Statistical Analysis Plan	RICHMOND Pharmacology

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STATISTICAL ANALYSIS PLAN

A Partially Randomized, Sequential Cohort, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Subcutaneous Ravulizumab Coadministered With rHuPH20 in Healthy Adult Volunteers

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Created by: [redacted]
Richmond Pharmacology
[redacted]

Signature [redacted]
Date 30 Apr 2019

Approved by: [redacted]
ICRC-Weyer GmbH
[redacted]

Signature [redacted]
Date 29-Apr-2019

Approved by: [redacted]
Alexion Pharmaceuticals, Inc

Signature DocuSigned by: [redacted]
Signing Reason: I approve this document
Date 26-Apr-2019 | 08:51:28 EDT

Approved by: [redacted]
Alexion Pharmaceuticals, Inc

Signature [redacted]
Date 27-APR-2019

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
%CV	Coefficient of Variation
ADA	Antidrug Antibodies
AE	Adverse Event
AUC	Area under the Concentration Time Curve
$AUC_{0-\infty}$	Area under the Serum Concentration versus Time Curve from Time Zero Extrapolated to Infinity
AUC_{0-t}	Area under the Serum Concentration versus Time Curve from Time Zero to the Last Quantifiable Concentration
BLQ	Below the Level of Quantification
BDRM	Blind Data Review Meeting
C5	Complement Component 5
CI	Confidence Interval
CL	Total Body Clearance
C_{max}	Maximum Observed Serum Concentration
CSR	Clinical Study Report
cRBC	Chicken Red Blood Cell
ECG	Electrocardiogram
F	Absolute Bioavailability
F_{rel}	Relative Bioavailability
IV	Intravenous
λ_z	Terminal Elimination Rate Constant
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PK	Pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
rHuPH20	Recombinant Human Hyaluronidase PH20
RPL	Richmond Pharmacology Ltd
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
$t_{½}$	Terminal Elimination Half-Life
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Serum Concentration
V_d (V_d/F)	Apparent Volume of Distribution

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the variables and analysis methodology to address the study objectives.

The protocol dated 20 Jul 2018, Amendment 1, was used in the preparation of this SAP.

Pharmacokinetic (PK) parameters calculations and statistical analyses will be the responsibility of Richmond Pharmacology Ltd (RPL). Tables, figures, and listings (TFLs) will be produced using Statistical Analysis Software (SAS), Version 9.3 or higher.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

The objectives of this study are:

Primary

- To estimate the absolute bioavailability of subcutaneous (SC) ravulizumab coadministered with recombinant human hyaluronidase PH20 (rHuPH20)
- To assess the safety and tolerability of ravulizumab SC/rHuPH20.

Secondary

- To estimate the relative bioavailability of ravulizumab SC/rHuPH20 compared with ravulizumab SC.
- To explore the pharmacodynamic (PD) effects of ravulizumab SC coadministered with rHuPH20

2.2 Endpoints

Primary

- Serum concentration of ravulizumab will be used to determine the geometric mean ratio of the area under the concentration time curve (AUC) values
- Safety assessed by incidence of treatment-emergent adverse events (TEAEs) and serious adverse events, physical examination, vital sign measurements, clinical laboratory and electrocardiogram (ECG) results, and measurement of antidrug antibodies (ADA).

Secondary

- Serum concentration of ravulizumab will be used to determine the geometric mean ratio of the AUC values
- Change in serum levels of total and free complement component 5 (C5) concentrations over time
- Change in ex vivo chicken red blood cell (cRBC) hemolysis activity over time

3. TRIAL DESIGN

This is a Phase 1 study designed to evaluate the safety, tolerability, PK, PD, immunogenicity, and absolute and relative bioavailability of single ascending doses of ravulizumab SC coadministered with rHuPH20 compared to a single dose of ravulizumab intravenous (IV) 400 mg or a single dose of ravulizumab SC 400 mg in 48 healthy adult subjects. Five treatment cohorts are planned.

A Safety Review Committee (SRC) will evaluate the study data for subject safety and make recommendations on dose escalation, dose modification, or termination of the study. When cohorts are being enrolled in parallel, subject assignment to a cohort will be done through randomization. The study will be conducted at a single site in the United Kingdom (UK).

3.1 Overall Design

Eighteen subjects will be randomly assigned in a 1:2 ratio between the first two cohorts to receive either a single dose of ravulizumab SC 400 mg (Cohort 1, n = 6) or a single dose of ravulizumab SC 500 mg/rHuPH20 10,000 units (Cohort 2, n = 12). The SRC will review Cohort 2 ravulizumab SC/rHuPH20 safety data and make their recommendation for escalating the dose of the ravulizumab SC/rHuPH20 cohort.

If the SRC recommendation following the review of data from Cohort 2 is to initiate the next cohort and proceed with the planned dose escalation, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC 1000 mg/rHuPH20 20,000 units or a single dose of ravulizumab IV 400 mg, respectively. The SRC will subsequently review Cohort 3 ravulizumab SC/rHuPH20 safety data and make their recommendation to proceed with planned dose escalation in Cohort 4 or a reduced dose in Cohort 4.

Whether the SRC recommendation is to initiate Cohort 4 with the planned dose escalation or at a reduced dose, 12 subjects will be enrolled in Cohort 4 to receive a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation).

If the recommendation following the review of ravulizumab SC/rHuPH20 safety data from Cohort 2 is to proceed with Cohort 3 at a reduced dose, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation) or a single dose of ravulizumab IV 400 mg, respectively. In this scenario, Cohort 4, if conducted, will be enrolled at a reduced dose, following completion of Cohort 3 based on SRC review of ravulizumab SC/rHuPH20 safety data from Cohort 3 and a favorable recommendation to enroll subjects in Cohort 4.

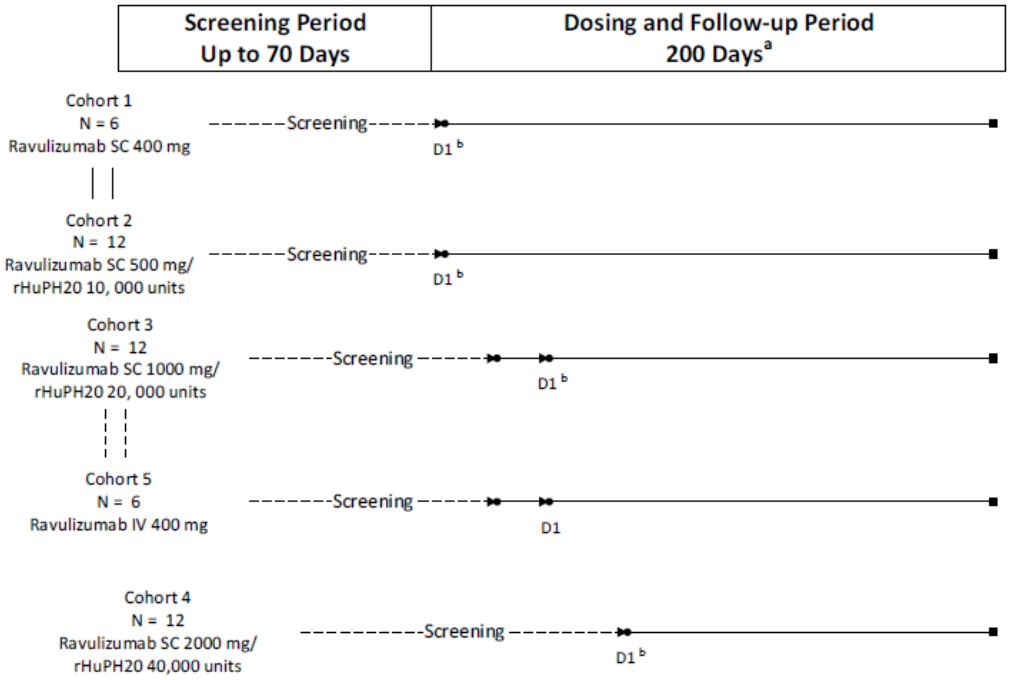
If the SRC determines that no further ravulizumab SC/ rHuPH20 combination dosing cohorts should be enrolled following Cohort 2, then Cohort 5 may still be enrolled as a stand-alone cohort at the discretion of the Sponsor.

Cohort	N	Study Drug	Route (SC/IV)	Planned Dose
1	6	ravulizumab	SC	400 mg
2	12	ravulizumab/rHuPH20	SC	500 mg / 10,000 units
3	12	ravulizumab/rHuPH20	SC	1000 mg / 20,000 units
4	12	ravulizumab/rHuPH20	SC	2000 mg / 40,000 units
5	6	ravulizumab	IV	400 mg

Table 1: ALXN1210-HV-105 Study Design

3.2 Duration of Study

The planned study duration is approximately 39 weeks; up to 70 days for screening and approximately 200 days for dosing and follow-up. For the first 5 days during the Dosing and Follow-up Period, subjects will be admitted to an inpatient facility. Dosing will be staggered within and between cohorts, but the end of study for each individual subject is anticipated to be Day 200 or the time point at which complement activity has normalized, if later than Day 200.



Note: Subjects will be randomly assigned to Cohort 1 or Cohort 2, randomly assigned to Cohort 3 or Cohort 5, and sequentially assigned to Cohort 4.
[a] Dosing will be staggered, but the end of study for each subject is Day 200 or the time point at which complement activity has normalized, if later than Day 200.
[b] For Cohorts 1 through 4, a sentinel dosing approach will be used (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort).
Abbreviations: D = day; IV = intravenous; N = number [of subjects]; SC = subcutaneous.

Figure 1: Study ALXN1210-HV-105 Schematic

3.3 Sample Size

The sample size is based on PK rather than statistical considerations. A total sample size of 48 subjects (6 subjects each in the control cohorts [Cohort 1 and 5] and 12 subjects each in the combination cohorts [Cohorts 2, 3, and 4]) will serve to estimate bioavailability.

3.4 Randomization and Blinding

This is an open-label study. Eligible subjects who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment and randomization. Randomization will only be used when cohorts are being enrolled in parallel.

- In order to minimize selection bias in treatment assignment, subjects will be randomly or sequentially assigned subject numbers, depending upon cohort, up to 7 days prior to dosing on Day 1, in the same order as they have become eligible.

- Sentinel dosing will be employed in Cohorts 1 through 4 (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort). Remaining subjects within the cohort will be dosed at least 24 hours following dosing of the sentinel subjects.
- At the Sponsor's discretion, and after consultation with the SRC, up to 16 additional subjects may be enrolled as replacement subjects if any subject discontinues prior to Day 50 for reasons other than drug-related adverse events (AE).
- Study numbers will not be reallocated once assigned

4. STATISTICAL ANALYSES

In general, descriptive statistics for continuous variables will include number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Descriptive statistics for PK parameters will include number of observations (n), arithmetic mean, standard deviation (SD), arithmetic coefficient of variation (%CV), geometric mean, geometric %CV, median, minimum and maximum.

Categorical variables will be summarized using frequency counts and percentages.

For all tables, except PK parameter tables, descriptive statistics for minimum and maximum will be presented with the same decimal digits as the original data, and with 1 more decimal place than the original data for mean and median; SD will be reported with 2 more decimal places than the original data.

PK parameters will be presented as follows in the listing: Cmax and Tmax will be presented as given in the raw data; AUC0-t, AUC0-∞, λz , t1/2, CL or CL/F, and Vd or V_d/F will be presented with 3 decimal places, that is special characters will not be presented in the tables, listings or figures. Descriptive statistics for PK parameters will be presented with decimal places as appropriate for the particular parameter and treatment group.

The analyses will be presented by treatment group, i.e. cohorts. All collected data will be presented in by-subject listings. Listings will be ordered by treatment group and subject number and will include all randomized subjects.

Baseline will be defined as the last non-missing value among assessments recorded prior to first administration of study drug. Changes from baseline values will be calculated as the post-baseline assessment value minus the baseline value. Only observed values from scheduled time points will be used to create summary tables.

Early Termination (ET) visits will be recoded to ET visits where necessary and reported as ET.

Deviations from the planned analyses will be described in the final clinical study report (CSR).

Page layout of the TFLs will be in landscape mode and will be provided in Microsoft Word. Final TFLs will additionally be created as bookmarked PDF. Further details of page layout will be provided in the TFL shell document. Individual RTF files for tables may be provided to assist medical writing. RTF files will not be compiled into a single document.

4.1 Interim Analysis

An interim assessment of PK data through Day 50 may be performed.

4.2 Analysis Populations

Inclusion and exclusion from each analysis set will be decided at the Blind Data Review Meeting (BDRM) prior to database lock. Further exclusions may be made from PK/PD/Immunogenicity sets based on the concentrations.

Safety Population

The safety population will consist of all subjects who receive at least 1 dose of the study drug.

PK Population

The PK population will consist of all subjects who have sufficient serum concentration data to enable the calculation of PK parameters of at least Area Under the Curve (AUC). Subjects who did not receive the full dose of study drug will be excluded from the PK population.

PD Population

The PD population will consist of all subjects who have sufficient free C5 concentration data which will enable the evaluation of the PD effects. Subjects who are replaced will not be included in the PD population.

Immunogenicity Population

The immunogenicity population will consist of all subjects who have a predose and post-dose ADA sample collected.

4.3 Subject Disposition

All subjects will be included in the summary of subject disposition. This will present the overall number of subjects screened and by treatment group and overall the frequency and percentage of subjects randomized and treated, and who completed or discontinued from the study, along with reason for discontinuation.

Furthermore, the number and percentage of subjects in each study population will be tabulated. Discontinued subjects will be listed. Subject assignment to study populations will be listed. Screen Failures will not be listed or included in summary tables.

4.4 Demographic Characteristics

Individual subject demographics (including age, sex, race and ethnicity) and body measurement data (height, body weight and body mass index) at screening will be listed and summarized by each treatment group and overall for the safety population. If the remaining populations are different from the safety population by more than 5%, separate demographic tables will be produced.

Height will be measured in centimeters and weight in kilograms. Body mass index will be given in kg/m^2.

4.5 Baseline and Other Safety Characteristics

Data collected from vaccine and antibiotic prophylaxis, vaccine titer, tuberculosis testing, virus serology, serum pregnancy test, alcohol breath test and urine drug screen will be listed by subject.

4.6 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be listed together with the overall eligibility for each subject.

4.7 Protocol Deviations

The final review of protocol deviations will be performed at the BDRM prior to database lock. The protocol deviations will be listed.

4.8 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 21.0 (or higher) and listed individually. Surgical histories will be listed separately.

4.9 Study Drug Administration

Study drug administration data will be listed individually.

4.10 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version June 1, 2018 or higher and will be listed individually. The frequency and percentage of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical and Preferred Name. Separate tables will be given for prior and concomitant medications. Prior medications are defined as those for which the end date and time is prior to the date, and time of first study drug administration. Concomitant medications are defined as those with start date and time on or after the date and time of first study drug administration and those with start date and time prior to the first study drug administration but with end date an time on or after the date and time of first

study drug administration. Non-pharmacologic therapies and procedures and prophylactic antibiotic treatment will be listed.

Prior and concomitant medications with missing start (end) date or time will be classified as concomitant medication.

4.11 Infusion/Injection Site (Pain) Evaluation

Data from the injection/infusion site evaluations and from pain at infusion/injection site will be listed individually. Injection/infusion site evaluations will be summarized by treatment group.

4.12 Safety Analysis

Safety analyses will be performed on the safety population, and will be reported at each time point by treatment group, reporting criteria will be outlined for each safety parameter Safety parameters will also be summarized overall and for the rHuPH20 treatment groups combined.

Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data, vital sign measurements and physical examination results and will be presented using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study.

4.12.1 Adverse Events

A Treatment Emergent Adverse Event (TEAE) is any adverse event that commences after the start of administration of study drug.

The incidence of TEAEs (after dosing) will be summarized using the safety population. The MedDRA dictionary Version 21.0 (or higher) will be used to classify all AEs reported during the study by System Organ Class (SOC) and Preferred Term. A summary of TEAEs including the incidence of subjects who experienced TEAEs (number and percentage of subjects) and incidence of TEAEs (number of events) will be presented for each treatment group and overall, by severity and by relationship to study drug.

TEAEs and serious TEAEs will be summarized by SOC and Preferred Term for each treatment group and overall, and by relationship to study drug.

Subjects having multiple AEs within a category (e.g., overall, SOC and Preferred Term) will be counted once in that category. For severity tables, a subject's most severe event within a category will be counted. For relationship tables, a subject's event with greatest relationship to study drug within a category will be counted. In each table, SOC and Preferred Term will be presented in descending order of overall incidence rate (alphabetical order will be used in case of equal rates).

All adverse events will be listed. Serious TEAEs will be listed, if required.

4.12.2 Laboratory Data

Clinical laboratory parameters (including blood chemistry, hematology, coagulation, urinalysis and other laboratory results) will be listed and abnormal parameters will be flagged as high (H) or low (L) according to reference ranges. Absolute (observed) values and changes from baseline (continuous variables) will be summarized for each parameter and scheduled time point by treatment group. The last lab value will be used for summary analysis if repeated measurements are made at any time point.

For summary statistics, a lab value with "<" will be replaced with a numeric value by removing the "<" sign. In the listings, the values will be displayed as originally reported by the laboratory.

Laboratory parameter values will be graded according to the Common Terminology Criteria for Adverse Events. Non-protocol parameters will only be listed, in a separate listing, if required. Shift tables by treatment group will be produced for these laboratory parameters. These tables will summarize the number of subjects with each baseline grade relative to the normal ranges and changes to the worst highest grade assessed post-dose during the study.

4.12.3 Electrocardiograms

ECG parameters will be measured at the specified time points and will include heart rate, PR, RR, QRS, QT, and corrected QT interval corrected using Fridericia's formula (QTcF)(QTcF=QT/RR^1/3). The variables will be listed individually.

Three or more replicate measurements are taken at each protocol time point and the arithmetic mean of the evaluable/available measurements will be taken as the measurement to be used for summary statistics. Arithmetic mean values will also be included into the listings.

For ECG variables, the change from baseline will be derived using the arithmetic mean value ofeach time-point triplicate minus the arithmetic mean of baseline triplicate values.

Absolute (observed) values and changes from baseline in the ECG variables will be summarized by treatment group and time point.

An outlier analysis will be performed that will summarize the frequency and percentage of subjects who meet any of the following outlier criteria at each visit by treatment group:

- QT, QTcF interval > 450 msec to ≤ 480 msec
- QT, QTcF interval > 480 msec to ≤ 500 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec to ≤ 60 msec
- QT, QTcF interval increases from baseline > 60 msec

4.12.4 Telemetry

Cardiac telemetry data will be listed individually.

4.12.5 Vital Signs

Vital signs data (systolic and diastolic blood pressure, heart rate, temperature and respiration rate) will be listed for individual subjects. Summary statistics of absolute (observed) values and changes from baseline will be calculated for each parameter and scheduled time point by treatment group.

4.12.6 Physical Examination

Physical examination data will be listed individually.

4.13 Pharmacokinetic Analysis

All serum concentration data will be listed for each individual subject and summarized at each time point by treatment group. Individual and mean concentrations versus nominal time on linear and semi-log scales will be presented graphically. The PK population will be used to present the summary of PK parameters.

4.13.1 Values Below the Limit of Quantification and Missing Values

If a Below the Level of Quantification (BLQ) value occurs in a profile before the first measurable concentration, it will be assigned a value of zero concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower level of quantification, then the BLQ value will be omitted following visual inspection of the serum concentration versus time profile to assess the appropriateness of this assignment. If a BLQ value occurs at the end of a collection profile (after the last quantifiable concentration), the value will be treated as missing data. If 2 BLQ values occur in succession, the profile will be deemed to have terminated at the first BLQ value and any subsequent concentrations will be omitted from PK calculations following visual inspection of the serum concentration versus time profile to assess the appropriateness of this assignment.

Samples with no reportable value due to a bioanalytical issue or missing samples will be set to missing, and will not be included in the PK calculations.

When calculating the mean or median value for a concentration at a given time point, all BLQ values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

For tabulation, graphical representation, and calculation purposes, all samples with no reportable value (or missing samples) observed after dosing will be set to missing.

4.13.2 Pharmacokinetic Parameters

Individual serum concentration data for ravulizumab IV-, ravulizumab SC/rHuPH20-, ravulizumab SC-treated subjects, with actual sampling dates and times calculated relative to the start of the infusion/injection, will be used to derive the PK parameters by non-compartmental analyses using Phoenix WinNonlin Version 6.3 or higher. If missing actual sampling dates and times, then the nominal time relative to start of infusion/injection will be used.

The following PK parameters will be derived for each subject:

- **C_{max} [µg/mL]:** Maximum observed serum concentration
    - For multiple peaks, the highest post-dose concentration will be reported as C_{max}
- **Cmax/D[µg/mL]/[mg]:** Dose normalized maximum observed serum concentration
- **T_{max} [h]:** Time to maximum observed serum concentration
    - In case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported
- **AUC_{0-t} [h* µg/mL]:** Area under the serum concentration versus time curve from time zero (dosing) to the last quantifiable concentration
- **AUC_{0-t}/D [h* µg/mL]/[mg]:** Dose normalized area under the serum concentration versus time curve from time zero (dosing) to the last quantifiable concentration
- **$AUC_{0-\infty}$ [h* µg/mL]:** Area under the serum concentration versus time curve from time zero (dosing) extrapolated to infinity
- **$AUC_{0-\infty}$/D [h* µg/mL]/[mg]:** dose normalized area under the serum concentration versus time curve from time zero (dosing) extrapolated to infinity
- **Body weight adjusted $AUC_{0-\infty}$/D [h* µg/mL]/[mg]:** body weight adjusted dose normalized area under the serum concentration versus time curve from time zero (dosing) extrapolated to infinity. Dose and body weight normalized $AUC_{0-\infty}$ will be calculated as follows:

  Body weight adjusted $AUC_{0-\infty}/D$ = $AUC_{0-\infty}$ / dose / (body weight/70)^(-0.652)*

  * -0.652 came from the population PK model report (Population pharmacokinetic and pharmacodynamics analysis to support ravulizumab dosing for the treatment of patients with paroxysmal nocturnal hemoglobinuria).
- **λ_z [1/h]:** Apparent terminal-phase elimination rate constant
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression

- A minimum number of 3 data points in the terminal phase will be used in calculating λ_z, with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope)

- **$t_{½}$ [h]:** Terminal elimination half-life
  - Calculated as ln(2)/ λ_z
- **CL [L/h] or CL/F:** Apparent total clearance
  - Calculated as dose/AUC_{∞}
- **V_d** or **V_d/F [L]**: Apparent volume of distribution during terminal phase
  - Calculated as dose/(λ_z*AUC_{∞})

Dose normalized parameters will be derived using the actual dose (weight of the drug administered).

PK parameters will be listed for each individual subject and summarized by treatment group. Descriptive statistics for PK parameters will include number of observations (n), arithmetic mean (Mean), standard deviation (SD), arithmetic coefficient of variation (%CV), geometric mean, geometric %CV, median, minimum and maximum.

Some PK parameters may not be calculated for all or some subjects if the concentration data are not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated will be provided in the CSR.

Additional PK parameters may be calculated, as appropriate.

4.13.3 Absolute and Relative Bioavailability

The absolute bioavailability (**F**) for the ravulizumab SC/rHuPH20 cohorts will be defined by the ratio of the geometric means for the dose normalized $AUC_{0-\infty,n}$ parameter for the ravulizumab SC/rHuPH20 cohort over the ravulizumab IV cohort.

The relative bioavailability (**F_{rel}**) for the ravulizumab SC/rHuPH20 cohorts will be defined by the ratio of the geometric means for the dose normalized $AUC_{0-\infty}$ parameter for the ravulizumab SC/rHuPH20 cohort over the ravulizumab SC cohort.

For the absolute and relative bioavailability estimates, a 95% CI for each of the ratio of the geometric means will be provided. To calculate CIs of geometric mean ratios, $AUC_{0-\infty}$/D and body weight adjusted $AUC_{0-\infty}$/D will be log-transformed and CIs will be constructed for the mean difference of log-transformed parameters, assuming that log-transformed parameters are normally distributed. The CIs are then back-transformed to receive CIs for the geometric mean ratios. The geometric mean ratios and their 95% CIs will be tabulated.

4.14 Pharmacodynamic Analyses

The pharmacodynamic endpoints will be evaluated using the PD population as follows:

- Changes and percent changes in serum total and free C5 concentration over time.
- Change and percent change in cRBC hemolysis over time.

PD data will be listed for each individual subject and absolute (observed) values as well as changes and percent changes from baseline will be summarized at each time point by treatment group.

Individual and mean percent change from baseline versus nominal time profiles will be presented graphically for each PD parameter.

4.15 Immunogenicity Analyses

Immunogenicity, as measured by ADA, will be listed, and summarized over time by treatment group using the Immunogenincity population. A summary of the number and proportion of patients who are ever positive and always negative will also be provided by treatment group.

4.16 Methods for Withdrawals, Missing Data and Outliers

The individual serum concentration data and the actual timing of study drug administration and blood sampling will be used throughout the analyses. If there is any doubt about the actual time at which a sample was taken, then the scheduled time will be used. For PK data analysis, please see Section 4.12.1 regarding the handling of missing and BLQ values. For PD data analysis, there will be no imputation for missing values.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first administration of study drug. Otherwise missing or partial dates will be listed as such.

There will be no further imputation of missing data (i.e., subjects who prematurely discontinue from the study will not be included in summary statistics or analyses beyond the time of discontinuation).

Depending on the extent of missing values, the appropriateness of the methods described for handling missing data may be reassessed prior to database lock (to examine the sensitivity of results to handling of missing data).