beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (SBP and DBP) (millimeters of mercury [mm Hg]) will be assessed.

Body weight will be measured in kilograms (kg).

5.2.3. Laboratory Assessments

Clinical chemistry, hematology, coagulation, urinalysis, arterial blood gas (partial pressure of oxygen [PaO2]), pregnancy test, and direct Coombs test will be collected as outlined in the protocol (see Protocol Section 1.3 and Protocol Table 9) and will be analyzed by the local laboratory.

5.2.4. Other Safety Assessments

5.2.4.1. Physical Examination

Complete or abbreviated physical examination is to be performed at the timepoints indicated in the SoA (see Protocol Section 1.3). A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and musculoskeletal. An abbreviated physical examination consists of at least an evaluation of the respiratory and cardiovascular systems. Clinically significant abnormalities or findings will be recorded as AEs.

5.2.4.2. Electrocardiogram (ECG)

A single 12-lead ECG will be conducted to obtain HR, PR interval, QRS interval, RR interval, QT interval, and QTcF. Whether the ECG is within normal limits and the clinical significance of abnormal results will be documented.

5.3. Pharmacokinetic/Pharmacodynamic/Immunogenicity

Samples will be collected as specified in the SoA (see Protocol Section 1.3) to determine serum concentrations of ravulizumab and total and free C5. The actual date and time (24-hour clock time) of each sample will be recorded.

Antibodies to ravulizumab (ie, antidrug antibody [ADA]) will be evaluated in serum samples collected from patients according to the SoA (see Protocol Section 1.3). Serum samples will be screened for antibodies binding to ravulizumab. Confirmed antibody positive samples will be further evaluated for antibody titer and the presence of neutralizing antibodies.

5.4. Biomarkers

Blood samples for biomarker analyses will be collected at the timepoints indicated in the SoA (see Protocol Section 1.3) to evaluate complement activation and related pathways and cardiovascular health, and their clinical response to ravulizumab. These biomarkers include complement pathway proteins (eg, total and free C5, soluble C5b-9 [sC5b-9]), cytokines associated with inflammation and disease (eg, interleukin [IL]-1, IL-2R, IL-6, IL-8, IL-21, tumor necrosis factor [TNF]-b, Pentraxin-3, Citrullinated histone H3, and monocyte chemoattractant protein [MCP]-1), Factor II, and markers associated with cardiovascular disease (procalcitonin, myoglobin, high sensitivity troponin I [hs-TnI] and N-terminal pro-b-type natriuretic peptide [NT-proBNP]).

6. DATA SETS ANALYZED (STUDY POPULATIONS)

This study will employ a two-arm parallel treatment design. Analyses of efficacy endpoints will be performed on the Intent-to-Treat (ITT) population as well as the Per Protocol Set (PPS). The safety analyses will be based on the Safety Set (SS). Subgroups may be analyzed, as indicated in this SAP.

6.1. Intent-to-Treat (ITT) Population

The ITT population consists of all randomized patients and participants will be analyzed as randomized. The ITT population will be used for the analysis of efficacy data and is considered the primary analysis population.

6.2. Per Protocol Set (PPS)

The PPS is a subset of the ITT population without any important protocol deviations that could impact efficacy analyses. The PPS will include all patients who:

- Have no important protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy,
- Are randomized to the ravulizumab + BSC group and receive 100% of the required treatment doses while they were in the treatment period in the ICU.

Important protocol deviation and key inclusion/exclusion criteria that will result in excluding patients from the PPS are discussed in Section 7.1.2.

For ITT patients in the study who either die or are discharged from the ICU prior to Day 29, the compliance calculation for the per protocol set will include only the time period from the day of first dose to the day of death or ICU discharge.

The PPS will be determined prior to database lock and will be used in a sensitivity analysis of the primary and secondary efficacy endpoints.

6.3. Safety Set (SS)

The SS consists of all randomized patients who receive at least 1 dose of ravulizumab for patients randomized to ravulizumab + BSC or who are randomized to BSC alone. The SS will be used for the analysis of safety data.

Patients who have signed informed consent but are not randomized (or treated for ravulizumab + BSC group) in the study are not included in the SS. However, if these patients report SAEs after the signing of informed consent, these events will be summarized separately in listings, as appropriate.

6.4. Other Sets

6.4.1. Pharmcokinetic/Pharmcodynamic (PK/PD) Set

The PK/PD analyses will be performed on the PK/PD Set. This population includes patients in the ITT population with at least one post-dose PK or PD result.

7. STATISTICAL ANALYSIS

This study is a multicenter Phase 3, open-label, randomized, controlled trial designed to evaluate the safety and efficacy of IV ravulizumab + BSC, compared with BSC alone in patients with a confirmed diagnosis of SARS-CoV-2 infection, and a clinical presentation consistent with COVID-19 severe pneumonia, acute lung injury, or ARDS. The primary endpoint is survival (based on all-cause mortality) at Day 29.

An interim analysis for efficacy and futility is planned when approximately 50% of patients have completed Day 29. If the stopping criteria are met, the study may be terminated early for efficacy or futility depending on which stopping boundary is crossed. The early stopping boundaries for efficacy and futility (non-binding) will be constructed using an α-spending function as Lan-DeMets (O'Brien-Fleming) and a β-spending function as Gamma(-4), respectively.

Provided the study is not stopped early for efficacy or futility, the final primary analysis will be conducted when all patients have completed the Primary Evaluation Period, which is Day 29 (or early termination [ET]). This analysis will include all efficacy, safety, and available PK/PD/immunogenicity study data for regulatory submission purposes. This analysis will not be considered an interim analysis. A final analysis will be conducted when all participants have completed the study follow-up visits (or ET).

Day 1 will be defined as the date of the first infusion of ravulizumab for patients randomized and dosed with ravulizumab and as the later of the date of randomization or the date of Day 1 visit for patients randomized but not dosed with ravulizumab.

For this SAP, the randomization stratification factor refers to two strata based on endotracheal intubation status on Day 1: intubated or not intubated.

Summary statistics will be computed and displayed by treatment group and visit, where applicable. Descriptive statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate. Statistical analyses, other than for the primary analysis, will be performed based on a 2-sided Type I error of 5%.

Analyses will be performed using the Statistical Analysis Software (SAS®) Version 9.4 or higher.

7.1. Study Patients

7.1.1. Disposition of Patients

A table summarizing the number of screened patients, number and percentage of screen failures, number and percentage of randomized patients among all screened patients and number of patients treated with ravulizumab among those randomized to ravulizumab + BSC will be provided. By-patient listing of the reasons for screen failure will also be produced.

Summaries and by-patient listings of patient disposition will include all patients randomized in the study. The following summaries will be generated:

- Patients who were randomized

  - In the study
  - By region (United States, Europe, Asia)
  - By country
  - By site
- Patients who completed the study
- Patients who discontinued the study with reason for discontinuation
- Patients in the analysis datasets and reason for exclusion from specific datasets
- Patients with inclusion/exclusion criteria violations

7.1.2. Protocol Deviations

Protocol deviations will be summarized in a tabular format and listing.

For the purposes of defining the PPS, important protocol deviations are:

- Not meeting all of the key inclusion/exclusion criteria.

  Key inclusion criteria are:

  - Confirmed diagnosis of SARS-CoV-2 infection (eg, via polymerase chain reaction [PCR] and/or antibody test) presenting as severe COVID-19 requiring hospitalization.
  - Severe pneumonia, acute lung injury, or ARDS confirmed by computed tomography or x-ray at Screening or within the 3 days prior to Screening, as part of the patient's routine clinical care.
  - Respiratory distress requiring mechanical ventilation , which can be either invasive (requiring endotracheal intubation) or noninvasive (with continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]).

  Key exclusion criteria are:

  - Patient is not expected to survive for more than 24 hours.
  - Patient is on invasive mechanical ventilation with intubation for more than 48 hours prior to Screening.
  - Severe pre-existing cardiac disease (ie, New York Heart Association Class 3 or Class 4, acute coronary syndrome or persistent ventricular tachyarrhythmias).
- Patients who took less than 100% of the required treatment doses while alive and in the ICU.

7.1.3. Demographics, Disease Characteristics, and Medical History

Patient demographic and baseline disease characteristics will be summarized by treatment group and randomization stratification factor using the ITT population and the PPS. Summary statistics will be presented. No formal hypothesis testing will be performed. By-patient listings will be produced.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (at first dose date in years)
- Sex
- Race and ethnicity
- Region and country
- Baseline weight (kg)

7.1.3.2. Disease Characteristics

The following disease characteristics will be summarized:

- Number (percentage) of patients with a positive SARS-CoV-2 test
- Number (percentage) of patients hospitalized
- Number of days from onset of signs and symptoms to hospitalization and to Day 1
- Number of days from hospitalization to Day 1
- Number (percentage) of patients in the ICU
- Number of days from first ICU date to Day 1
- Oxygen saturation level (SpO2), PaO2 from arterial blood gas, amount of supplemental oxygen (FiO2) received, SpO2/FiO2 and PaO2/FiO2 at baseline
- Number (percentage) of patients on respiratory support and method of support on Day 1
- SOFA score at baseline
- Number (percentage) patients by smoking status

7.1.3.3. Medical History and Baseline Physical Examination

Medical histories will be coded by primary System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0 or higher). Baseline medical history information, ie, number (percentage) of patients who have a medical history, will be summarized by SOC and PT for the ITT population and by the randomization stratification factor. Baseline physical examination information will also be summarized for the ITT population. By-patient listings will be created for medical history and physical examinations.

7.1.4. Prior and Concomitant Medications or Therapies

Prior medications or therapies are defined as medications taken or therapies received by patients prior to Day 1 in the study. Concomitant medications or therapies are defined as medications taken or therapies received by patients during the study on or after Day 1. Medications will be coded using the World Health Organization Drug Dictionary (WHO DD Mar 2018 or higher). Therapies will be coded using MedDRA (version 23.0 or higher). Summaries will be performed

on the ITT population. The number (percentage) of patients using prior and concomitant medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 4 Class code and generic name. The number (percentage) of patients using prior and concomitant therapies will be summarized by SOC and PT.

Prior and concomitant medications will be summarized overall and by potential subgroups of medications (eg, antivirals, immunomodulators, steroids, hydroxychloroquine/chloroquine, convalescent plasma) depending on the distribution of medications used by patients in the study. By-patient listings of all reported medications will be produced.

If prohibited medications are used by patients in this study, then a listing of those patients and the respective prohibited medication(s) will be produced.

7.2. Efficacy Analyses

Efficacy analyses will be performed on the ITT population and the PPS will be used for sensitivity analyses. Baseline is defined as the last available assessment on or before Day 1 for all patients. By-patient listings of all efficacy data will be produced.

7.2.1. Primary Analysis

The primary efficacy endpoint is survival (based on all-cause mortality) at Day 29 and will be compared between the 2 treatment groups using a one-sided Mantel-Haenszel (MH) test of the difference in two proportions stratified by intubated or not intubated on Day 1 and a family-wise Type I error of 0.025. The estimated MH risk difference will be summarized along with the 2-sided 95% confidence interval (CI) using Mantel-Haenszel stratum weights (Mantel, 1959) and the Sato variance estimator. Handling of missing data for the primary analysis is described in Section 7.2.1.1.

Survival will also be analyzed using the method of Kaplan and Meier (KM) and compared using a log-rank test stratified by intubated or not intubated on Day 1 as a sensitivity analysis. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model stratified by intubated or not intubated on Day 1. Confidence intervals (95%) will be presented for the survival estimate at Day 29 based on the complementary log-log transformation. Kaplan-Meier curves for both treatment groups will be produced.

A sensitivity analysis of the primary endpoint will also be performed using a 3-level categorical outcome of 3 (alive and discharged from the ICU); 2 (alive and in the ICU); or 1 (death). The 2 treatment groups will be compared using a proportional odds model with covariates for treatment group and the randomization stratification factor. If the assumption of proportional odds is rejected, a different approach will be considered.

Additional sensitivity analyses will include:

- A logistic regression with covariates for treatment group, age, sex, region, and randomization stratification factor. The estimate of the difference in survival proportions will be based on this logistic regression (Ge, 2011).

- A Cox proportional hazards model with covariates for treatment group, age, sex, region, and randomization stratification factor. The treatment group hazard ratio and risk reduction from the model will be summarized.

A summary table and listing of patients who died during the study will also be provided with reason for death, where available.

An interim analysis of the primary endpoint will also be conducted as described in Section 7.4.

7.2.1.1. Handling of Dropouts or Missing Data

Missing survival data for the primary analysis will be imputed using a multiple imputation approach assuming the data are missing at random (MAR) and using a logistic regression model with covariates for treatment group, the randomization stratification factor, age, sex and presence of a pre-existing condition at baseline (diabetes mellitus, obesity, respiratory condition, and/or coronary artery disease). Sensitivity analyses will include:

- Worst-case scenario: missing survival data for patients randomized to ravulizumab + BSC group are imputed as death and missing survival data for patients randomized to BSC alone group are imputed as survived
- All available data: no imputation of missing data
- Best-case scenario: missing survival data for patients randomized to ravulizumab + BSC group are imputed as survived and missing survival data for patients randomized to BSC alone group are imputed as death
- Assuming death: all missing survival data is imputed as a death
- Assuming survival: all missing survival data is imputed as survived
- Delta-adjustment tipping point analysis (O'Kelly and Ratitch, 2014): this approach assumes that patients randomized to the ravulizumab + BSC group with missing survival data experience less survival, defined by an adjustment (delta), compared to patients with observed survival in the ravulizumab + BSC group; missing values for patients randomized to ravulizumab + BSC group are imputed by shifting the survival probability of the observed patients downward by delta until any positive conclusion drawn from the primary analysis is reversed; refer to Appendix 9.5.2.1 for additional details

In another sensitivity analysis of the primary endpoint (ie, time to event), the patients who survive will be censored and will have a censor time that is based on the patient's time from Day1 to the end of the Analysis Period, as described in Appendix 9.5.1. A censoring indicator will be equal to 1 if the patient survived (was censored), and 0 if the patient died.

For the other sensitivity analyses of the primary endpoint (3-level categorical outcome and logistic regression model), missing data will be imputed using a multiple imputation approach assuming the data are missing at random (MAR) and using a logistic regression model with covariates for treatment group, the randomization stratification factor, age, sex and presence of a pre-existing condition at baseline (diabetes mellitus, obesity, respiratory condition, and/or coronary artery disease).

Missing data for the primary analysis of secondary endpoints will be handled as described in the secondary analyses in Section 7.2.2.

7.2.1.2. Subgroup Analysis

A summary of survival at Day 29 will be produced by the following subgroups:

- Randomization stratification factor: intubated, not intubated
- Age group: <50 years, 50 to <70 years, ≥ 70 years
- Sex: Male, Female
- Region: United States, Europe, Asia
- Race: Asian, Black or African American, White, Other
- Ethnicity: Hispanic/Latino/Spanish origin, Not of Hispanic/Latino/Spanish origin
- Smoking status: Current/Former, Never
- Subgroups based on anticipated pre-existing conditions at baseline. Additional subgroups may be summarized depending on the distribution of medical histories of the patients in the study
  - Hypertension
  - Diabetes mellitus
  - Obesity
  - Respiratory conditions (eg asthma, COPD, pulmonary fibrosis/hypertension)
  - Coronary artery disease
- Subgroups based on anticipated concomitant medications used as BSC. Additional subgroups may be summarized depending on the distribution of medications used by patients during the study.
  - Use of any antivirals
  - Use of any immunomodulators
  - Use of any steroids
  - Use of any hydroxychloroquine/chloroquine
  - Use of any convalescent plasma

For each subgroup, the following descriptive summaries of survival will be produced:

- Summary of the number of patients
- Summary of the number (percentage) of patients with survival at Day 29
- Estimated risk difference between the 2 treatment groups along with a 95% CI
- Two-sided p-value from a stratified test of the difference in 2 proportions (if the sample size within a subgroup is too small, an unstratified test will be used)

- Hazard ratio and 95% CI from a Cox proportional hazards model with treatment covariate

If the use of concomitant medications is imbalanced by treatment group, the patients randomized to the ravulizumab + BSC group as a whole may be compared to subgroups of the BSC alone group with certain medication use (eg, antivirals, immunomodulators, hydrochloroquine/chloroquine).

7.2.1.3. Multicenter Studies

Since a small number of patients may be anticipated at certain sites, site will not be used in efficacy analyses; region will be used instead.

7.2.1.4. Hypothesis Testing and Significance Level

All hypothesis testing other than for the primary analysis will be 2-sided and performed at the 0.05 level of significance. All estimates of efficacy parameters will be accompanied by 2-sided 95% CIs.

7.2.1.5. Sensitivity and Supplementary Analyses

Sensitivity and supplementary analyses for the primary endpoint are described in Section 7.2.1. Briefly these analyses include:

- Different missing data mechanisms to assess the impact of missing data
- Time to event analysis
- Categorical analysis
- Logistic regression model
- Cox proportion hazards model
- The primary analyses described for the ITT population will also be performed using the PPS

7.2.2. Secondary Analyses

A closed testing procedure will be applied to control the type I error for the analyses of the primary and secondary endpoints at Day 29. If the primary endpoint is statistically significant in favor of ravulizumab, the secondary endpoints will be evaluated according to the following rank order:

1. Number of days free of mechanical ventilation at Day 29,
2. Duration of ICU stay at Day 29,
3. Change from baseline in SOFA score at Day 29,
4. Change from baseline in SpO2/FiO2 at Day 29,
5. Duration of hospitalization at Day 29.

The hypothesis testing will proceed from highest rank (#1) the number of days free of mechanical ventilation at Day 29 to the lowest rank (#5) duration of hospitalization at Day 29, and if statistical significance is not achieved at an endpoint ($p \geq 0.05$), then endpoints of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure.

An additional secondary endpoint will be assessed beyond Day 29 regardless of the results of the closed testing procedure: Survival (based on all-cause mortality) at Day 60 and Day 90.

The PPS will be used in a sensitivity analysis for all secondary efficacy endpoints.

7.2.2.1. Number of Days Free of Mechanical Ventilation at Day 29

The number of days free of mechanical ventilation at Day 29 will be summarized by treatment group for all patients and by mortality. The number of days free of mechanical ventilation at Day 29 will be compared between treatment groups using an analysis of covariance (ANCOVA), adjusting for age and the randomization stratification factor, among survivors (ie, the number of days alive and free of mechanical ventilation).

Missing data will be imputed using a multiple imputation approach assuming the data are MAR and using a regression model with covariates for treatment group, the randomization stratification factor, age, sex and presence of a pre-existing condition at baseline (diabetes mellitus, obesity, respiratory condition, and/or coronary artery disease). Sensitivity analyses will include:

- Worst-case scenario: missing days up to Day 29 for patients randomized to ravulizumab + BSC group will be considered as alive and not free of mechanical ventilation and missing days for patients randomized to BSC group will be considered as alive and free of mechanical ventilation for the remaining days up to Day 29
- All available data: no imputation of missing data
- Best-case scenario: missing days up to Day 29 for patients randomized to ravulizumab + BSC group will be considered as alive and free of mechanical ventilation and missing days for patients randomized to BSC group will be considered as alive and not free of mechanical ventilation for the remaining days up to Day 29
- Delta-adjustment tipping point analysis (O'Kelly and Ratitch, 2014): missing data for patients randomized to ravulizumab + BSC group are imputed by shifting the number of days alive and free for the observed patients downward by delta until any positive conclusion drawn from the primary analysis is reversed; refer to Appendix 9.5.2.2.1 for additional details

7.2.2.2. Duration of ICU Stay at Day 29

The duration of ICU Stay at Day 29 will be summarized by treatment group for all patients and by mortality. Duration of ICU stay at Day 29 will be compared between the 2 treatment groups using an ANCOVA, adjusting for age and randomization stratification factor, among survivors (ie, the number of days alive and not in the ICU). Missing data will be handled as described for number of days free of mechanical ventilation at Day 29. The proportion of patients discharged

from the ICU will also be summarized and compared between the 2 treatment groups in a similar manner as the primary analysis of the primary endpoint.

7.2.2.3. Change from Baseline in SOFA Score at Day 29

Changes in SOFA score from Day 1 to Day 29 will be summarized by treatment group and study visit for all patients and by mortality.

Changes in SOFA score will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (i.e. MMRM, Mallinckrodt, 2008) and all available longitudinal data. The model will include fixed effects for baseline SOFA score, age, randomization stratification factor, treatment group indicator, study day (Day 5, 10, 15, 22, 29), and study day by treatment group interaction. An unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC): first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. For patients who die, remaining values up to Day 29 will be imputed as a score of 24, the worst possible value.

A sensitivity analysis will be performed using a missing not at random (MNAR) mechanism for the missing data, where it will be assumed that unobserved outcomes for patients who discontinue early from the ravulizumab + BSC group will follow the trajectory of outcomes similar to the control group (BSC alone), taking into account observed values prior to discontinuation (O'Kelly and Ratitch, 2014). Patients discontinuing early from the BSC alone group will be assumed to have outcomes similar to the BSC alone patients who remain on their randomized treatment. Refer to Appendix 9.5.2.2.2 for additional details.

7.2.2.4. Change from baseline in SpO2/FiO2 at Day 29

Changes in SpO2/FiO2 from Day 1 to Day 29 will be summarized daily by treatment group for all patients and by mortality.

Changes in SpO2/FiO2 will be also be analyzed using a REML-based repeated measures approach (i.e. MMRM, Mallinckrodt, 2008) and all available longitudinal data. The model will include fixed effects for baseline SpO2/FiO2, age, randomization stratification factor, treatment group indicator, study day (Day 5, 10, 15, 22, 29), and study day by treatment group interaction. An unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC): first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The daily post-baseline SpO2/FiO2 scores will be mapped to study day as described in Appendix 9.4.6. For patients who die, remaining values up to Day 29 will be imputed as a score of 0, the worst possible value.

A sensitivity analysis will be performed using a control-based MNAR mechanism for the missing data as described for change from baseline in SOFA score at Day 29.

This analysis will be repeated for changes in PaO2/FiO2, where available, as a sensitivity analysis.

7.2.2.5. Duration of Hospitalization at Day 29

Duration of hospitalization at Day 29 will be analyzed in a similar manner as duration of ICU stay (ie, the number of days alive and not hospitalized). Missing data will be handled as described for number of days free of mechanical ventilation at Day 29. The proportion of patients discharged from the hospital will also be summarized and compared between the 2 treatment groups in a similar manner as the primary analysis of the primary endpoint.

7.2.2.6. Survival at Day 60 and Day 90

Survival (based on all-cause mortality) at Day 60 and Day 90 will be estimated using the KM method and compared using a log-rank test stratified by intubated or not intubated on Day 1. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model stratified by intubated or not intubated on Day 1. Confidence intervals (95%) will be presented for the survival estimates at Day 60 and Day 90 based on the complementary log-log transformation. KM curves for both treatment groups will be produced.

7.2.3. Exploratory Analyses

7.2.3.1. Incidence of Progression to Renal Failure Requiring Dialysis at Day 29

The incidence of progression to renal failure requiring dialysis at Day 29 will be compared between the treatment groups using a MH test of the difference in 2 proportions stratified by intubated or not intubated on Day 1 for patients not on dialysis at Day 1. The estimated MH risk difference will be summarized along with the 95% CI using Mantel-Haenszel stratum weights and the Sato variance estimator. Deaths will be assumed as failures and missing data will be handled as described for the primary analysis of the primary endpoint.

Time to progression to renal failure will also be analyzed using the KM method and compared using a log-rank test stratified by intubated or not intubated on Day 1 as a sensitivity analysis. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model stratified by intubated or not intubated on Day 1. Confidence intervals (95%) will be presented for the survival estimate at Day 29 based on the complementary log-log transformation. Kaplan-Meier curves for both treatment groups will be produced.

7.2.3.2. Time to Clinical Improvement over 29 Days

In addition, the time to clinical improvement will be evaluated, as defined by live discharge from the hospital, a decrease of 2 points from baseline on a 6-point ordinal scale, or both. Time to clinical improvement will be analyzed using the KM method and compared using a log-rank test stratified by intubated or not intubated on Day 1 as a sensitivity analysis. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model stratified by intubated or not intubated on Day 1. Confidence intervals (95%) will be presented for the clinical improvement estimate at Day 29 based on the complementary log-log transformation. Kaplan-Meier curves for both treatment groups will be produced.

7.2.3.3. SF-12 PCS and MCS Scores at Day 29 (or discharge), Day 60 and Day 90

SF-12 PCS and MCS scores at Day 29 (or discharge), Day 60 and Day 90 will be compared between treatment groups using an analysis of covariance (ANCOVA), adjusting for age and the randomization stratification factor.

7.2.3.4. EQ-5D-5L Scores at Day 29 (or discharge), Day 60 and Day 90

EQ-5D-5L index and VAS scores at Day 29 (or discharge), Day 60 and Day 90 will be compared between treatment groups using an analysis of covariance (ANCOVA), adjusting for age and the randomization stratification factor.

7.2.4. Other Efficacy Analyses

7.2.4.1. Pharmacokinetic and Pharmacodynamic Analyses

Blood samples will be collected to evaluate ravulizumab concentrations over time. Descriptive statistics of ravulizumab concentration data will be presented for patients randomized and treated with ravulizumab for each scheduled sampling time point.

Blood will also be collected to evaluate total and free C5 concentrations. Descriptive statistics will be presented by treatment group and for each scheduled sampling time point. Total and free C5 concentrations will be evaluated by assessing the absolute values and changes and percentage changes from baseline, as appropriate.

By-patient listings of ravulizumab concentrations, as well as total and free C5 concentrations will be produced.

7.2.4.2. Biomarker Analyses

Serum and plasma biomarkers actual values and changes from baseline will be summarized by treatment group over time, as appropriate. By-patient listings of all biomarker data will be produced. Biomarker data will only be summarized at the final analysis at the end of the study.

7.3. Safety Analyses

All safety analyses will be conducted on the SS. All safety data will be presented in by-patient listings. No formal hypothesis testing is planned. Baseline is defined as the last available assessment on or before Day 1.

7.3.1. Study Duration, Treatment Duration, and Exposure

Study duration will be summarized by treatment group for the ITT population and SS. Treatment duration and exposure will be summarized for the ravulizumab + BSC group for the SS. Each patient's study duration, treatment duration, and exposure will be summarized in patient listings, as appropriate.

Study duration will be calculated as the time in days from Day 1 until the date of discontinuation/completion of the study (ie, study duration (days) = the earlier of [data cutoff date or disposition/death date] – Day 1 date + 1). See Appendix 9.5.1 for the definition of the data cutoff date. Treatment duration will be calculated only for those patients randomized and

treated with ravulizumab as the time in days from the first dose date of ravulizumab until the last dose date of ravulizumab (ie, treatment duration (days) = Last Dose Date – First Dose Date + 1).

7.3.2. Adverse Events (AEs)

The AEs will be coded by primary System Organ Class (SOC) and Preferred Term (PT) using MedDRA (version 23.0 or higher).

For the purposes of this SAP, only Treatment-Emergent Adverse Events (TEAEs) will be summarized. TEAEs are AEs that onset on or after Day 1 in the study. Both tabular outputs and listings will be created for TEAEs as described in this SAP; additional details regarding AEs are outlined in Appendix 9.4.7.

7.3.2.1. Overall Summary of AEs

An overview of TEAEs will be presented showing the number of TEAEs and the number and percentage of patients who:

- Experienced any TEAE
- Discontinued study drug due to an AE
- Experienced an AE considered related to study drug
- Experienced an AE considered not related to study drug
- Experienced a TEAE by each toxicity grade: Grades 1 to 5
- Experienced a TEAE leading to death

These statistics will be prepared for all TEAEs and, separately, for TESAEs (except toxicity grade) and non-serious TEAEs.

Additional overall summary tables by age, sex, race and region will also be provided.

7.3.2.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs/TESAEs and the number and percentage of patients with events will be presented by SOC and PT and by PT alone. Patients will be counted once in each SOC and PT. Percentages will be based on the total number of patients in the SS in the treatment group. The SOCs will be listed alphabetically and PTs within each SOC will be listed in order of decreasing frequency of occurrence (percentage) overall. A summary by PT alone will also be produced for events occurring in ≥ 5% of patients in either treatment group.

Additional summary tables stratifying TEAEs and TESAEs by age, sex, race and region will also be provided.

The number of non-serious AEs and the number and percentage of patients with non-serious events will be presented by SOC and PT.

The incidence of TEAEs leading to study drug discontinuation, study discontinuation, and death will be summarized.

Detailed listings of patients who experience TEAEs (including PTAEs) will be presented. These listings will include seriousness, toxicity grade and relationship to treatment, as well as action

taken regarding study treatment, other action taken, and patient outcome. A separate listing of patients who discontinued from the study due to a TEAE will also be provided, as well as TEAEs resulting in death.

7.3.2.3. AEs and SAEs by SOC, PT, and Relationship

Summaries of TEAEs and TESAEs by relationship (related vs not related) will be provided for the patients in the ravulizumab + BSC group.

7.3.2.4. AEs by SOC, PT, and Toxicity Grade

Summaries of TEAEs by toxicity grade (Grades 1 to 5) will be provided.

7.3.2.5. Other Significant Adverse Events

A by-patient listing of TEAEs of special interest (meningococcal infections) will be provided.

7.3.3. Other Safety

Other safety parameters will be summarized by treatment group for all patients in the SS where available. All data will be presented in by-patient listings.

7.3.3.1. Analyses for Laboratory Tests

Each laboratory parameter will be summarized by treatment group and visit and by site, as applicable. Changes from baseline will be presented. An overall shift table will also be summarized by visit. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the local laboratory.

7.3.3.2. Vital Signs

Vital signs (SBP, DBP, temperature, respiratory rate, and HR)) and body weight (kg), and changes from baseline in vital signs and body weight will be summarized by treatment group and visit and in by-patient listings.

7.3.3.3. Other Safety Parameters of Special Interest

Urine and serum pregnancy tests will be summarized in by-patient listings. A listing of meningococcal vaccinations will be produced showing the medication and date of vaccination for each patient. Listings of physical examinations will also be produced.

7.3.3.3.1. Electrocardiogram (ECG)

ECG results will be summarized by treatment group and visit. Descriptive statistics will be presented for each ECG parameter (including HR, PR interval, QRS interval, QT interval, RR interval, and QTcF) value and for change from baseline. Listings of ECG results will be produced.

7.3.3.3.2. Immunogenicity

For assessment of immunogenicity, the presence of confirmed positive ADAs will be summarized by visit for patients randomized and treated with ravulizumab. A by-patient listing

showing ADA results by visit will include positive/negative ADA, and for confirmed positive ADA samples, the ADA titer and presence of neutralizing antibodies will also be assessed.

7.4. Interim Analysis

The primary null hypothesis that is being tested is that there is no difference in survival between 2 treatment groups (ravulizumab + BSC and BSC alone) as measured by the difference in the proportions surviving at Day 29 between the 2 treatment groups.

The alternative hypothesis is that ravulizumab + BSC will improve survival by 20% at Day 29 compared to BSC alone.

Hence, the treatment effect is $\delta = \pi_{rav+BSC} - \pi_{BSC,}$ where π = proportion of patients surviving on study arm and they hypotheses are

Null hypothesis H_0: $\delta = 0$

Alternative hypothesis H_1: $\delta > 0$ (specifically 0.2).

With this treatment effect, an overall 1-sided Type I error of 0.025 and 2:1 randomization, approximately 243 patients will be required to achieve at least 90% power. Considering 10% nonevaluable subjects, a total of 270 patients will be enrolled in the study.

A pre-planned interim analysis for efficacy and futility will be conducted when approximately 50% of the information is available, that is after approximately122 patients have completed Day 29. If the stopping criteria are met, the study may be terminated early for efficacy or futility depending on which stopping boundary is crossed.

The early stopping boundaries for efficacy and futility (non-binding) will be constructed using α-spending function as Lan-DeMets (O'Brien-Fleming) spending function, published by Lan and DeMets (1983) and β-spending function as Gamma(-4) that was first published by Hwang et al (1990).

Use of these spending functions ensures the control of Type I error to 0.025.

The p-value efficacy and futility boundaries for the interim analysis with 122 patients are 0.0016 and 0.5016. The [1-sided] p-value from the t-test statistic based on the results from combining all imputed datasets for overall inference (ie, from PROC MIANALYZE) will be compared with these stopping boundaries. The study will be terminated and ravulizumab will be declared as being statistically significant and more efficacious than BSC if the nominal [1-sided] p-value is less than 0.0016 and the study can be terminated for futility if the nominal [1-sided] p-value is greater than 0.5016.

Table 3: Stopping Boundaries

Analysis	Efficacy Boundary (p-value scale)	Futility Boundary (p-value scale)
Interim (~122 patients)	0.0016	0.5016
Final (243 patients)	0.0245	0.0245

If the study is not stopped early for efficacy or futility at the interim analysis, the final primary analysis will be conducted when all patients have completed the Primary Evaluation Period, which is Day 29 (or ET). This analysis will include all efficacy, safety, and available PK/PD/immunogenicity study data for regulatory submission purposes.

7.4.1. **Independent DMC Analysis**

An independent data monitoring committee (IDMC) will be formed before study initiation. The IDMC's objectives and operational details will be defined in an IDMC Charter. The IDMC will conduct regular planned safety and efficacy reviews of study data as outlined in the IDMC SAP.

The planned interim analysis will be performed by the independent data analysis center and the IDMC SAP will describe the planned interim analyses in greater detail.

8. REFERENCES

Ge M, Durham LK, Meyer RD, Xie W, and Thomas N. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug Inf J 2011; 45:481-493.

Hwang IK, Shih WJ, DeCani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990; 9(12):1439-1445.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983; 70(3):659-663.

Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inf J 2008; 42:303-319.

Mantel N, Haenszel W. Statistical aspects of analysis of data from retrospective studies of disease. 1959; J Natl Cancer Inst. 1959; 22(4):719-748.

O'Kelly M, Ratitch B (2014). Clinical trials with missing data: a guide for practitioners, 1st ed. John Wiley & Sons.

Optum® PRO CoRE 1.5 Smart Measurement® System User's Guide (2019). Optum, Inc, Johnston, RI.

Pandharipande P, Sanders N, St Jacques P, et al. Calculating SOFA scores when arterial blood gasses are not available: validating SpO2/FiO2 rations for imputing PaO2/iO2 ratios in the SOFA score. Crit Care Med. 2006;34:A.

Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. Value Health 2019; 22(8):931-941.

Vincent J-L, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Crit Care Med. 1998; 26(11):1793-1800.

9. APPENDICES

9.1. Protocol Schedule of Activities

Refer to Protocol Section 1.3 for the Schedule of Activities.

9.2. Changes from Analyses Specified in the Previous Version of the SAP

See Section 4.2 of this SAP.

9.3. Sample Size, Power, and Randomization

A sample size of 243 patients (162 ravulizumab + BSC, 81 BSC alone) is required to ensure at least 90% power and detect an improvement in survival from 60% in the BSC alone group to 80% in the ravulizumab + BSC group at Day 29.

This sample size calculation was performed in EAST 6.5 and assumes:

- 1-sided Z-test of the difference in 2 proportions,
- Type I error = 0.025,
- Pooled variance,
- 2:1 randomization on the 2 treatment groups,
- One interim analysis at 50% information which will be after collecting primary efficacy data on approximately 122 patients. The early stopping boundaries for efficacy and futility (non-binding) will be constructed using α-spending function as Lan-DeMets spending function with O'Brien-Fleming flavor and β-spending function as Gamma(-4) (Lan, 1983; Hwang, 1990).

Considering a nonevaluable rate of 10%, this study is planned to randomize approximately 270 patients (180 ravulizumab + BSC, 90 BSC alone).

9.4. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis. For all dates (except AE and medication dates), in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

9.4.1. Age at First Dose

Age at first dose will be calculated as: Year of first dose - Year of birth.

9.4.2. Definition of Baseline Values

Baseline is defined as the last available assessment on or before Day 1 for all patients. Day 1 will be defined as the date of the first infusion of ravulizumab for patients randomized and dosed with ravulizumab and as the later of the date of randomization or the date of Day 1 visit for patients randomized but not dosed with ravulizumab.

9.4.3. Change from Baseline

Change from baseline will be calculated as

Change from baseline = Assessment value – Baseline assessment value.

9.4.4. Units Conversion

The amount of supplemental oxygen received (FiO2) may be recorded in either % or liters/minute (L/min) units. It will be assumed that percentage increases by 4% for every additional liter of oxygen flow administered. Hence, the following conversion to % will be used for L/min:

Liters Per Minute	Percentage
0	21
1	24
2	28
3	32
4	36
5	40
6	44
7	48
8	52
9	56
10	60

PaO2 maybe recorded in either millimeters of mercury (mmHg) or kilopascal (kPa). The following conversion factor will be used to convert kPa to mmHg: 1 kPa = 7.50062 mmHg

9.4.5. Definition of Durations

9.4.5.1. Number of Days Free of Mechanical Ventilation at Day 29

The number of days free of mechanical ventilation at Day 29 among survivors (ie, the number of days alive and free of mechanical ventilation) will be defined as:

Number of days alive – Number of days on mechanical ventilation, where

- Number of days alive = Earliest of Day 29 Visit Date or Disposition Date (for death) – Date of Day 1 + 1; set to 29 if > 29.

- Number of days on mechanical ventilation = sum of total number of days with mechanical ventilation from Date of Day 1 to Date of Day 29 Visit or Disposition Date (for death) ; set to 29 if > 29.

9.4.5.2. Duration of ICU Stay at Day 29

The duration of ICU stay at Day 29 among survivors (ie, the number of days alive and not in the ICU) will be defined as:

Number of days alive – Number of days in ICU, where

- Number of days alive is as defined in Section 9.4.5.1.
- Number of days in ICU = sum of total number of days in ICU from Date of Day 1 to Earliest of Date of Day 29 Visit or Disposition Date (for death); set to 29 if > 29.

Number of days from first ICU date to Day 1 = Date of Day 1 – Date of first ICU entry; set to zero if negative.

9.4.5.3. Duration of Hospitalization at Day 29

The duration of hospitalization at Day 29 among survivors (ie, the number of days alive and not hospitalized) will be defined as:

Number of days alive – Number of days in hospital, where

- Number of days alive is as defined in Section 9.4.5.1.
- Number of days in hospital = sum of total number of days in hospital from Date of Day 1 to Earliest of Date of Day 29 Visit or Disposition Date (for death); set to 29 if > 29.

Number of days from hospitalization to first dose date = Date of Day 1 – Date of hospitalization.

9.4.6. Visit Window Definitions for SpO2/FiO2 and PaO2/FiO2 Repeated Measures Analyses

The following study days will be analyzed in a repeated measures analysis for changes in SpO2/FiO2 and PaO2/FiO2: Days 5, 10, 15, 22, 29. The value for each study day will be taken as the last observed value on or prior to the Date of Visit for each study day. Both SpO2 or PaO2 and FiO2 must be available on the same date.

9.4.7. Adverse Events

The analysis of AEs is described in Section 7.3.2.

Treatment-emergent AEs are events with onset dates on or after Day 1 in the study. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to Day 1, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of Day 1, then the AE is treatment-emergent; else,
- If the start year is the same as the year of Day 1 and
  - the start month is missing, then the AE is treatment emergent; else if

  - the start month is present and is the same or after the month of Day 1, then the AE is treatment-emergent; else,

- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered PTAEs.

Patient percentages will be based on the total number of patients in the particular treatment group.

AEs with missing relationship will be assumed to be related to study treatment. AEs with missing toxicity grade will be summarized as a separate category.

9.4.8. Medication Dates

For medication start dates, if day is missing, the first day of the month will be used. If month is missing, January will be used. For medication end dates, if day is missing, the last day of the month will be used. If month is missing, December will be used. If year is missing for start or end date, the analysis date will be considered missing.

9.4.9. SF-12 Calculations

The SF-12v2® Health Survey with a 1-week recall period will be used in this study. The Optum PRO CoRE Scoring Software 1.5 will be used to derive the 8 domain scores and 2 component summary scores. The algorithms used by the software to the score the data are descried below (excerpted from the User's Guide).

9.4.9.1. Data Cleaning and Item Recoding

First, the data are checked for out-of-range values. Out-of-range values are any values that are outside the range of acceptable item response values for the SF-12v2® Health Survey. Out-of-range values will be converted to missing values. Next, four items (GH01, BP02, MH03, VT02) are reversed scored. Reverse scoring of these items is required so that a higher item response value indicates better health for all SF-12v2® Health Survey items and summary measures.

9.4.9.2. Item Recalibration

For 11 of the SF12v2 items, research to date offers good support for the assumption of a linear relationship between the item scores and the underlying health concept defined by their scales. However, empirical work has shown that one item, GH01, requires recalibration to satisfy this important scaling assumption. The recommended scoring for item GH01 is: Excellent = 5.0, Very good = 4.4, Good = 3.4, Fair = 2.0 and Poor = 1.0.

9.4.9.3. Computation of Raw Scores

After recoding and recalibrating the required item values, a raw score is computed for each scale. This score is the simple algebraic sum of the final values for all items in that scale. For single-item scales, the raw score is simply the final item value.

9.4.9.4. Standardization of the SF-12v2 Health Survey Scales

The first step in scoring the component summary measures consists of standardizing each SF-12v2® Health Survey scale using a z-score transformation. The z-score for each scale is computed by subtracting the mean (0-100) score observed in the 1998 general U.S. population from each SF-12v2® Health Survey scale score (0-100) scale and dividing the difference by the corresponding scale standard deviation observed in the 1998 general U.S. population.

9.4.9.5. Aggregation of the Scale Scores

After a z-score has been computed for each SF-12v2® Health Survey scale, the second step involves computation of aggregate scores for the physical and mental summaries using weights (factor score coefficients) from the 1990 general U.S. population. An aggregate physical score is computed by multiplying the z-score of each SF-12v2® Health Survey scale by its associated physical factor score coefficient and summing the eight products. If any of the scale scores are missing, then the aggregate physical score is not computed. An aggregate mental score by multiplying the z-score of each SF-12v2® Health Survey scale by its associated mental factor score coefficient and summing the eight products. If any of the scale scores are missing, then the aggregate mental score is not computed.

9.4.9.6. Transformation of Summary Scores

The third step involves transforming the aggregate physical and mental summary scores to the T-score Based (50, 10) scoring. This is done by multiplying each aggregate summary score obtained from Step 2 by 10 and adding the resulting product to 50.

9.4.9.7. Imputation of Missing Items

The Maximum Data Recovery option will be used for missing data estimation. This results in the application of algorithms that compute a scale score for those respondents who have answered at least one item that represents that construct. For the four multi-item scales (PF, RP, RE, MH), item parameters obtained through IRT methods are used to estimate a missing value on an item based upon a respondent's response to an answered item. Additionally, a PCS and MCS score is calculated for those respondents who have calculated scores on at least seven of the eight SF-12v2® Health Survey scales. However, PCS is not estimated if the PF scale is missing, and MCS is not estimated if the MH scale is missing.

9.4.10. EQ-5D-5L Calculations

The EQ-5D-5L version will be used in this study. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set. EQ-5D-5L index scores for this study will be obtained using the composite time trade-off (cTTO) method based on the Tobit model (Pickard, 2019). The calculation is illustrated below.

US cTTO		Example: the value for health state 21354
Full health (11111)		Full Health=1
Mobility level 2	-0.096	-0.096
Mobility level 3	-0.122	
Mobility level 4	-0.237	
Mobility level 5	-0.322	
Self-Care level 2	-0.089	0
Self-Care level 3	-0.107	
Self-Care level 4	-0.220	
Self-Care level 5	-0.261	
Usual Activity level 2	-0.068	
Usual Activity level 3	-0.101	-0.101
Usual Activity level 4	-0.255	
Usual Activity level 5	-0.255	
Pain/Discomfort level 2	-0.060	
Pain/Discomfort level 3	-0.098	
Pain/Discomfort level 4	-0.318	
Pain/Discomfort level 5	-0.414	-0.414
Anxiety/Depression level 2	-0.057	
Anxiety/Depression level 3	-0.123	
Anxiety/Depression level 4	-0.299	-0.299
Anxiety/Depression level 5	-0.321	
Health State Index Score		=1-0.096-0-0.101-0.414-0.299=0.090

9.5. Additional details on Statistical Methods

9.5.1. Time to Death, Censoring Time, and Calculations

For the primary analysis, only deaths up to Day 29 will be considered, where time to death ≤ 29 days.

For the KM sensitivity analysis of the primary endpoint, a censoring indicator will be equal to 1 if the patient did not die (was censored), and 0 if the patient died on or before 29 days.

For patients who die during the Primary Analysis Period, the time to event (in days) is defined as:

$$Time\ to\ Death = (Date\ of\ Death - Date\ of\ Day\ 1 + 1)$$

For patients who do not die during the Primary Analysis Period, the censoring time (in days) is defined as:

$$Censoring\ Time = \min(29\ days, time\ on\ study)$$

where time on study is Disposition Date – Date of Day 1 +1 for patients who have left the study before 29 days or Data Cutoff Date (when the last patient has the Day 29 visit) – Date of Day 1 + 1.

For the secondary endpoint of survival at Day 60 and Day 90, the following will be used:

For patients who die during the Analysis Period, the time to event (in days) is defined as:

$$Time\ to\ Death = (Date\ of\ Death - Date\ of\ Day\ 1 + 1)$$

For patients who do not die during the Analysis Period, the censoring time (in days) is defined as:

$$Censoring\ Time = (EOAP\ Date - Date\ of\ Day\ 1 + 1)$$

where End of Analysis Period (EOAP) Date is the minimum non-missing value of the following dates: the Data Cutoff Date (when the last patient has the Day 29 visit) and the Final Disposition Date for patients who have left the study before the data cutoff date. Deaths observed after the EOAP date will not be included in the analysis.

These derivations will be repeated with the data cutoff date defined as when the last patient has competed the study.

9.5.2. SAS Code for Efficacy Analyses

9.5.2.1. SAS Code for the Primary Efficacy Endpoint

The primary efficacy endpoint is survival (based on all-cause mortality) at Day 29 and will be compared between the 2 treatment groups using a 1-sided MH test of the difference in 2 proportions stratified by intubated or not intubated on Day 1. The basic SAS code for this is:

```
Proc freq data=adeff;
        tables intub*trt01p*surv / commonriskdiff (test=mh column=2);
run;
```

where intub is the randomization stratification factor, trt01p is the patient's randomized treatment group, and surv is the survival status (0=death, 1=survive).

For the primary efficacy analysis, missing data will be imputed using a multiple imputation approach assuming the data are MAR and using a logistic regression model. The basic SAS code for this is:

```
Proc mi data=adeff out=outmi seed=1306528 nimpute=pctmissing;
        class trt01p intub sex comorbid surv;
        var trt01p intub sex age comorbid surv;
        monotone logistic(surv = trt01p intub sex age comorbid / details);
run;
```

where intub is the randomization stratification factor, trt01p is the patient's randomized treatment group, age is patient age on Day 1, sex is the patient's sex, and comorbid is a dichotomous variable to indicate if the patient has at least one pre-existing condition at baseline

(diabetes mellitus, obesity, respiratory condition, and/or coronary artery disease) and surv is the survival status (0=death, 1=survive).

The imputed data sets will then be analyzed by imputation using the MH method described above and the PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters. The basic SAS code for this is:

```
Proc mianalyze data=commonpdifftests;
        modeleffects riskdifference;
        stderr stderr;
run;
```

A sensitivity analysis of the primary endpoint will use a delta-adjustment tipping point approach where the missing survival data for patients randomized to ravulizumab + BSC group are imputed by shifting the survival probability of the observed patients downward by delta. For each value of delta, the treatment effect will be determined, and the value of delta for which the nominal 1-sided p-value crosses 0.025 will be considered as the 'tipping point' in the sense that the positive conclusion drawn from the primary analysis is reversed. The basic SAS code for this is:

```
Proc mi data=adeff out=outmi seed=1306528 nimpute=pctmissing;
        class trt01p intub sex comorbid surv;
        var trt01p intub sex age comorbid surv;
        monotone logistic(surv = trt01p intub sex age comorbid / details);
        mnar adjust (surv(event='1') / shift=delta adjustobs=(trt01p='Ravulizumab + BSC'));
run;
```

where delta is the shift parameter for the imputed values of survival for patients randomized to ravulizumab + BSC group.

A sensitivity analysis of the primary endpoint will use a log-rank test including strata for the randomization stratification factor. The basic SAS code for this is:

```
proc lifetest data = adtte;
        time aval*cnsr(1);
        strata intub  / group=trt01p;
run;
```

where trt01p is a variable that indicates the patient's randomized treatment group, aval is a variable for the patient's time in analysis period at time of death or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event), intub is the randomization stratification factor.

The hazard ratio and risk reduction will be estimated from a stratified Cox proportional hazards model. The basic SAS code for this analysis is:

```
proc phreg data = adtte;
```

```
    class trt01p intub;
    model aval*cnsr(1) = trt01p;
    strata intub;
    hazardratio trt01p;
run;
```

A sensitivity analysis of the primary endpoint will use a proportional odds model. The basic SAS code for this analysis is:

```
proc logistic data=adtte;
    class trt01p intub / param=glm;
    model survcat=trt01p intub;
    oddsratio trt01p;
    lsmeans trt01p / diff;
run;
```

where intub is the randomization stratification factor, trt01p is the patient's randomized treatment group, and survcat is the survival category (1 = death, 2 = alive and in ICU, 3 = alive and discharged from ICU).

A sensitivity analysis of the primary endpoint will use a multivariate logistic regression analysis. The SAS macro LR (Ge, 2011) will be used for this analysis. The following macro call will be used:

```
%LR(data=adeff, var1=age, var2=trt01p sex region intub, p1=1, p2=4, resp=surv, ntrt=1);
```

A sensitivity analysis of the primary endpoint will use a multivariate Cox proportional hazards model. The basic SAS code for this analysis is:

```
proc phreg data = adtte;
    class trt01p sex region intub;
    model aval*cnsr(1) = trt01p age sex region intub;
    hazardratio trt01p;
run;
```

9.5.2.2. SAS Code for the Secondary/Exploratory Efficacy Endpoints

9.5.2.2.1. Analysis of Covariance (ANCOVA)

For some secondary endpoints, an ANCOVA model will be used to compare the 2 treatment groups. The basic SAS code for this analysis is given by:

```
proc glm data = adeff;
    class trt01p intub;
    model aval = trt01p age intub  / solution;
```

```
        lsmeans trt01p / cl diff stderr;
run;
```

where aval is the number of days.

Missing data will be imputed using a multiple imputation approach assuming the data are MAR and using a regression model. The basic SAS code for this is:

```
Proc mi data=adeff out=outmi seed=1306528 nimpute=pctmissing round=. . . . . 1 maximum=. . . . . 29 minimum=. . . . . 1;
        class trt01p intub sex comorbid;
        var trt01p intub sex age comorbid aval;
        monotone reg(aval = trt01p intub sex age comorbid / details);
run;
```

If an imputed value for a patient is less than the observed number of days until dropout, then the observed number will be used. The imputed data sets will then be analyzed by imputation using the ANCOVA method described above and the PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters. The basic SAS code for this is:

```
Proc mianalyze data=parameterestimates;
        modeleffects estimate;
        stderr stderr;
run;
```

A sensitivity analysis will use a delta-adjustment tipping point approach where the missing data for patients randomized to ravulizumab + BSC group are imputed by shifting the number of days for the observed patients downward by delta. For each value of delta, the treatment effect will be determined, and the value of delta for which the nominal 2-sided p-value crosses 0.05 will be considered as the 'tipping point' in the sense that the positive conclusion drawn from the primary analysis is reversed. The basic SAS code for this is:

```
Proc mi data=adeff out=outmi seed=1306528 nimpute=pctmissing round=. . . . . 1 maximum=. . . . . 29 minimum=. . . . . 1;
        class trt01p intub sex comorbid;
        var trt01p intub sex age comorbid aval;
        monotone reg(aval = trt01p intub sex age comorbid / details);
        mnar adjust (aval / shift=delta adjustobs=(trt01p='Ravulizumab + BSC'));
run;
```

where delta is the shift parameter for the imputed values of days for patients randomized to ravulizumab + BSC group.

9.5.2.2.2. Mixed Model for Repeated Measures (MMRM) Anlaysis

For some secondary endpoints, the analysis of changes over time involves an MMRM analysis. The basic SAS code this analysis is given by:

```
proc mixed data = adeff method = reml;
    class subjid avisit trt01p intub;
    model chg = trt01p avisit trt01p*avisit base age intub / ddfm = kr solution;
    repeated avisit / type=un subject=subjid;
    lsmeans trt01p*avisit / cl diff;
    where 1< avisitn;
run;
```

where trt01p is a variable that indicates the patient's randomized treatment group, subjid is the patient variable, avisit is the study day variable (0 representing Day 1), base is the value at baseline, age is patient age on Day 1, chg is the change from baseline at a particular visit, and intub is the randomization stratification factor.

The following illustrates the sensitivity analysis for missing data using the control-based approach, where for patients who discontinued treatment, responses after treatment discontinuation for both treatment groups will be imputed with multiple imputation methodology based on the response for BSC alone patients. Markov Chain Monte Carlo (MCMC) imputation method will be used to fill in the intermittent missing values under the assumption of MAR and generate a monotone pattern. Subsequently, multiple imputation will be performed at each visit sequentially, using a regression method obtained from BSC alone patients with terms for baseline score, the randomization stratification variable, and previous visits. After obtaining complete data sets for each visit, these complete data sets will be analyzed using MMRM analysis, and inferences from each complete data set will be combined to obtain an overall test statistic for treatment effect. The basic SAS code for this is:

```
Proc mi data=adefft out=monotone seed=1306528 nimpute=pctmissing;
        by trt01p;
        mcmc impute=monotone;
        var intubn base Day5 Day10 Day15 Day22 Day29;
run;
```

where trt01p is a variable that indicates the patient's randomized treatment group, base is the value at baseline, Day5 – Day29 are the changes from baseline at a particular visit, and intubn is a dummy variable for the randomization stratification factor.

The following is a partial SAS code for the BSC alone-based imputation at Day X:

```
Proc mi data=monotone out=outmi seed=1306539 nimpute=1;
        by _imputation_;
        class trt01p intub;
```

```
    var intub base Day5 Day10 Day15 Day22 Day29;
    monotone reg(Day X = intub base prev_DayX(s) / details);
    mnar model (Day X / modelobs=(trt01p='BSC'));
run;
```

The imputed data sets are then analyzed using MMRM by imputation as described above and the PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters. The basic SAS code for this is:

```
Proc mianalyze data=diffs;
    by avisit;
    modeleffects estimate;
    stderr stderr;
run;
```