# Statistical Analysis Plan

**A Randomized, Double-blind, Active-controlled Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)**
Test Drug: ABP 959

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|---|---|
| **Sponsor:** | Amgen Inc. |
| **Protocol No:** | 20150168 |
| **PRA Project Id:** | AMGAB959-ABP959 |
| **SAP Version Date:** | 26 January-2022 |
| **SAP Version No.:** | 2.0 Final |

## 1.0 Approvals

| | |
|---|---|
| **Sponsor** | |
| **Sponsor Name:** | Amgen Inc. |
| **Representative/ Title:** | [redacted] MS / Biostatistics Senior Manager |
| **Signature /Date:** | [redacted] Electronically signed by: [redacted] Reason: I am approving this document Date: Jan 28, 2022 09:17 EST |
| | |
| **Representative/ Title:** | [redacted] MD / Executive Medical Director |
| **Signature /Date:** | [redacted] MD Electronically signed by: [redacted] MD Reason: I am approving this document Date: Jan 27, 2022 14:43 PST |
| | |
| **PRA** | |
| **Project Manager/Title:** | [redacted] / Project Director |
| **Signature /Date:** | [redacted] Electronically signed by: [redacted] Reason: I am approving this document Date: Jan 28, 2022 10:40 EST |
| **Biostatistician / Title (Owner):** | [redacted] MS, MD / Senior Principal Biostatistician |
| **Signature /Date:** | [redacted] Electronically signed by: [redacted] Reason: I am approving this document Date: Jan 27, 2022 19:18 EST |





NCT Number: NCT03818607
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov




## Table of Contents

## 2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Amgen Inc. Protocol 20150168 dated 05 March 2020, Version 4.0.

## 3.0 Scope

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse event handling, laboratory data, pharmacokinetics, and immunogenicity

## 4.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 05 March 2020, Version 4.0 and CRF dated 09 October 2019, Version 3.0. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP will be finalized and approved prior to the database lock and unblinding for the primary analysis of the study (which is the primary analysis for the parallel comparison of the study).

### 4.1 Change from Protocol

The protocol states that the disposition summaries will include a summary of the number and percentage of subjects on study at each visit. This summary is not included in the SAP.

## 5.0 Study Objectives

### 5.1 Primary Objective

The primary objective for this study is to evaluate the efficacy of ABP 959 compared with that of eculizumab based on control of intravascular hemolysis.

### 5.2 Secondary Objectives

The secondary objective is to assess the safety, pharmacokinetics (PK), and immunogenicity of ABP 959 compared with that of eculizumab.

## 6.0 Study Design

This is a randomized, double-blind, active-controlled, 2-period crossover study in adult subjects with paroxysmal nocturnal hemoglobinuria (PNH).

Approximately 40 subjects will be randomized (1:1) to 1 of the 2 treatment sequences, either treatment T followed by treatment R (TR) or treatment R followed by treatment T (RT). Treatments will be administered over 2 periods. Period 1 will be 52 weeks in duration; Period 2 will start at week 53, with a crossover in treatment, and will be 26 weeks in duration. Randomization will occur within 8 days before the first dose of

IP administration and will be stratified by red blood cell (RBC) transfusion received within the last 12 months before randomization (yes vs. no).

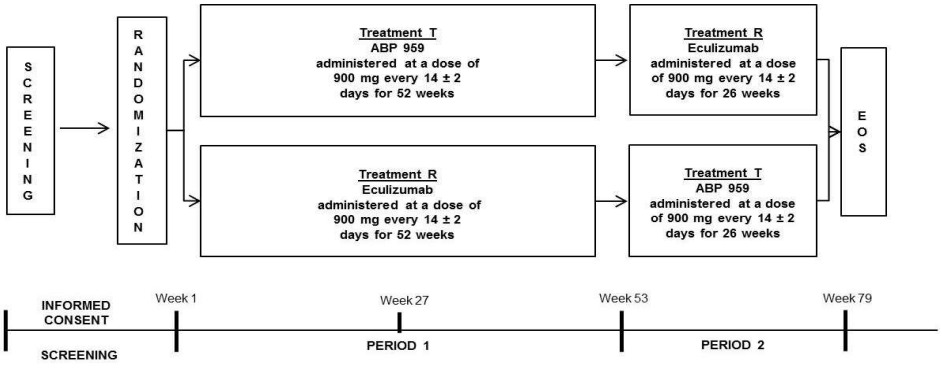
The treatment sequences will be as shown in Figure 1:

Sequence TR: ABP 959 for 52 weeks in Period 1 followed by eculizumab for 26 weeks in Period 2, each at a dose of 900 mg administered as an intravenous (IV) infusion every 14 ± 2 days

Sequence RT: Eculizumab for 52 weeks in Period 1 followed by ABP 959 for 26 weeks in Period 2, each at a dose of 900 mg administered as an IV infusion every 14 ± 2 days.

Subjects will remain on the treatment phase until 14 days after the last planned dose of IP in Period 2 (i.e, at week 79).

**Figure 1 Study Diagram**




EOS – End of Study

The primary analysis for the parallel comparison of the study will be conducted when all subjects have completed or have had the chance to complete the week 53 visit or have completed the EOS visit prior to week 53. After the database for the primary analysis for the parallel comparison has been locked, identified personnel from Amgen and PRA will be unblinded to the study randomization schedule and to the aggregate results of the analyses. Members of the study operation and data management team will remain blinded to the individual randomization schedule and to the aggregated results unless otherwise identified. Subjects and investigators will remain blinded throughout the study. Details on how to disseminate data and results of the primary analysis for the parallel comparison while maintaining integrity of the ongoing blinded study will be documented in a data dissemination plan. The primary analysis for the crossover comparison of the study will be conducted when all subjects have completed the EOS visit.

## 6.1 Sample Size Considerations

The sample size of 40 was chosen to provide approximately 87% power to demonstrate noninferiority (NI) at a 1-sided significance level of 0.025 on the primary endpoint of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, an NI margin of 2.873, and a 10% dropout rate. The 2.873 margin is considered appropriate to rule out a potential clinically relevant difference, as it essentially equates to a mean LDH in the ABP 959 arm of less than 1.5-fold of the mean LDH in the eculizumab arm.

The sample size of 40 will also provide greater than 95% power to demonstrate similarity at a 2-sided significance level of 0.05 on the primary endpoint of time-adjusted area under the effect curve (AUEC) of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79 for the crossover

comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a similarity margin of (0.77, 1.30), and a 10% dropout rate.

Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed. If the aggregated intra-subject CV of AUEC is greater than 44%, additional subjects will be enrolled if feasible. If the aggregated inter-subject CV of LDH is greater than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79. Refer to section 10 for details on the interim analysis.

### 6.2 Randomization

Subjects will be randomized 1:1 to receive ABP 959 and eculizumab in 1 of 2 treatment sequences in a 2-period crossover design. Randomization will be performed using an interactive voice/web randomization system (IXRS). Randomization will occur within 8 days before the first dose of investigational product (IP) administration and will be stratified by RBC transfusion received within the last 12 months before randomization (yes vs. no). The randomization schedule will be prepared by a statistician not otherwise involved in the conduct of the study.

## 7.0 Study Variables

### 7.1 Primary Variables

The primary efficacy endpoint for the parallel comparison is hemolysis as measured by LDH at week 27. The primary endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, week 39 to week 53, and from week 65 to week 79.

### 7.2 Secondary Variables

The secondary efficacy endpoints are:

- Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79.
- Crossover comparison of hemolysis as measured by LDH at week 53 and week 79
- Lactate dehydrogenase-time profile
- Red blood cell transfusion

The secondary PK endpoints are:

- Total and unbound pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to week 15, and trough PK.

### 7.3 Safety Variables

The safety endpoints include the following:

- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Treatment-emergent events of interest
- Incidence of antidrug antibodies

### 7.4 Predetermined Covariates and Prognostic Factors

Unless stated otherwise, the stratification factor RBC transfusion received within the last 12 months before randomization (yes vs. no) will be adjusted as a covariate in the model, will be used as a stratification variable in stratified analysis, and will be used to examine efficacy in subgroups.

Analyses that are intended to evaluate the treatment effect and include the stratification variable as a covariate in the model will be based on the eCRF stratification value, regardless of the subject's IXRS stratification value, to provide unbiased estimates of the effects of treatment and stratification variable without loss of efficiency (Ke et al, 2017).

In addition, the following covariates may be used for further exploration in subgroups or as covariates:

- Sex
- Age group (≤ 54 years vs. > 54 years)
- Packed RBC units received within 12 months prior to randomization

## 8.0 Definitions

### 8.1 General

**Actual Treatment Received**

The actual dose for each period will be defined according to the majority of actual doses of the IP received, regardless of what the subject was randomized to. The actual treatment sequence received for the entire study will be based on the combination of the actual treatment received for each period. In cases where a subject is not treated in period 2, the actual treatment sequence received for the entire study will be determined by the actual treatment of period 1 and the intended treatment of the second period per protocol. The actual treatment sequence for the study will be unplanned if the actual treatment is the same for both periods.

**Period 1**

Period 1 is defined as the date of first dose of study IP through first dose of the crossover treatment. If subjects discontinue before receiving the cross-over treatment, the end of Period 1 is end of study.

**Period 2**

Period 2 is defined as the date of first IP dose of the crossover treatment through the end of study or data cutoff date, whichever is earlier.

**Change From Baseline**

Change from baseline is defined as (value at post-baseline visit – value at study baseline).

**Completed Period 1 IP Dosing**

A subject is considered to have completed Period 1 IP dosing if they have received a dose of IP between study day 349 (targeted Week 51 dosing date – 2 day window) and the end date of Period 1.

**Completed Study**

A subject is considered to have completed the study if they indicated they completed study on the EOS eCRF at the Week 79 visit.

**Concomitant Medication**

Concomitant medications are defined as any medications ongoing at the start of IP treatment or with a start date on or after the first dose date.

**Duration on Eculizumab Prior to Enrollment**

The duration of eculizumab prior to enrollment is the number of months from the eculizumab start date on the PNH history eCRF to the date of randomization, which will be derived based on the table below. No imputation will be done for missing eculizumab start date (Year, Month, Day), but to avoid a duration of zero, 1 month may be added.

**Table 1. Calculation for Duration on Eculizumab Prior to Enrollment**

| Observed Portion | Missing Portion | Formula to Calculate Duration |
|---|---|---|
| Year, Month, Day | | (Date of Randomization – Eculizumab Start Date + 1)*12/365.25 |
| Year, Month | Day | [Year (Date of Randomization) – Year (Eculizumab Start Date)]*12 + [Month (Date of Randomization) – Month (Eculizumab Start Date)]* |
| Year | Month, Day | [Year (Date of Randomization) – Year (Eculizumab Start Date)]*12* |

*If the duration equals 0, add 1 month.

**Duration of IP exposure**

Overall duration of IP exposure in weeks will be defined as (minimum of ( end of study [EOS] date, cutoff date) – date of first dose of IP + 1) / 7. Duration of IP exposure in Period 1 will be defined as (Period 1 end date – Period 1 start date + 1) / 7. Duration of IP exposure in Period 2 will be defined as (Period 2 end date – Period 2 start date + 1) / 7.

**End of Study Date**

The end of study (EOS) date for a subject is the EOS date from the EOS eCRF.

**Study Baseline**

The study baseline is defined as the last non-missing assessment taken prior to the first dose of IP. In cases where baseline assessments are taken on the same day as IP, and either no times are reported, or the IP and assessment times are the same, it will be assumed that these assessments are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline is defined as the last non-missing assessment prior to or on the date of randomization.

**Days On-study**

Study Start Day (Day 1) is defined as the first day that IP is administered to the subject.

Days On-study is defined as the number of days from Study Start Day (Day 1).

Days before Study Start Day (Day 1) are computed as follows:

- Days Before Study Start Day = (Date of Interest – Date of Study Start Day 1)

Days On-study are computed as follows:

- Days On-study = (Date of Interest – Date of Study Start Day 1) + 1:

Therefore, the day prior to Study Day 1 is -1.

For randomized subjects who do not receive any study IP, Day 1 is defined as the randomization date.

**Study Investigational Product**

Study IP is referred to as ABP 959 or eculizumab.

**Study Randomization**

Study randomization is defined as when the subject receives a random treatment allocation via the IXRS system.

**Study Analysis Visit**

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit.

In general, if more than one actual visit (including unscheduled visits) falls within the same defined window (e.g., within same defined interval dates), the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

**Time Since Original Diagnosis**

The time since original diagnosis is the number of months from the date of original diagnosis of PNH to the date of randomization, which will be derived based on the table below. No imputation will be done for missing disease diagnosis date (Year, Month, Day), but to avoid a disease duration of zero, 1 month may be added.

**Table 2. Calculation for Time Since Original Diagnosis**

| Observed Portion | Missing Portion | Formula to Calculate Duration |
|---|---|---|
| Year, Month, Day | | (Date of Randomization – Date of Diagnosis + 1)*12/365.25 |
| Year, Month | Day | [Year (Date of Randomization) – Year (Date of Diagnosis)]*12 + [Month (Date of Randomization) – Month (Date of Diagnosis)]* |
| Year | Month, Day | [Year (Date of Randomization) – Year (Date of Diagnosis)]*12* |

*If the duration equals 0, add 1 month.

**Age at PNH Diagnosis**

The age at PNH diagnosis is the number of years from the date of birth to the date of diagnosis of PNH, which will be derived based on the table below. No imputation will be done for missing disease diagnosis date (Year, Month, Day).

**Table 3. Calculation for Age at PNH Diagnosis**

| Observed Portion | Missing Portion | Formula to Calculate Duration |
|---|---|---|
| Year, Month, Day | | (Date of Diagnosis – Date of Birth + 1)/365.25 |
| Year, Month | Day | [Year (Date of Diagnosis) – Year (Date of Birth)] + [Month (Date of Diagnosis) – Month (Date of Birth)]/12 |
| Year | Month, Day | [Year (Date of Diagnosis) – Year (Date of Birth)] |

## 8.2 Efficacy

**Area Under the Effect Curve of LDH**

The area under the effect curve (AUEC) of LDH will be calculated for the following time periods:

- Week 13 to week 27 (study day 78 to study day 189), week 39 to week 53 (study day 260 to study day 371, only using results prior to first IP dose date in Period 2)
- Week 65 to week 79 (study day 442 to study day 553)

AUEC of LDH for each subject will be calculated by time period using all LDH results in the corresponding time periods, except those determined to be elevated due to confounding events by the LDH review committee (see section 9.0). The start and end dates for the AUEC for each time period will be the dates of the first and last LDH results, respectively, within the given 14-week time period. The AUEC for a given time period will only be calculated if there are at least 3 LDH measurements within the time period. The AUEC for each time interval t1 to t2 will be calculated using the following equation:

$AUEC(t1\text{-}t2) = \delta(t1\text{-}t2) \times (LDH1+LDH2)/2$

where LDH1 and LDH2 are the LDH results at t1 and t2 respectively (t1 and t2 are days from first dose of IP to actual LDH sample times), and $\delta(t1\text{-}t2) = (t2\text{-}t1)$ calculated in days.

The AUEC over the entire time period will be obtained by summing the AUEC calculated for each time interval in the time period.

**Time-adjusted AUEC of LDH**

The time-adjusted AUEC of LDH for each individual subject for each time period will be calculated by dividing the AUEC for the given time period by the total duration of observed LDH data (in weeks) within the 14-week assessment period. For example, the total duration for the week 39 to week 53 time period will be calculated as the (date of latest LDH assessment between study day 260 and study day 371) – (date of earliest LDH assessment between study day 260 and study day 371). The result will be divided by 7 (days) to express AUEC per week.

## 8.3 Safety

**Event of Interest (EOI)**

An EOI is defined as a noteworthy treatment-emergent adverse event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences (CIOMS) VI, 2005). The EOIs for ABP 959/eculizumab are defined below and analyzed from the clinical database:

| EOI | Name | Category | Scope | Details |
|---|---|---|---|---|
| Serious infections<br>(Meningococcus, aspergillus, and other serious infections/sepsis) | Infections and Infestations | SOC | Broad | all SAEs and AEs with toxicity of grade 3 or higher |
| Infusion reactions | Hypersensitivity<br>Infusion reactions | Standard MedDRA Query (SMQ)<br>Amgen MedDRA Query | Broad<br>Broad | all events that occur with start date same as, or one day after, IP administration start date |

**Subject Incidence Rate**

For adverse event summaries, subject incidence rate for a given event is defined as the number of subjects with at least 1 reported occurrence of the event divided by the number of subjects that received the given treatment. For subjects with multiple occurrences of the same event while on the given treatment, the event will only be counted once per subject.

**Treatment-emergent Adverse Event**

A treatment-emergent AE (TEAE) is defined as an AE that begins or increases in severity or frequency on or after the date of first IP and up to the EOS visit. If the AE starts on the same day as the first dose of IP then the flag indicating whether the AE started prior to the first dose on the adverse event CRF page will be used. In the event that the flag is missing, the AE that starts on the same day as the first dose of IP will be considered a TEAE. If the AE starts on the same day as the EOS visit, the AE will be considered as a TEAE.

A TEAE will be assigned to Period 1 if the start date was on or after the first IP dose date and before the Period 1 end date. If the AE starts on the same day as the first dose of IP then the flag indicating whether the AE started prior to the first dose on the AE CRF page will be used. A TEAE will be assigned to Period 2 if the start date was after the first IP dose date in Period 2. If the AE started on the first IP dose date in Period 2 (week 53 visit) and the checkbox on the week 53 AE CRF page indicates the TEAE started before the start of infusion, the TEAE will be assigned to Period 1. If the week 53 AE CRF page indicates the TEAE started after the start of infusion, the TEAE will be assigned to Period 2.

A TEAE will be assigned to the 14-week assessment period between week 13 to week 27 if the start date was on or after study day 78 and on or before the study day 189. A TEAE will be assigned to the final 14 weeks of Period 1 (i.e. weeks 39 to 53) if the start date was on or after study day 260 and on or before the minimum of study day 371 and Period 1 end date. A TEAE will be assigned to the final 14 weeks of Period 2 (i.e. weeks 65 to 79) if the start date was on or after study day 442 and on or before study day 553. These windows are defined to be consistent with the efficacy evaluation windows.

**Treatment-emergent Adverse Event Leading to Discontinuation of IP**

AEs leading to discontinuation of IP are those with an action taken with Investigational Medicinal Product of “dose discontinued”. If an AE leads to multiple actions taken with IP, only the last action will be captured on the eCRF.

**Treatment-emergent Adverse Event Leading to Study Discontinuation**

AEs leading to discontinuation from the study are those with another action taken of “discontinued from study”.

**Presumed COVID-19 Start Date**

The presumed start date of COVID-19 is the date of the earliest COVID-19 Standardized MedDRA Query (SMQ) defined preferred term.

## 8.4 Pharmacokinetic

**Area Under the Curve (week 13 to week 15)**

The area under the curve (AUC) from week 13 to week 15 will be calculated using both the total and unbound (concentrations at the following 4 time points: week 13 pre-dose, week 13 post-dose, week 14, week 15 pre-dose. The AUC for each time interval t1 to t2 will be calculated using the following equation:

$AUC(t1\text{-}t2) = \delta(t1\text{-}t2) \times (C1+C2)/2$

where C1 and C2 are the concentrations at t1 and t2 respectively (t1 and t2 are days from first dose of IP to actual PK sampling times), and $\delta(t1\text{-}t2) = (t2\text{-}t1)$ calculated in days (precision will be in hours based on actual sampling time).

The AUC from week 13 to week 15 will be obtained by summing the AUC calculated for each of the time intervals defined by the available PK concentration values between week 13 and week 15. AUC from week 13 to week 15 will be calculated for subjects if (1) week 13 pre-dose and week 13 post-dose PK concentrations are available and (2) week 14 PK concentration or week 15 pre-dose PK concentration is available. In the calculation of AUC, concentration values below the limit of quantification (BLQ) will be substituted with zero.

**Study Analysis Visit for PK Summaries**

For the pre-dose PK analysis visits, the actual visit date is mapped to the study analysis visit using the analysis visit window that is defined as target day with +6/-7 days window, and the target day is defined as study week visit x 7 – 6.

Predose PK samples recorded as collected post-dose will be excluded. In instances where the dose start and/or stop times are missing, the pre-infusion or post-infusion checkbox from the PK CRF will be used if available.

For the calculation of AUC from week 13 to week 15, the week 13 visit must also fall in the window of study day 78 to 91. The week 13 post-infusion PK will be excluded if the collection timing does not occur at or after the prior dose stop time.

## 8.5 Full Analysis Set

The full analysis set (FAS) will consist of all randomized subjects, with treatment as the randomized treatment sequence, regardless of treatment actually received.

## 8.6 Modified Full Analysis Set

The Modified Full Analysis Set (mFAS) will consist of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within at least one of the following 14-week assessment periods: week 13 to week 27, week 39 to week 53, and week 65 to week 79, according to treatment per the randomized sequence regardless of treatment actually received. The LDH-time profile within weeks 13 to 27 is considered evaluable if there are at least 3 LDH values between study day 78 and study day 189. The LDH-time profile within weeks 39 to 53 is considered evaluable if there are at least 3 LDH values between study day 260 and study day 371. The LDH-time profile within weeks 65 to 79 is considered evaluable if there are at least 3 LDH values between study day 442 and study day 553.

## 8.7 Per Protocol Sets

### 8.7.1 Per-protocol Analysis Set for the Primary Endpoint of Lactate Dehydrogenase at Week 27 for the Parallel Comparison

The per-protocol analysis set for the primary endpoint of LDH at week 27 for the parallel comparison (PPP) will be a subset of the FAS, which includes subjects who did not experience an important protocol deviation between week 13 and week 27 (study day 78 to 189) that affects their primary efficacy evaluation for the parallel comparison. The protocol deviations that affect primary efficacy evaluation will be determined based on a blinded data review prior to database snapshot for the primary analysis of week 27 LDH for the parallel comparison. Analyses for the PPP analysis set will be based on actual treatment received.

### 8.7.2 Per-protocol Analysis Set for the Primary Endpoint of AUEC for the Crossover Comparison

The per-protocol analysis set for the primary endpoint of time-adjusted AUEC for the crossover comparison (PPC) will be a subset of the mFAS, which includes subjects who did not experience an important protocol deviation during week 13 to week 27 (study day 78 to 189), week 39 to week 53 (study day 260 to 371) and week 65 to week 79 (study day 442 to 553) that affects their primary efficacy evaluation for the crossover comparison. The protocol deviations that affect primary efficacy evaluation will be determined based on a

blinded data review prior to database lock for the crossover comparison. Analyses for the PPC analysis set will be based on actual treatment received.

### 8.8 Safety Analysis Set

The safety analysis set will consist of all treated subjects with treatment assignment based on actual treatment received.

### 8.9 Pharmacokinetic Analysis Sets

#### 8.9.1 Pharmacokinetic Concentration Analysis Set

The Pharmacokinetics Concentration Analysis Set will be defined as the subset of subjects in the safety analysis set who have at least 1 serum concentration (including results below the quantifiable limit) of ABP 959 or eculizumab. Analyses for the PK Concentration Analysis Set will be based on actual treatment received.

#### 8.9.2 Pharmacokinetics Parameter Analysis Set

The Pharmacokinetics Parameter Analysis will be defined as a subset of subjects in the safety analysis set who have an evaluable ABP 959 or eculizumab serum concentration time profile from week 13 to week 15. Subjects to be excluded from the PK Parameter Analysis Set will be determined based on a blinded data review prior to the database lock for the primary analysis if one of the evaluability criteria is not met: receiving the full scheduled dose (900 mg) at week 13, having 4 PK samples with valid results between week 13 and week 15, not receiving an additional dose between weeks 13 and 15 (e.g. due to a break through event), and a valid PK sample collected in the week 15 analysis visit window if the week 15 dose was withheld. Analyses for the PK parameter analysis set will be based on actual treatment received.

## 9.0 LDH Review

The LDH Review Committee will review blinded data and identify LDH values impacted by confounding events (e.g. acute infection, or trauma including surgery), unrelated to efficacy of IP that trigger dose adjustment for exclusion in the primary analysis of LDH and AUEC of LDH. Details on the LDH review committee and related processes can be found in the LDH Review Charter. The final LDH review results (one record for each LDH result with a flag indicating if the result should be excluded from analysis) will be used in the programming of the LDH-related analyses. Unless otherwise specified, LDH results flagged to be excluded will be excluded from all derivations and analysis models.

## 10.0 Interim Analyses

Blinded assessments of the inter-subject coefficient of variation (CV) of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed.

The first blinded interim check of CV will take place prior to the end of enrollment. If the aggregated intra-subject CV of AUEC is greater than 44%, additional subjects will be enrolled if feasible. The AUEC will be calculated for week 1 to week 15 and for week 15 to week 29 (if available) for each subject. All non-missing AUECs for the two time intervals will be included in the calculation of the aggregated intra-subject CV.

The second blinded interim check of CV will take place when approximately all subjects complete their week 27 visit. If the aggregated inter-subject CV of LDH is greater than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

An independent data monitoring committee (DMC) will perform safety reviews of unblinded data approximately every 6 months (or as determined by the DMC) throughout the study. Details regarding the DMC are provided in the DMC Charter. In DMC meeting #4 and future DMC meetings, a table and a listing of SAEs occurring on or after the start date of COVID-19 infection were added for review. Adverse event

data collected on the adverse events eCRF is used to identify the subset of subjects diagnosed with COVID-19 using the search strategy of the COVID-19 SMQ.

# 11.0 Statistical Methods

The data cut for the primary analysis for the parallel comparison will be performed when all subjects have completed the Week 53 visit or had the EOS visit prior to Week 53. All data collected by the time of the data cut will be included in this analysis. The primary analysis for the crossover comparison (which is also considered the final analysis for the study) will be performed when all subjects have completed the EOS visit.

All statistical analyses will be performed using SAS® Version 9.4 or higher.

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. For continuous outcomes, the descriptive statistics include number of subjects with observations (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. The mean, median, Q1, and Q3, will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data. Geometric mean will have 1 decimal place more than the raw data. CV(%) and Geometric CV(%) will have 1 decimal place. Geometric mean ratio and associated CI will have 4 decimal places. Confidence intervals (CIs) will be provided when specified.

Categorical outcomes will be summarized by number and percent of subjects falling into each category. Confidence intervals (CIs) will be provided when specified. Percentages will be rounded to one decimal place.

## 11.1 Subject Disposition

The following information will be summarized for subject disposition and accountability:

- Subject disposition (including number of subjects who were treated with IP in each period and overall, completed each period IP dosing, discontinued IP during each period with reason for discontinuation, discontinued IP during each period with COVID-19 related reasons for discontinuation, completed the study and discontinued the study early with reason for discontinuation, discontinued the study early with COVID-19 related reason for discontinuation
- Randomization by stratification factor (RBC transfusion within 12 months before randomization)
- Number of randomized subjects by country and site
- Summaries of analysis populations with reason for exclusion
- Randomization list of subjects and their actual versus randomized treatment sequence (for the FAS)
- Listing of subject analysis sets

## 11.2 Protocol Deviations

Protocol deviations (PD) data will be entered into the Clinical Trials Management System (CTMS). The study team will conduct on-going reviews of the PD data from CTMS and the resulting set of subjects to be included in the PPP and PPC analysis sets throughout the study, adjusting the PD criteria as seems appropriate. The subjects to be included in the PPP analysis set will be finalized prior to the database lock for the primary analysis of the parallel comparison. The subjects to be included in the PPC analysis set will be finalized prior to database lock.

Based on the PD data entered CTMS, a summary of important PDs (IPDs) will be tabulated using number and percentage of subjects with important PD by deviation type and randomized treatment sequence and whether the IPDs are related to COVID-19. A summary table of deviations of the inclusion/exclusion criteria will also be tabulated. A listing of subjects with important PDs and deviations of the inclusion/exclusion

criteria will be provided (with a flag indicating whether the deviation leads to exclusion from the PPP or PPC analysis sets). In addition, COVID-19 related PDs will be tabulated using number and percentage of subjects by deviation type and randomized treatment sequence, and a listing of COVID-19 related PDs will be provided.

## 11.3 Treatments

All analyses in this section will be performed on the safety analysis set based on a subject's actual treatment received.

### 11.3.1 Extent of Study Drug Exposure

Study drug exposure will be summarized separately for Period 1, Period 2 and overall. Summary statistics will be provided for the total number of IP doses administered, cumulative dose, and duration of IP exposure. The number of subjects with at least one dose interruption and the number of subjects with at least one dose delay/not administered as well as the reasons will be tabulated by study period. Separate rows show the frequency related to COVID-19 reasons. The number of subjects with at least one increase in dose and/or frequency will also be summarized by study period.

A listing of the lot number(s) for IP for each subject and a listing of unique manufacturing lot numbers will be provided.

### 11.3.2 Concomitant Medications

Concomitant medications include all medications and therapies during the study except for planned IP administration. Concomitant medications will be coded by the current version of the World Health Organization Drug Dictionary (WHO-DD). The numbers and percentages of subjects will be summarized by preferred term and actual treatment group for Period 1, Period 2, and overall for the study. Medications with a stop date before study day 1 will not be summarized. For subjects who return to eculizumab or other PNH treatment after EOS, their PNH medications with a start date on or after the EOS date will be excluded from the summaries. For subjects who will not receive eculizumab or other PNH treatment after EOS, medications received on the same as the EOS visit will be included in the summaries.

## 11.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for FAS, mFAS, PPP, PPC, and safety analysis sets: age (in years, at time of signing informed consent), age group (≤54 years versus >54 years), age at time of PNH diagnosis (in years), race, sex, ethnicity, height, and weight. Study baseline characteristics including time since original diagnosis (months), time since start of eculizumab (months), and baseline LDH and hemoglobin values will also be summarized. The number and percentage of subjects having RBC transfusion within 12 months before randomization (as entered on the eCRF) will be tabulated. A summary of the number of packed RBC units received within 12 months before randomization will also be included.

Medical conditions at screening will be summarized by preferred term (PT) and primary system organ class (SOC) separately by status (unresolved versus resolved) for the FAS.

## 11.5 Efficacy Analyses

### 11.5.1 Primary Endpoints

#### 11.5.1.1 Parallel Comparison

##### 11.5.1.1.1 Primary Analysis

The primary endpoint for the parallel comparison is hemolysis, as measured by LDH at week 27. The primary analysis for the parallel comparison will be conducted on the FAS. It will be analyzed when all subjects have completed or have had the chance to complete their week 53 visits.

The clinical similarity of the week 27 LDH between treatments will be assessed by comparing the 1-sided 97.5% upper confidence interval (CI) limit for the GMR of the LDH at week 27 between ABP 959 and eculizumab treatment with a NI margin of 2.873. The point estimate of the mean difference in the log-transformed LDH and the corresponding 1-sided 97.5% upper CI limit will be estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable) and treatment by time interaction term as fixed effects, and subject as a random effect. An unstructured covariance structure will be used. If convergence criteria is not met, then use compound symmetry option. The point estimate and the upper CI limit for the GMR will then be calculated by transforming back to the original scale. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 (i.e. study day 78 to study day 189) will be included in the mixed model. LDH values impacted by confounding events unrelated to efficacy of IP, as determined by the LDH review committee, will be excluded from the analysis (see section 9.0 for more details).

#### 11.5.1.1.2 Secondary Analysis

To assess the robustness of the primary parallel comparison, the parallel comparison will also be conducted in the PPP population.

The parallel comparison of LDH at week 27 will also be examined in subgroups by the levels of the stratification factor per the eCRF value and levels of baseline covariates, including age (≤ 54 vs > 54 years old) and gender. The statistical model for the analysis of baseline covariate subgroups will not include the stratification factor as a covariate.

### 11.5.1.2 Crossover Comparison

#### 11.5.1.2.1 Primary Analysis

The primary endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, week 39 to week 53, and from week 65 to week 79. The primary analysis for the crossover comparison will be conducted on the mFAS. See section 8.4 for details on derivation of AUEC of LDH. LDH values that are determined to be elevated due to confounding events by the LDH review committee will be excluded.

The clinical similarity of the AUEC between treatments will be assessed by comparing the 2-sided 90% CI for the GMR of the time-adjusted AUEC of LDH (week 13 to week 27, week 39 to week 53, and week 65 to week 79) between ABP 959 and eculizumab treatment with a similarity margin of (0.77, 1.30). The point estimate of the mean difference in the log-transformed time-adjusted AUEC and the corresponding 2-sided 90% CI will be calculated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect. An unstructured covariance structure will be used. If convergence criteria is not met, then compound symmetry option will be used The point estimate and CI for the GMR will then be calculated by transforming back to the original scale.

#### 11.5.1.2.2 Secondary Analysis

To assess the robustness of the primary crossover comparison, the crossover comparison will also be conducted in the PPC population.

The crossover comparison AUEC of LDH will also be examined in subgroups by the levels of the stratification factor per the eCRF value and levels of baseline covariates, including age (≤ 54 vs > 54 years old) and gender.

### 11.5.1.3 Methods for Handling Dropouts and Missing Data

Missing LDH values will not be imputed.

### 11.5.1.4 Multiplicity

The primary analysis for the parallel comparison and the primary analysis for the crossover comparison are for separate regulatory agencies; therefore, no adjustment for multiplicity is needed.

#### 11.5.1.5 Pooling of Sites

All sites will be pooled together for all analyses.

### 11.5.2 Secondary Endpoints

#### 11.5.2.1 Secondary Efficacy Lab Endpoints

Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes (%) will be summarized descriptively at week 27, week 39, week 53, week 65, and week 79 in the FAS. For continuous endpoints, the values and the change from baseline will be summarized by treatment at each of the specified visits. For categorical endpoints, the number and percent of subjects falling into each category will be presented by treatment. Analysis visit windows for the relevant time points will be defined as below:

| Study Analysis Visit | Target Day | Range of Study Day | Interval (days) |
|---|---|---|---|
| Week 27 | 183 | 176 – 189 | 14 |
| Week 39 | 267 | 260 – 273 | 14 |
| Week 53 | 365 | 358 – 371 | 14 |
| Week 65 | 449 | 442 – 455 | 14 |
| Week 79 | 547 | 540 – 553 | 14 |

A mean (+/- SD) plot of total complement at each analysis visit (target day with +6/-7 days window) will be presented in the FAS. In general, the target day is defined as (study week visit x 7 – 6).

#### 11.5.2.2 Crossover Comparison of LDH at Week 53 and Week 79

The secondary endpoint of the crossover comparison of LDH at week 53 and week 79 will be evaluated descriptively in the FAS. The point estimate of the mean difference in the log-transformed LDH between treatments and the corresponding 1-sided 97.5% upper CI limit will be calculated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects and subject as a random effect..The point estimate and 1-sided 97.5% upper CI limit for the GMR will then be calculated by transforming back to the original scale. LDH values impacted by confounding events unrelated to efficacy of IP, as determined by the LDH review committee, will be excluded from the analysis (see section 9.0 for more details).

The week 53 LDH result is the last LDH result prior to the first dose of IP in Period 2. The week 79 LDH result is the last LDH result on study. Subjects missing both the week 53 and week 79 LDH results will be excluded from this analysis.

#### 11.5.2.3 Lactate Dehydrogenase-time Profile

A descriptive summary of LDH at each time point through the EOS visit will be presented for the FAS. Individual and mean LDH with one standard deviation at each analysis visit (target day with +6/-7 days window) through the EOS visit will also be presented graphically. LDH values impacted by confounding events unrelated to efficacy of IP, as determined by the LDH review committee, will be excluded from the analysis (see section 9.0 for more details).

#### 11.5.2.4 Red Blood Cell Transfusion

Summary statistics for the number of packed RBC units transfused per month will be presented separately for Period 1 and Period 2. For each subject, the number of packed RBC units transfused per month for Period 1 is calculated as the total number of units transfused from week 13 to week 53 (study day 78 to Period 1 end date) divided by the time in months from study day 78 to Period 1 end date. For each subject, the number of packed RBC units transfused per month for Period 2 is calculated as the total number of units transfused from week 65 (study day 442) to Period 2 end date divided by the time in months from study day 442 to the Period 2 end date.

## 11.6 Pharmacokinetics

PK concentrations will be reviewed by a PK scientist and some concentrations may be flagged as not evaluable prior to unblinding for the analysis.

The point estimate and 90% CI for geometric mean ratio (GMR) of ABP 959 to eculizumab for total and unbound PK AUC from week 13 to week 15 in the PK parameter analysis set will be estimated using an ANOVA. The ratio of the geometric means for the treatment comparison will be obtained by exponentiating the difference of the means on the log scale. The 90% CI will be obtained by back-transforming the CI for the difference between the means on the log scale.

Total and unbound serum ABP 959 and eculizumab trough concentrations will be summarized descriptively in the PK concentration analysis set by visit through the EOS visit.

A boxplot of the total and unbound trough serum concentrations at each pre-dose PK visit will be presented for the PK concentration analysis set. Mean serum concentrations from week 13 to week 15 will be plotted for subjects in the PK parameter analysis set. A listing of both total and unbound PK concentration values from week 13 to week 15 along with the AUC will also be presented for subjects in the PK parameter analysis set.

Subjects whose PK AUC between week 13 and week 15 are derived with either week 14 PK concentration or week 15 pre-dose PK concentration missing (and hence are not in the PK parameter analysis set) will be flagged in the dataset.

## 11.7 Safety Analyses

All safety analyses will be performed on the safety analysis set based on a subject's actual treatment received.

### 11.7.1 Adverse Events

All reported treatment emergent adverse events (TEAE) will be summarized. Each reported TEAE will be coded to the appropriate SOC and PT according to the most current version of Medical Dictionary for Regulatory Activities (MedDRA), and the severity of each TEAE will be graded per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.

Subject incidence of the following TEAEs will be tabulated by treatment for the entire study through the EOS visit, for period 1, for period 2, and for each of the 14 week assessment periods (i.e. week 13 to week 27, weeks 39 to 53, and weeks 65 to 79):

- Overall summary of treatment-emergent AEs
- TEAEs by PT
- TEAEs by SOC, PT, and maximum CTCAE grade
- TEAEs by SOC and PT
- Grade ≥ 3 TEAEs by PT
- Treatment-emergent AEs leading to discontinuation from study/IP by PT
- Overall summary of treatment-emergent EOIs

Subject incidence of the following TEAEs will be tabulated by treatment for the entire study through the EOS visit, for period 1, and for period 2:

- Treatment Emergent COVID-19 AEs by PT
- Each treatment-emergent EOI category by PT
- Each treatment-emergent EOI category by PT and maximum CTCAE grade.

An overall summary of treatment-emergent AEs will also be provided by treatment sequence for the study through the EOS visit, in which subjects experiencing events in both treatment periods, subjects experiencing an event in Period 1 only, subjects experiencing an event in Period 2 only, and subjects not experiencing an event in either period will be summarized.

Counting of TEAEs will be by subject, and subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a SOC or PT will be counted under the category of their most severe event within that SOC or preferred term.

In addition to summarizing the subject incidence of EOI by category, the risk difference with 95% CI of each EOI category between treatment groups will be provided. The 95% CI will be calculated by exact method for Period 1 and Period 2 using SAS proc freq with method = fmscore in the exact statement. For the overall summary through EOS the risk difference (ABP 959 - eculizumab) and 95% CI are calculated by the generalized estimating equation (GEE) method using SAS proc genmod with treatment and period as fixed effects, and subject as a random effect. A within subject variance-covariance structure of exchangeable is used.

All treatment-emergent AEs will be listed by treatment group separately.

### 11.7.2 Fatal and Serious Adverse Events

Subject incidence of the following TEAEs will be tabulated by treatment for the entire study through the EOS visit, for period 1, and for period 2 and for each of the 14 week assessment periods (i.e. week 13 to week 27, weeks 39 to 53, and weeks 65 to 79):

- Treatment-emergent serious adverse events (SAEs) by PT
- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by SOC, PT and maximum CTCAE grade
- Fatal Treatment-emergent AEs by PT

Adverse event data collected on the adverse events eCRF is used to identify the subset of subjects diagnosed with COVID-19 using the search strategy of the COVID-19 SMQ. Subject incidence of treatment emergent serious adverse events occurring on or after presumed start date of COVID-19 infection will be presented by preferred term for Period 1, Period 2 and the complete study by treatment. A listing of SAEs on or after presumed start date of COVID-19 infection, as defined for the incidence table, is also presented.

### 11.7.3 Laboratory Data

Laboratory test results will be reported in International System of Units (SI) units.

Laboratory values and change from baseline will be summarized using descriptive statistics at each analysis visit (target day with +6/-7 days window) by treatment.

Based on CTCAE v5.0, laboratory tables for shift from baseline grade or category (if baseline grade is not available, see Appendix 3) to maximum post-baseline grade will be presented by treatment group. Shift summaries will be presented separately for Period 1 and Period 2. Period 1 baseline values are from the latest laboratory results before the first IP treatment in Period 1. Period 2 baseline values are from the latest laboratory results before the first IP treatment in Period 2. All post-baseline laboratory assessments will be included in the determination of maximum post-baseline grade.

Standard ranges will be used for the laboratory analysis. In addition, subject incidence of grade ≥ 3 laboratory toxicities will be summarized by treatment.

Lab assessments will be grouped for summary as follows:

- Hematology – white blood cell parameters: white blood cell count and absolute neutrophil count
- Hematology – red blood cell parameters: red blood cell count, hemoglobin and packed cell volume or hematocrit

- Hematology – other parameters: platelets
- Hematology – hemolysis-related parameters: Type III cells (erythrocytes, monocytes, and granulocytes) and serum-free hemoglobin.
- Total complement (CH50)
- Serum chemistry – hepatobiliary parameters: alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, LDH, haptoglobin
- Serum chemistry – renal function tests: creatinine, blood urea nitrogen, uric acid, potassium

### 11.7.4 Vital Signs and Physical Examination

Vital sign assessments include pulse, respiration rate, temperature, and blood pressure (BP). Change from baseline in vital signs will be summarized by treatment group. Descriptive statistics will be shown for baseline, and the change from baseline at each analysis visit (target day with +6/-7 days window).

### 11.7.5 Immunogenicity

The number and percentage of subjects developing binding, neutralizing, and treatment boosted anti-drug antibody (ADA) will be tabulated for each treatment for Period 1 and for the study through EOS by treatment sequence using the safety analysis set. The overall antibody incidence will also be tabulated. Pre-existing antibody incidence (on or before the first dose of study IP) and developing antibody incidence (including transient antibody incidence) will be summarized. Pre-existing antibody incidence is defined as the number of subjects with a positive antibody result at study baseline divided by the number of subjects with a result at study baseline. Developing antibody incidence through Period 1 is defined as the number of subjects with a binding negative or no antibody result at study baseline and a positive antibody result at any post-baseline time point before Period 1 end date divided by the number of subjects with any postbaseline result before Period 1 end date. Developing antibody incidence through EOS is defined as the number of subjects with a binding negative or no antibody result at study baseline and a positive antibody result at any post-baseline time point divided by the number of subjects with any postbaseline result. A transient antibody result is defined as a positive post-baseline result with a negative result at the subject's last timepoint tested within the study period.

Treatment boosted ADA is defined as total number and percentage of subjects with a positive immunoassay result at baseline and at least 1 post-baseline immunoassay result that is >=4x magnitude of baseline result.

Developing antibody incidence through specific study visits will also be presented. Developing antibody incidence at a given study visit week is defined as the number of subjects with a binding negative or no antibody result at study baseline and positive antibody result at any timepoint up to the given visit divided by the number of subjects with any postbaseline result up to the given visit. Transient status is not defined for given study visit week summaries. For determining developing incidence "by week x", the following window upper limits will be used

| Visit | Target Day | Upper Limit |
|---|---|---|
| by Week 7 | 43 | 49 |
| by Week 27 | 183 | 189 |
| by Week 39 | 267 | 273 |
| by Week 53 | 365 | 371 |
| by Week 65 | 449 | 455 |

### 11.7.6 Imputation for Partial or Missing Dates

Partial or missing admission and discharge dates for hospitalizations will not be imputed.

If dates are missing or incomplete for an AE (including deaths) or concomitant medication, the following algorithm will be used for imputation:

Table 4. Imputation Rules for Partial or Missing Start Dates

| Start Date | | Stop Date: Complete: *yyyymmdd* <1st dose | Complete: *yyyymmdd* ≥1st dose | Partial: *yyyymm* <1st dose *yyyymm* | Partial: *yyyymm* ≥1st dose *yyyymm* | Partial: *yyyy* <1st dose *yyyy* | Partial: *yyyy* ≥1st dose *yyyy* | missing |
|---|---|---|---|---|---|---|---|---|
| Partial: *yyyymm* | = 1st dose *yyyymm* | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyymm* | | 2 | 2 | 2 | 2 | 2 | 2 |
| Partial: *yyyy* | = 1st dose *yyyy* | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyy* | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date "mmyyyy", impute the last day of the month.
    b. For partial stop date "yyyy", impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date (i.e. set the stop date as missing).

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    a. If "mmyyyy" for last contact date = "mmyyyy" for death date, set death date to the day after the last contact date.
    b. If "mmyyyy" for last contact date < "mmyyyy" for death date, set death date to the first day of the death month.
    c. If "mmyyyy" for last contact date > "mmyyyy" for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

The imputed dates will be used to assess whether AEs should be considered as treatment-emergent and if concomitant medications should be included in the safety summaries, however the original, partial dates will be included in data listings.




## 12.0 Validation

The programming (including quality control) of the analysis datasets and tables, figures, and listings (TFLs) will be conducted under PRA's standard processes PRS 050 and documented accordingly. The entire set of TFL will be checked for completeness and consistency prior to its delivery to the client by the lead statistician and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process is repeated any time TFL are redelivered using different data. Execution of this validation process is documented through the study Table of Programs that is provided to the client at study conclusion.

## 13.0 References

Ke C, Wang J, Zhang C, Jiang Q, Snapinn S. On errors in stratified randomization. Statistics in Biopharmaceutical Research 2017; 9 (2): 225-33.

## Appendix 1 Glossary of Abbreviations

| Glossary of Abbreviations: | |
|---|---|
| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| AUC | Area Under the Curve |
| AUEC | Area Under the Effect Curve |
| BLQ | Below Limit of Quantification |
| BP | Blood Pressure |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence Interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMS | Clinical Trials Management System |
| CV | Coefficient of Variation |
| DMC | Data Monitoring Committee |
| EAIR | Exposure-adjusted Incidence Rate |
| eCRF | Electronic Case Report Form |
| EOI | Event of Interest |
| EOS | End of Study |
| FAS | Full Analysis Set |
| GMR | Geometric Mean Ratio |
| IP | Investigational Product |
| IV | Intravenous |
| IXRS | Interactive Voice/Web Response System |
| LDH | Lactate Dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mFAS | Modified Full Analysis Set |
| NI | Noninferiority |
| PD | Protocol Deviation |
| PK | Pharmacokinetic |
| PNH | Paroxysmal Nocturnal Hemoglobinuria |
| PPC | Per-protocol Analysis Set for the Crossover Comparison |
| PPP | Per-protocol Analysis Set for the Parallel Comparison |
| PT | Preferred Term |




| | |
|---|---|
| P-Y | Patient-Year |
| Q1 | 25th Percentile |
| Q3 | 75th Percentile |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SI | International System of Units |
| SMQ | Standard MedDRA Query |
| SOC | System Organ Class |
| TEAE | Treatment-emergent Adverse Event |
| TFL | Tables, Figures, and Listings |
| WHO-DD | World Health Organization Drug Dictionary |




## Appendix 2 MedDRA Query SMQ - COVID-19

Methodology: The PT's related to the COVID-19 MedDRA SMQ dictionary will be used to define subjects with presumed COVID-19 infection. For the search the narrow criteria of the SMQ query definitions will be used.




## Appendix 3 Baseline Gradings for ALT, AST, Total Bilirubin and Alkaline Phosphatase

For the lab parameters ALT, AST total bilirubin and alkaline phosphatase the CTCAE v5.0 grading are not defined for baseline. The following definitions will be used for baseline categories:

| Lab Parameter | Baseline Categories |
|---|---|
| AST and ALT | Missing<br>≤ 1x ULN<br>> 1x ULN to ≤ 3x ULN<br>> 3x ULN |
| Total bilirubin<br>Alkaline phosphatase | Missing<br>≤ 1x ULN<br>> 1x ULN |




# Appendix 4 List of Post-text Tables, Figures, and Listings and Supportive SAS Output Appendices

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