STATISTICAL ANALYSIS PLAN	
Study Code	D9289C00008
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A Phase 3, Single-arm, Open-label, Multicenter Study to Assess the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Ravulizumab in Complement Inhibitor Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

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LIST OF ABBREVIATIONS

Abbreviation or Term	Explanation
ADA	Antidrug Antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BTH	Breakthrough Hemolysis
CI	Confidence Interval
CM	Concomitant Medication
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DPS	Data Point Set
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
Hgb	Hemoglobin
HR	Heart Rate
IAS	Immunogenicity Analysis Set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identity
INT	Integer
IPD	Important Protocol Deviation
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MAVE	Major Adverse Vascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model for Repeated Measures
NAb	Neutralizing Antibody
NC	Not Calculated
NDA	New Drug Application

NQ	Not Quantifiable
PD	Protocol Deviation
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
pRBC	Packed Red Blood Cells
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PT	Preferred Term
Q1	Fist Quartile
Q3	Third Quartile
QT	Interval between the start of the Q wave and the end of the T wave in an ECG
QTc	Corrected QT Interval
QTcF	Corrected QT Interval by Fredericia Formula
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistics Analysis System
SD	Standard Deviation
SE	Standard Error
SoA	Schedule of Activities
SOC	System Organ Class
SS	Safety Set
PNH	Paroxysmal Nocturnal Hemoglobinuria
TA	Transfusion Avoidance
TEADA	Treatment-emergent ADA
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	30 September 2024	Initial approved SAP	N/A	N/A
Data presentation	2 July 2025	Section 3.3: Clarify the rule to keep decimal place for Q1 and Q3.		Provide additional clarification
Data presentation	2 July 2025	Section 3.3.1.2: 1. Add "Different data points are selected for different analysis purposes and analysis periods."; 2. Change IE to intercurrent events.		Provide additional clarification
Data presentation	2 July 2025	Section 4.1.1.1: Remove "Participants who did not receive treatment".		Remove for simplification
Data presentation	2 July 2025	Section 4.1.5.1: Add weight group.		Add to support the subgroup analysis
Data presentation	2 July 2025	Section 4.1.6.1: 1. Remove the summary of PNH symptoms experienced and PNH associated conditions, and add to section 4.1.7.2; 2. Correct unit of absolute reticulocyte count; 3. Clarify to keep one decimal place of PNH disease duration.		Provide additional clarification
Data presentation	2 July 2025	Section 4.1.7.2: Surgical history is summarized by SOC and PT, not only by PT.		In line with AZ standards.
Data presentation	2 July 2025	Section 4.1.8.2: Change "ATC Level 3" to "ATC".		Provide clarity for TLFs
Primary endpoint(s)	2 July 2025	Section 4.2.1.4: Delete "Akaike's information criterion" from the description of covariance matrix structure of MMRM model.		Correct for clarification
Secondary endpoint(s)	2 July 2025	Section 4.2.2.4: 1. Delete "Akaike's information criterion" from the description of covariance matrix structure of MMRM model. 2. Remove "extension period".		Correct for clarification

Data presentation	2 July 2025	Section 4.2.3.2: Correct the definition of hemoglobin normalization.		No changes to analyses, correct the definition
Data presentation	2 July 2025	Section 4.2.3.4: 1. Add the censor rule for time to first occurrence of LDH. 2. Change box plot to line plot for LDH, FACIT-Fatigue Score, and Hgb by visit summary. 3. Change line plot to bar graph for numbers (percentage) of LDH < 1.5× UL, LDH normalization and hemoglobin normalization by visit.		Provide clarity for TLFs
Data presentation	2 July 2025	Section 4.3.2: Add the rule to handle the results with serum free C5 concentrations below LLOQ.		Provide clarity for TLFs
Data presentation	2 July 2025	Section 4.4.2: 1. Add the description to clarify the results with data issue. 2. Clarify the rule to keep decimal place for PK concentration descriptive statistics. 3. Add the rule to handle the results with serum free ravulizumab concentrations below LLOQ. 4. Add descriptive statistics by body weight.		Provide clarity for TLFs
Data presentation	2 July 2025	Section 4.6.2.2: 1. Remove “TEAEs leading to drug interrupted”. 2. Remove “The number and percentage of participants with MAVE”		Remove for simplification
Data presentation	2 July 2025	Section 4.6.5.2: Remove HIV related description.		Remove for clarification
Data presentation	2 July 2025	Section 4.6.6.2: Remove the summary of baseline versus treatment emergent maximum and minimum values shift tables for vital sign.		Remove for simplification
Data presentation	2 July 2025	Section 4.6.7.2: Remove “overall study”.		Correct for clarification

Data presentation	2 July 2025	Section 7.1: 1. Only keep the Drug category and Prohibited drug name. 2. Remove Ravulizumab.		Remove for simplification

1 INTRODUCTION

The purpose of this document is to give details for statistical analysis of study D9289C00008 (ALXN1210-PNH-323) supporting the clinical study report. The reader is referred to the clinical study protocol (CSP) for details of study conduct. This statistical analysis plan (SAP) contains a more detailed description of the analysis in the CSP for the ALXN1210-PNH-323 study and is based on original signed version of the CSP dated 2024-03-12.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Two Database Locks (DBLs) are planned in this study. The primary DBL will be conducted when all participants have completed 26-week Primary Treatment Period or withdraw from the 26-week Primary Treatment Period. The final DBL will be conducted upon the completion of the study at Week 58.

An interim efficacy and safety assessment will be conducted as primary analysis following the primary DBL. A CSR will be developed based on efficacy and safety data collected through the end of the 26-week Primary Treatment Period. It will be utilized for the submission of the NDA in China.

The final analysis will be performed after the final DBL. A final CSR to summarize long-term efficacy and safety data will be developed at study completion.

3.2 Analysis Populations

Six main analysis populations are defined of this study, the Screened Set, the Safety Set (SS), the Full Analysis Set (FAS), the Pharmacokinetic Analysis Set (PKAS), the Pharmacodynamic Analysis Set (PDAS), the Immunogenicity Analysis Set (IAS).

3.2.1 Screened Set

All consented participants.

3.2.2 Safety Set

All enrolled participants who receive at least 1 dose (full or partial) of the study intervention.

3.2.3 Full Analysis Set

All enrolled participants who receive at least 1 dose (full or partial) of the study intervention.

3.2.4 Pharmacokinetic Analysis Set

All ravulizumab treated participants with at least 1 post-baseline PK concentration available.

3.2.5 Pharmacodynamic Analysis Set

All ravulizumab treated participants who have evaluable PD data.

3.2.6 Immunogenicity Analysis Set

All enrolled participants who receive at least 1 dose (full or partial) of the ravulizumab and have at least 1 reportable post-dose result in the ADA assay.

3.3 General Considerations

In order to provide an overview of the data, descriptive statistics will be utilized. The type of descriptive statistic will depend on the variable being summarized, with number of participants with available data (n), mean, standard deviation, median, quartiles (if applicable), minimum, and maximum used to summarize continuous variables, and counts and percentages used to summarize categorical variables.

Missing data will be ignored in the descriptive statistical summaries, and only participants with non-missing data at the relevant timepoints will be included. Unless otherwise stated, percentages will be calculated out of the population total and will be rounded to 1 decimal place. For continuous data, the mean, median, standard deviation (SD), standard error (SE) as well as Q1 and Q3 (if applicable) will be rounded to one additional place compared to the original data, and the minimum and maximum will be displayed to the same accuracy as the original data. If the number of decimal places of the original data is > 3, then the minimum and maximum will be assigned 3 decimal places, the mean, median, SD, and SE will be assigned 4 decimal places.

Results of all statistical analyses will be presented using a 95% confidence interval (CI) and one-sided p-value for primary endpoint, unless otherwise stated. All p-values will be presented to 3 decimal places. All p-values less than 0.001 will be presented as ‘<0.001’ and p-values greater than 0.999 will be presented as ‘>0.999’.

All of analyses will be conducted using SAS version 9.4 or higher.

3.3.1 General Study Level Definitions

3.3.1.1 Definition of Baseline

Baseline is defined as the last non-missing assessment prior to the first study intervention administration unless otherwise specified. In general, the baseline assessment will be the Day 1 assessment. If the Day 1 assessment is missing, the screening assessment, where available, will be used as the baseline assessment.

Efficacy Baseline

Baseline LDH is defined as the average of all non-missing LDH assessments analyzed by the central laboratory prior to first study intervention administration.

Participants with missing values at baseline will be excluded from the change from baseline relevant efficacy analysis.

Safety/PK/PD/ADA Baseline

If a measurement was taken on the date of first intervention administration and no time is recorded, it is assumed that the measurement was taken pre-intervention and will be considered a candidate for baseline.

Change from Baseline

Change from baseline will be calculated as the baseline value subtracted from the value at a particular time point. If one of the values is missing, a change from baseline will not be calculated.

Percentage Change in Assessments from Baseline

Percentage change in values from baseline will be calculated as follows.

Percentage Change in Value = (Change in Value) x 100% / (Baseline value)

Where Change in Value = (the value at a post baseline time point – baseline value), given that the baseline value is non-missing and non-zero and the subsequent value is non-missing.

3.3.1.2 Definition of Data Points Sets

Five data points sets for primary analysis and final analysis are defined for this study in Table 1. Different data points are selected for different analysis purposes and analysis periods.

Table 1 Data Points Sets for the Primary Analysis and Final Analysis

Data Points Set	Description
DPS1: All data up to intercurrent events during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of last dose + 8 weeks or withdrawal from study or administration of disallowed medication or end of Primary Treatment Period at Week 26
DPS2: All data during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of withdrawal from study or end of Primary Treatment Period at Week 26

Data Points Set	Description
DPS3: All data on treatment during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of last dose + 8 weeks or withdrawal from study or end of Primary Treatment Period at Week 26
DPS4: All data on study	All data points obtained at or after first dose up to the earliest date of withdrawal from study or the end of study
DPS5: All data on treatment	All data points obtained at or after first dose up to the earliest date of last dose+ 8 weeks or withdrawal from study or study completion

The analysis sets and data points sets will be used for each outcome are provided in Table 1.1 and Table 1.2.

Table 1.1 Summary of Outcome Variables, Analysis Populations, and Data Points Sets for the Primary Analysis at Week 26

Outcome Variable	Analysis Population	Data Points Set
Efficacy data		
Primary endpoint/variables	FAS	DPS1
Secondary endpoints/variables	FAS	DPS2
Exploratory endpoints/variables	FAS	DPS2
Study population		
Participant disposition[1]	Screened Set/ FAS	DPS2
Demography characteristics	FAS	DPS2
Baseline and disease characteristics	FAS	DPS2
Important protocol deviations	FAS	DPS2
Medical/surgical history	FAS	DPS2
Prior and concomitant medications	FAS	DPS2
Study drug compliance	SS	DPS3
Safety data		
Exposure	SS	DPS3/DPS2[2]
AEs	SS	DPS3/DPS2[2]
Laboratory measurements	SS	DPS3/DPS2[2]
Vital signs	SS	DPS3/DPS2[2]
ECG	SS	DPS3/DPS2[2]
Pharmacokinetics	PKAS	DPS3/DPS2[2]
Pharmacodynamics	PDAS	DPS3/DPS2[2]
Immunogenicity	IAS	DPS3/DPS2[2]

1. For participant disposition, the overview disposition summary table and listing of screen failure participants will be generated based on screened set. All other summary tables/listings will be generated based on FAS.
2. Tables and figures will be generated based on DPS3; listings will be based on DPS2.

Table 1.2 Summary of Outcome Variables, Analysis Populations, and Data Points Sets for the Final Analysis

Outcome Variable	Analysis Population	Data Points Set
Efficacy data		
Exploratory endpoints/variables	FAS	DPS4
Study population		
Participant disposition[1]	Screened Set/ FAS	DPS4
Demography characteristics	FAS	DPS4
Baseline and disease characteristics	FAS	DPS4
Important protocol deviations	FAS	DPS4
Medical/surgical history	FAS	DPS4
Prior and concomitant medications	FAS	DPS4
Study drug compliance	SS	DPS5
Safety data		
Exposure	SS	DPS5/DPS4[2]
AEs	SS	DPS5/DPS4[2]
Laboratory measurements	SS	DPS5/DPS4[2]
Vital signs	SS	DPS5/DPS4[2]
ECG	SS	DPS5/DPS4[2]
Pharmacokinetics	PKAS	DPS5/DPS4[2]
Pharmacodynamics	PDAS	DPS5/DPS4[2]
Immunogenicity	IAS	DPS5/DPS4[2]

1. For participant disposition, the overview disposition summary table and listing of screen failure participants will be generated based on screened set. All other summary tables/listings will be generated based on FAS.
2. Tables and figures will be generated based on DPS5; listings will be based on DPS4.

3.3.1.3 Handling of Missing Dates

No imputation rules will be applied for efficacy endpoints.

Partial or missing adverse event (AE), concomitant medication (CM) and PNH diagnosis dates will be imputed as follows:

- For adverse event (AE), concomitant medication (CM)

partial or missing start dates:

- Missing day: impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month: impute 1st January, unless the year is the same as first dose date and the end date does not suggest it could have started prior to first dose (i.e. end date is before first dose date), then impute first dose date.

- Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

partial or missing end dates:

- Missing day: impute the last day of the month unless month is same as month of last dose of study drug then impute last dose date.

- Missing day and month: impute 31st December unless year is the same as last dose date then impute last dose date.

- Completely missing: need to look at whether the AE or CM is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE or CM is still present (i.e. do not impute a date). If the AE or CM has stopped and start date is prior to first dose date then impute the last dose date, if it started on or after first dose date then impute a date that is after the last dose date + 1 day.

➢ For the partial or missing date of PNH diagnosis, the following rule will be applied:

- Missing day: impute the 15th of the month.

- Missing day and month: impute the June 30th.

- Completely missing: no imputation will be made.

However, the above imputation for PNH diagnosis will be modified by the following rules: if the imputed date of PNH diagnosis is on or after study consent date, then consent date – 1 will be used.

3.3.1.4 Handling of out of Quantification Limits Data

For safety data, if the assessment values are out of quantification limits (i.e. results recorded as "<x" or ">x", where x is the quantification limit of the assessment), then these values are imputed as x in the calculation of summary statistics while still displayed as "<x" or ">x" in the listings.

3.3.2 Statistical Hypothesis

The primary objective is to evaluate whether treatment with ravulizumab decreases LDH at Day 183 (Week 26) from baseline. 1-sided hypothesis is planned to be tested whether mean percent change from baseline in LDH at Day 183 (Week 26) is less than 0.

$$H_o: \mu \geq 0 \text{ versus } H_a: \mu < 0$$

Where μ represents the mean percent change from baseline in LDH at Day 183 (Week 26).

3.3.3 Visit Window

Summaries over postbaseline time points or analyses at specific postbaseline time points will be performed based on the list of visits described in the schedule of assessment of the protocol. For all assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) – (date of first study intervention) + 1. This number of days will be used to assign analysis visit. This may not always correspond to the electronic case report form visit.

All postbaseline records including those that occurred outside the specified protocol windows will be assigned to an appropriate analysis visit by using the following scheme and will be included in the analysis of the specific assessment.

For all visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of two adjacent scheduled visits. If the assessment date falls between the lower bound and the upper bound for a visit as defined in the protocol schedule of assessment, it will be assigned to that visit. If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value. For example, for an assessment with a scheduled visit Day 127, and a prior scheduled visit Day of 99 and subsequent scheduled visit Day of 155, the window will start at Day 114 and will go to Day 141.

If only one record is within an analysis visit window, the data from that record will be used in the analysis. If more than one record is within the same analysis window, the record closest to the midpoint of the interval will be used in the analysis. If two records are "tied" before and after the midpoint of the interval, the earlier record will be used in the analysis.

If there are multiple records on the same date, the last measurement will be used for analyses.

Listings will display all values including unscheduled visits contributing to a time point for a participant.

Visit windows are described in Table 2, Table 2.1, Table 2.2, Table 2.3, and Table 2.4.

Table 2 Time Windows for Allocation of Data to Visits

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline[1]	-28 to 1	-28	1[1]
Primary Treatment Period			
Day 8 (End of week 1)	8	2	11

Day 15 (End of week 2)	15	12	22
Day 29 (End of week 4)	29	23	36
Day 43 (End of week 6)	43	37	57
Day 71 (End of week 10)	71	58	85
Day 99 (End of week 14)	99	86	113
Day 127 (End of week 18)	127	114	141
Day 155 (End of week 22)	155	142	169
Day 183 (End of week 26)[2]	183	170	211
Extension Treatment Period			
Day 239 (End of week 34)	239	212	267
Day 295 (End of week 42)	295	268	323
Day 351 (End of week 50)	351	324	379
Day 407(EOS) (End of week 58)	407	380	414

1. The baseline starts from screening and lasts up to the date and time of the first dose.
2. Ravulizumab administration on Day 183 is considered to be part of the Extension Treatment Period. Any measurements collected after ravulizumab administration Day 183 are considered as measurements in the Extension Treatment Period.
3. The two footnotes above also apply to Table 2.1, 2.2, 2.3, and 2.4.
4. Visit window is not applicable for PK/PD endpoints.

Table 2.1 Time Windows for Allocation of PNH Clone Size Data to Visits

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 71 (End of week 10)	71	2	127
Day 183 (End of week 26)	183	128	211
Extension Treatment Period			
Day 239 (End of week 34)	239	212	267
Day 295 (End of week 42)	295	268	323
Day 351 (End of week 50)	351	324	379
Day 407(EOS) (End of week 58)	407	380	414

Table 2.2 Time Windows for Allocation of FACIT-Fatigue Data to Visits

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 8 (End of week 1)	8	2	18
Day 29 (End of week 4)	29	19	50
Day 71 (End of week 10)	71	51	99

Day 127 (End of week 18)	127	100	155
Day 183 (End of week 26)	183	156	267
Extension Treatment Period			
Day 351 (End of week 50)	351	268	358

Table 2.3 Time Windows for Allocation of ECG Data to Visits

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 71 (End of week 10)	71	2	127
Day 183 (End of week 26)	183	128	185

Table 2.4 Time Windows for Allocation of Urinalysis and Urine Chemistry Data to Visits

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 15 (End of week 2)	15	2	22
Day 29 (End of week 4)	29	23	50
Day 71 (End of week 10)	71	51	99
Day 127 (End of week 18)	127	100	155
Day 183 (End of week 26)	183	156	211
Extension Treatment Period			
Day 239 (End of week 34)	239	212	267
Day 295 (End of week 42)	295	268	323
Day 351 (End of week 50)	351	324	379
Day 407(EOS) (End of week 58)	407	380	414

3.3.4 Handling of Unscheduled Visits

Unscheduled visits are included in the method of assigning data to scheduled visits described in the rules in section 3.3.3 above. Unscheduled visits are not included as a separate visit in the summary tables, but they will be included in all listings of study data.

3.3.5 Multiplicity/Multiple Comparisons

The Type I error for the testing of the primary endpoint will be controlled at a 1-sided significance level of 0.025. No multiplicity adjustments will be made for the analyses of secondary and exploratory endpoints.

3.3.6 Handling of Protocol Deviations in Study Analysis

Important protocol deviations relating to participant-level and participant-visit level events are defined in the PD Plan. They will be reviewed by appropriate medical, clinical, data management, and statistical personnel and will be documented prior to each database lock.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain (study population, efficacy, pharmacodynamic, pharmacokinetics, immunogenicity, safety).

4.1 Study Population

The domain of study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, disease characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participant disposition and completion status will be provided for but not limited to the following:

- Consented participants
- Participants who received treatment
- Participants who completed Primary Treatment Period
- Participants who discontinued from Primary Treatment Period (along with the reasons of treatment discontinuation)
- Participants who completed Extension Treatment Period
- Participants who discontinued from Extension Treatment Period (along with the reasons of treatment discontinuation)
- Participants who completed the study
- Participants who withdrew from the study (along with the reasons of study discontinuation)

4.1.1.2 Presentation

A disposition summary table for all participants in the screened set will be provided. The number and percentages of participants will be presented by the categories in section 4.1.1.1, and the percentages are based on FAS.

Disposition listings will include participant ID, age, gender, race, disposition event, reason and date.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Refer to section 3.2 for the definition of analysis sets.

4.1.2.2 Presentation

The number and percentage of participants included in each analysis set, along with the reasons for exclusion from either of the analysis sets where relevant, will be summarized.

A listing of participants excluded from any analysis set will include participant ID and reasons for exclusion from analysis set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Refer to section 3.3.6 for the definition of protocol deviations.

4.1.3.2 Presentation

The number and percentage of participants with any important protocol deviations (IPD), as well as the number and percentage of participants experiencing an IPD in a particular category, will be summarized descriptively as categorical variables.

A listing of participants with any IPD will be presented and sorted by participant ID, IPD category, and the date of observation.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic data is recorded in the eCRF at the screening visit. Demographic variables summarized as part of the description of the study population are as follows:

- Age (years)
- Age group (<65, ≥65 years)
- Sex (Male, Female)

- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

4.1.4.2 Presentation

Demographics will be summarized and listed for all participants in the FAS. This listing will include participant ID, age, sex, ethnicity, and race, and will be presented sorted by participant ID.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics summarized as part of the description of the study population are as follows:

- Height (cm)

- Weight (kg)

- Weight group (>=40 - <60 kg, >=60 - <100 kg, >=100 kg)

- BMI (kg/m^2)

- Baseline LDH (U/L)

- Baseline FACIT-Fatigue

Refer to section 3.3.1.1 for definition of baseline. BMI will be calculated using the below formula:

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{Height^2\ (m^2)}$$

4.1.5.2 Presentation

Baseline characteristics will be listed and summarized for all participants in the FAS. This listing will include participant ID, age, sex, race, height, weight, BMI, baseline LDH, and baseline FACIT-Fatigue, and will be sorted by participants ID.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

PNH disease characteristics will be summarized for the following parameters:

- Age (year) at PNH diagnosis
- Method of PNH diagnosis (Flow cytometry and/or FLAER, Other)
- PNH disease duration (year)
- History of any major adverse vascular event (MAVE). The number of participants with any history of MAVE and within a particular MAVE category (e.g. thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infraction etc.) will be displayed
- Transfusion requirements within one year prior to first dose of study treatment including number of transfusion episodes and units transfused
- PNH clone size at screening (Granulocyte, Monocyte, Red blood cell type I/II/III, Total RBC clone size (RBC type II + type III))
- Absolute reticulocyte count (10^12/L)
- Hemoglobin (g/L)

Age at PNH diagnosis will be presented as the number of years between the date of birth and the date of PNH diagnosis (i.e. INT [(Date of PNH diagnosis - Date of birth + 1) / 365.25]).

PNH disease duration will be presented as the number of years between the date of first infusion and the date of PNH diagnosis (i.e. (Date of first infusion – Date of PNH diagnosis + 1) / 365.25, and will be rounded to 1 decimal place).

Missing date imputation refers to section 3.3.1.3.

4.1.6.2 Presentation

Disease characteristics will be summarized using descriptive statistics for all participants in FAS.

A listing of major adverse vascular events history will be presented sorted by participant ID, MAVE category, method of diagnosis, and data of diagnosis/resolution.

A listing of transfusion within one year prior to first dose will be presented and sorted by participant ID, transfusion date, blood product type, number of units transfused, and hemoglobin level prior to transfusion.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history including all relevant medical/surgical history and PNH medical history are collected at the screening visit are classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities.

4.1.7.2 Presentation

Medical history is grouped by MedDRA System Organ Class (SOC) and Preferred Term (PT) and is summarized by SOC and PT, for all participants in FAS. Surgical history is summarized by SOC and PT, for all participants in FAS. Participants with histories in more than one SOC/PT are counted only once in that SOC/PT. Tables will be sorted by international order for SOC and in alphabetical order for PT.

A listing of medical history will be presented sorted by participant ID, SOC category, PT category, reported term, and data/time of observation for the FAS.

PNH medical history is summarized by PNH symptoms experienced and PNH associated conditions that were diagnosed for all participants in FAS.

A listing of PNH medical history will be presented sorted by participant ID, date of initial PNH symptom onset, date of initial PNH diagnosis, method of initial PNH diagnosis, PNH symptoms that were experienced and PNH associated conditions that were diagnosed.

A listing of surgical history will be presented sorted by participant ID, PT category, reported term, and data/time of observation for the FAS.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior medications and concomitant medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment. Prior medications include all medications taken within 28 days prior to informed consent as well as all Neisseria meningitides vaccinations administered within 3 years of dosing with study treatment.

- Concomitant medications are those with a stop date on or after the first dose date of study treatment, and must have started prior to or during study so there is at least one day in common with the study period form first infusion of study treatment through last study visit.

Concomitant medications include allowed and disallowed medications taken by the participants. Missing medication start and stop dates will be imputed according to Section 3.3.1.3. For the definition of disallowed medications and therapy, see Appendix 7.1.

Procedures that the participant takes or undergoes during the study period will be recorded in the participant's eCRF.

4.1.8.2 Presentation

Prior and concomitant medications will be classified according to the latest version of the WHO Drug coding dictionary. Prior and concomitant medications will be summarized for all participants in FAS, and medications will be presented by WHO Drug Anatomical Therapeutic Chemical (ATC) and by WHO Drug generic name. Participants with the same medication multiple times will be counted once per medication.

Listings of prior (excluding Neisseria meningitides vaccinations administered) and concomitant medications will be produced. A by-participant listing of Neisseria meningitides vaccinations will be produced showing the date of vaccinations for each participant.

Procedure is grouped by System Organ Class and preferred term which will be coded by the latest version of the MedDRA, and is summarized by System Organ Class (SOC) and Preferred Term (PT), for all participants in FAS. Participants with procedure in more than one PT are counted only once in that PT. Tables are sorted by international order for SOC and in alphabetical order for PT.

Listings of procedures will be presented sorted by participant ID, procedure name, and date/time of observation.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Percent compliance of Primary Treatment Period = 100% * Total number of infusions taken from Day 1 to end of Primary Treatment Period / Total number of expected infusions of participants in Primary Treatment Period.

Percent compliance of Extension Treatment Period = 100% * Total number of infusions taken during Extension Treatment Period / Total number of expected infusions during Extension Treatment Period.

Percent compliance of study = 100% * Total number of infusions taken from Day 1 to end of study / Total number of expected infusions to end of participants in study.

In order to allow for subjects who discontinue treatment early in the compliance calculation, the total number of expected infusions will be up to the discontinuation date of treatment.

Compliance will be analysed as a continuous variable, as well as categorical variable, with categories defined as <80%, 80% to 120%, and >120%.

4.1.9.2 Presentation

Compliance during the study will be presented by means of descriptive summary statistics, as described in section 3.3. Treatment compliance will be summarized separately for Primary Treatment Period, Extension Treatment Period, and overall study.

4.2 Efficacy Analyses

This section covers details related to the efficacy analyses such as primary, secondary, other exploratory endpoints. All efficacy analyses will be performed using FAS.

Table 3 Summary of Estimands for Efficacy Endpoints

Statistical category	Endpoint	Population	Treatment	Intercurrent event strategy	Population level summary (analysis)
Primary Objective: To evaluate the efficacy of ravulizumab in adult participants with PNH from baseline to Day 183 (Week 26)					
Primary Endpoint (Primary Analysis)	Percentage change in LDH from baseline to Day 183 (Week 26)	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Hypothetical strategy for handling of intercurrent events (discontinuation of study intervention and initiation of disallowed medication): the measurements after premature discontinuation of study intervention will be included till last dose + 8 weeks; and the measurements after the occurrence of disallowed medication will be excluded in the analysis.	Mean percentage change in LDH from baseline to Day 183 (Week 26), estimated using a longitudinal mixed model

Statistical category	Endpoint	Population	Treatment	Intercurrent event strategy	Population level summary (analysis)
Primary Endpoint (Supplementary Analysis)	Percentage change in LDH from baseline to Day 183 (Week 26)	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Treatment policy: intercurrent events ignored	Mean percentage change in LDH from baseline to Day 183 (Week 26), estimated using a longitudinal mixed model
Secondary Objectives: To evaluate the effect of ravulizumab on the following endpoints from baseline to Day 183 (Week 26)					
Secondary Endpoint (Primary Analysis)	Participants achieving LDH < 1.5 × ULN at Day 183 (Week 26)	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Treatment policy: intercurrent events ignored	Proportion of participants achieving LDH < 1.5 × ULN at week 26, estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary Endpoint (Primary Analysis)	Participants achieving transfusion avoidance (TA) through Week 26	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Treatment policy: intercurrent events ignored	Proportion of participants achieving transfusion avoidance through week 26, estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary Endpoint (Primary Analysis)	Participants experiencing breakthrough hemolysis through Day 183 (Week 26)	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Treatment policy: intercurrent events ignored	Proportion of participants experiencing breakthrough hemolysis through week 26, estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary Endpoint (Primary Analysis)	Change in FACIT-Fatigue score from	Treatment Naïve Adult Participants with Paroxysmal	Ravulizumab	Treatment policy: intercurrent events ignored	Mean change in FACIT-Fatigue score from baseline to Day 183 (Week 26),

Statistical category	Endpoint	Population	Treatment	Intercurrent event strategy	Population level summary (analysis)
	baseline to Day 183 (Week 26)	Nocturnal Hemoglobinuria (PNH)			estimated using a longitudinal mixed model
Secondary Endpoint (Primary Analysis)	Change in Hgb from baseline to Day 183 (Week 26)	Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Ravulizumab	Treatment policy: intercurrent events ignored	Mean change in Hgb from baseline to Day 183 (Week 26), estimated using a longitudinal mixed model

4.2.1 Primary Endpoint

The primary endpoint is reduction in hemolysis as evaluated by percentage change from baseline in LDH at Week 26. Descriptive statistics will be presented for LDH values by visits from baseline to the Week 26. Percentage change from baseline will be summarized. In addition, mean LDH values, the change and the percentage change over time will be plotted.

4.2.1.1 Definition

The primary endpoint is reduction in hemolysis as evaluated by percentage change from baseline in LDH at Week 26. For the main analysis of the primary endpoint, a hypothetical strategy will be used to handle intercurrent events, where all LDH measurements after a participant using disallowed therapy or medicine are excluded from the analysis and the LDH measurements after premature discontinuation of study intervention will be included till last dose+8 weeks, reflecting hypothetical scenario where disallowed medication and premature discontinuation of study intervention are not available to participants (i.e. a “hypothetical strategy” type of approach, see ICH E9 (R1) 2017 p. 18).

However, a treatment policy will be applied for supplementary analysis aimed at evaluating the impact of efficacy ignoring intercurrent events.

4.2.1.2 Derivations

See section 3.3.1.1 for definition of baseline, change from baseline, and percentage change from baseline for the efficacy analyses.

4.2.1.3 Handling of Dropouts and Missing Data

Missing assessments of LDH for a particular patient at a particular visit will not be imputed by a particular imputation method. The available longitudinal data will be analyzed by MMRM assuming missing at random.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary efficacy endpoint will be analysed using a Mixed Model Repeated Measure (SAS PROC MIXED). The MMRM will be used to test whether mean percent change in LDH at Week 26 is less than zero. The model will include the percentage change from baseline in LDH at the scheduled visits from Day 8 to Day 183 as the dependent variable, with the fixed categorical effect of visit, fixed continuous effect of the LDH baseline value as covariates, and participant as random effect.

An unstructured covariance matrix will be used to model the within-patient variability. If this analysis model fails to converge, the covariance matrix structures will be evaluated in the following order until model convergence is met: first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The point estimate and 2-sided 95% confidence interval (CI) for the mean percent change in LDH at Week 26 and one-sided p-value will be provided.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

Not applicable.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

A treatment policy will be applied for supplementary analysis aimed at evaluating the impact of efficacy ignoring intercurrent events.

4.2.1.7 Subgroup Analyses

Subgroup analyses for primary endpoint will be conducted as needed.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

The secondary efficacy endpoints will include the following:

- Participants achieving LDH < 1.5 × ULN at Day 183 (Week 26)
- Participants achieving TA through Day 183 (Week 26)
- Participants experiencing breakthrough hemolysis through Day 183 (Week 26)
- Change in FACIT-Fatigue score from baseline to Day 183 (Week 26)
- Change in Hgb from baseline to Day 183 (Week 26)

4.2.2.2 Derivations

See section 3.3.1.1 for definition of baseline, change from baseline, and percentage change from baseline for the efficacy analyses.

Participants achieving TA defined as remaining transfusion free (i.e., have not received any transfusion) and not requiring transfusion as per protocol-specified guidelines.

Participant with breakthrough hemolysis is defined as at least one new or worsening symptom or sign of hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal [ULN], after prior LDH reduction to < 1.5 × ULN on therapy.

The FACIT-Fatigue scale (Version 4.0) is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. It is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. participants will score each item on a 5-point Likert scale: 0 (Not at all) to 4 (Very much). To calculate the FACIT-Fatigue score, the response from negatively stated items (i.e. all items except for FAC07007 and FAC07008) needs to be reversed by subtracting the response from 4. Then the fatigue score is calculated by multiplying the sum of each item scores by 13 and dividing by the number of items answered. When there are missing response, prorating the score in this way is acceptable as long as more than 50% of the items were answered. This score has a range of 0-52, with higher score indicating better QoL.

The Investigator or designee will record the presence or absence of the following signs and symptoms of PNH for each participant: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria at the timepoints specified in the SoA (CSR section 1.3).

4.2.2.3 Handling of Dropouts and Missing Data

For the secondary continuous endpoints, missing assessments for a particular patient at a particular visit will not be imputed by a particular imputation method. The available longitudinal data will be analyzed by MMRM assuming missing at random.

No imputation for the secondary categorical endpoints.

4.2.2.4 Primary Analysis of Secondary Endpoint

For the secondary continuous endpoints of change from baseline, such as FACIT-Fatigue score and Hgb, will be analysed using a Mixed Model Repeated Measure (SAS PROC MIXED). The model will include the change from baseline in FACIT-Fatigue score or Hgb at the scheduled visits from Day 8 to Day 183 as the dependent variable, with the fixed categorical effect of visit, fixed continuous effect of the FACIT-Fatigue score or Hgb baseline value as covariates.

An unstructured covariance matrix will be used to model the within-patient variability. If this analysis model fails to converge, the covariance matrix structures will be evaluated in the

following order until model convergence is met: first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The point estimate and 2-sided 95% confidence interval (CI) for the mean change in FACIT-Fatigue score or Hgb at Week 26 will be provided.

For the secondary categorical endpoints of LDH < 1.5× ULN at Day 183, TA and BTH through Day 183, the observed proportions of participants during the primary treatment period will be summarized along with 95% 2-sided Clopper-Pearson exact CIs.

A treatment policy strategy will be applied for the secondary analysis aiming at evaluating the impact of efficacy ignoring intercurrent events.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

A supplementary analysis for the secondary categorical endpoint will be conducted. A composite strategy will be used to handle intercurrent event premature discontinuation of study intervention due to lack of efficacy. Participants who withdraw from the study treatment due to lack of efficacy during the Primary Treatment Period will be considered as non-responders, which means participants not achieving transfusion avoidance through Day 183, participants not achieving LDH < 1.5 × ULN at Day 183, and participants experiencing breakthrough hemolysis through Day 183.

A supplementary analysis for the secondary endpoint Change in FACIT-Fatigue/Hgb from Baseline at Week 26 will also be conducted. A hypothetical strategy will be used to handle intercurrent events, where all FACIT-Fatigue/Hgb measurements from a participant using disallowed therapy or medicine are excluded from the analysis and the FACIT-Fatigue/Hgb measurements after premature discontinuation of study intervention are included till last dose+8 weeks, reflecting hypothetical scenario where disallowed medication and premature discontinuation of study intervention are not available to participants (i.e. a “hypothetical strategy” type of approach, see ICH E9 (R1) 2017 p. 18).

4.2.2.7 Subgroup Analyses

Subgroup analyses for secondary endpoint will be conducted as needed.

4.2.3 Exploratory Endpoint

4.2.3.1 Definition

The exploratory efficacy endpoints will include the following:

- Percentage change in LDH from baseline through end of study
- Participants achieving LDH < 1.5 × ULN through end of study

- Participants achieving TA through end of study
- Participants experiencing breakthrough hemolysis through end of study
- Change in FACIT-Fatigue score from baseline through end of study
- Change in Hgb from baseline through end of study
- Participants achieving LDH normalization through end of study
- Time to first occurrence of LDH normalization through end of study
- Participants achieving stabilized hemoglobin through end of study
- Participants achieving hemoglobin normalization through end of study
- Total number of units of pRBC transfused through end of study
- Participants experiencing MAVEs through end of study

4.2.3.2 Derivations

Refer to section 4.2.2.2 for the definitions of FACIT-Fatigue score, participants achieving TA, and participant with breakthrough hemolysis.

LDH normalization defined as LDH ≤ ULN.

Participants achieving stabilized hemoglobin is defined as avoidance of a ≥ 2g/dL decrease in hemoglobin level from baseline in the absence of transfusion.

Hemoglobin normalization defined as hemoglobin ≥ LLN.

4.2.3.3 Handling of Dropouts and Missing Data

No imputation for all exploratory endpoints.

4.2.3.4 Analysis of Other Endpoint

The exploratory analyses will be descriptive in nature.

The exploratory continuous endpoints will be evaluated by assessing the absolute values, changes from baseline and percentage change from baseline in LDH, FACIT-Fatigue score, and Hgb over time. Descriptive statistics include number of participants, mean, SD, median, Q1, Q3, minimum and maximum. In addition, a line plot of LDH, FACIT-Fatigue score, and Hgb by visit will be presented.

Descriptive statistics will also be calculated for total number of units of pRBC transfused through end of study. Kaplan-Meier curve and estimate of the time to first occurrence of LDH normalization through end of study will be produced. Subjects with no observed events are censored at the date of withdrawal from study, death or the end of study if any applicable.

For the exploratory categorical endpoints of LDH < 1.5× ULN by visit, TA, BTH, LDH normalization by visit, stabilized hemoglobin, hemoglobin normalization by visit, and experiencing MAVEs, the observed proportions of participants will be summarized along with 95% 2-sided Clopper-Pearson exact CIs. In addition, a bar graph of numbers (percentage) of LDH < 1.5× UL, LDH normalization and hemoglobin normalization by visit will be presented.

Listings of PNH symptomatology, FACIT-Fatigue score, transfusions during the study, breakthrough hemolysis, and major adverse vascular events (MAVE) will be provided.

4.2.3.5 Additional Analyses of the Other Endpoint

Not applicable.

4.2.3.6 Subgroup Analyses

Not applicable.

4.3 Pharmacodynamic Endpoint(s)

4.3.1 Definitions and Derivations

Serum samples will be collected for measurement of free C5 as specified in the SoA (CSP section 1.3).

4.3.2 Presentation

Any analyses of pharmacodynamic data will be made on the PD Analysis Set.

The PD effects of ravulizumab will be evaluated by assessing the absolute values, changes from baseline and percentage change from baseline in serum free C5 concentrations over time. Descriptive statistics will be calculated for serum free C5 concentration data by timepoints (i.e pre-dose, post dose or anytime for each scheduled visit), including number of participants, mean, SD, CV (%), median, minimum and maximum. For any result with a value below the LLOQ, LLOQ/2 is used in the analysis.

Serum free C5 concentrations vs. scheduled visits will be graphically demonstrated in boxplots (linear scale and semi-log scale) over study days based on the timepoints (i.e pre-dose, post-dose or anytime) in each scheduled visit.

A listing of serum free C5 concentrations will also be provided.

4.4 Pharmacokinetics

4.4.1 Definitions and Derivations

Blood samples will be collected for measurement of serum concentrations of ravulizumab as specified in the SoA (CSP section 1.3). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing.

4.4.2 Presentation

Any analyses of pharmacokinetics data will be made on the PK Analysis Set. Any issues considered to impact the PK data (such as, but not limited to participants not receiving complete/full intended dose) may result in the exclusion of concentration data from the PK analysis or exclusion from the PK summaries or descriptive statistics. The available concentration data for any participants excluded from the PK data summaries or descriptive statistics will be listed.

Graphs of mean and individual serum ravulizumab concentration-time profiles will be provided. Descriptive statistics will be calculated for serum drug concentration data at each sampling time (i.e pre-dose, post dose or anytime for each scheduled visit), including number of participants, mean, SD, CV (%), geometric mean, geometric CV (%), median, minimum and maximum. PK concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures. Ravulizumab concentrations vs. scheduled visits will be graphically demonstrated in boxplots (linear scale and semi-log scale) over study days based on the timepoints (i.e pre-dose, post-dose or anytime) in each scheduled visit.

Concentrations that are below the LLOQ will be handled as follows for the provision of descriptive statistics:

- At a time point where less than or equal to 50% of the concentration values are NQ (Not Quantifiable), all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.

- At a time point where more than 50% (but not all) of the values are NQ, the geometric mean, geometric SD and geometric CV (%) will be set to NC (Not Calculated). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.

- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The mean, geometric mean, minimum, median and maximum will be reported as NQ, and the geometric CV (%), SD and geometric SD will be reported as NC.

- The number of values below LLOQ will be reported for each time point together with the total number of collected values (n).

Descriptive statistics will also be calculated for serum drug concentration data at each sampling time by body weight (≥40 - <60 kg, ≥60 - <100 kg, ≥100 kg).

A listing of serum ravulizumab concentrations will also be provided.

4.5 Immunogenicity

4.5.1 Definitions and Derivations

Immunogenicity variables include ADA status, ADA response category, ADA titers and NAb status over the duration of the study.

ADA status categories:

- ADA positive: collected sample is tested positive at any time during the study, including baseline and/or post-baseline

- ADA negative: collected samples are tested negative at all time points, including baseline and post-baseline

Participants who are ADA positive will be further categorized into ADA response categories as follows:

- Pre-existing immunogenicity: ADA positive at baseline

- Treatment-emergent ADA responses: any post-treatment positive ADA assay response when the baseline ADA result is negative or missing

- Treatment-boosted ADA responses: post-baseline increase in pre-existing baseline ADA titres by ≥ 4-fold during the study period

Participants with treatment-emergent response will be further categorized as:

- Persistent treatment-emergent responses: treatment induced ADA (participant is ADA negative at baseline) detected at ≥ 2 post-baseline assessments with at least 16 weeks (112 days) between the first and last positive measurement, irrespective of missing samples.

- Indeterminant treatment-emergent responses: treatment induced ADA detected at the last available assessment.

- Transient treatment-emergent responses: at least one treatment induced (participant is ADA negative at baseline) ADA positive measurement, but not fulfilling the conditions for a persistently positive nor an indeterminant response.

ADA positive samples will be further characterized for neutralizing activity in a NAb assay. NAb status categories are as follows:

- NAb positive: NAb-positive at any time during the study, including baseline and/or post-baseline

- NAb negative: NAb-negative at all time points, including baseline and/or post-baseline

4.5.2 Presentation

All immunogenicity analyses will be performed on the Immunogenicity Analysis Set.

ADA status and ADA response categories will be summarized as absolute occurrence (n) and percentage of all participants.

NAb status will be summarized as absolute occurrence (n) and percentage of all participants.

A listing of ADA samples results will also be provided.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Tables are provided for the participants in the safety set. Listings are provided for the safety set depending on the availability of data.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure duration of Primary Treatment Period is total time on study intervention (days) calculated as the time in days from first study drug infusion date until the last study drug infusion date during the Primary Treatment Period (i.e. intervention duration = last study intervention date from the Primary Treatment Period - first study intervention date + 56). Note that intervention on Day 183 is the start of the Extension Treatment Period and will not be included in these calculations.

Exposure duration of Extension Treatment Period is total time on study intervention (days) calculated as the time in days from first study drug infusion date until the last study drug infusion date from the Extension Treatment Period (i.e intervention duration = last study intervention date from the Extension Treatment Period - first study intervention date from the Extension Treatment Period + 56).

Exposure duration of entire study is total time on study intervention (days) calculated as the time in days from first study intervention date until the last study intervention date from entire study (i.e. study intervention duration = last study intervention date in the study – first study intervention date + 56)

4.6.1.2 Presentation

Summary tables of the extent of exposure will be presented, including the Primary Treatment Period, Extension Treatment Period, and throughout the entire study. The duration on treatment (in days), the number of infusions, the number of infusion interruption, and the total dose (in mg) through the first 26 weeks (i.e. Primary Treatment Period) will be summarized using descriptive statistics.

Individual participant data for study drug administration will be listed for all participants respectively in the SS.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse events (AE) and serious adverse events (SAE) are defined as per CSP section 10.3. AEs will be classified by SOC and PT using the latest available version of MedDRA. The adverse event will be determined as occurring prior to treatment (pre-treatment) or as on or after first treatment (treatment-emergent). Treatment-emergent adverse event (TEAE) is defined as any AE that starts during or after the first infusion of study intervention.

In this study, meningococcal infection is considered to be AESI.

4.6.2.2 Presentation

The onset date of the AE determines the phase in which the AE will be summarized. AEs will be summarized separately for Primary Treatment Period, Extension Treatment Period, and overall study. All AEs, including those considered pre-treatment AEs, will be included in safety listings.

Overall Summary of Adverse Events

An overall summary table of AEs will be presented using summary statistics. The number and percentage of participants with events will be displayed for the following events subcategories. Corresponding detailed by-participant AE listings will also be provided separately.

- The number and percentage of participants with TEAEs
- The number and percentage of participants with TEAEs by maximum CTCAE grade

- The number and percentage of participants with related TEAEs
- The number and percentage of participants with SAEs
- The number and percentage of participants with related SAEs
- The number and percentage of participants with TEAEs leading to treatment discontinuation
- The number and percentage of participants with TEAEs with an outcome of fatal
- The number and percentage of participants with AESI

TEAEs by System Organ Class (SOC) and Preferred Term (PT)

The number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Tables will be sorted by international order for SOC and in alphabetical order for PT.

Related TEAEs, SAEs, related SAEs, TEAEs leading to treatment discontinuation, TEAEs with an outcome of fatal, and AESI will be summarized similarly.

TEAEs by SOC, PT, and Relationship

The number and percentage of participants with events will be presented by SOC and PT as described above by relationship (related/not related). If a participant has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

TEAEs by SOC, PT, and Severity

The number and percentage of participants with events will be presented by SOC and PT as described above by severity (CTCAE grade 1 - 5). If a participant has more than one occurrence of an AE, the highest grade to study treatment will be used in the summary table. Related TEAEs and SAEs will be summarized similarly.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

A full list of laboratory parameters in provided in CSP section 10.2. The tests will be performed by the central laboratory. Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation.

4.6.3.2 Presentations

The clinical haematology and chemistry will be summarized based on central laboratory. Local laboratory results will only be listed in the listings.

Descriptive statistics by time of assessment will be presented for each laboratory parameters. For each summary of continuous variables, the number of non-missing observations, mean, median, Q1, Q3, standard deviation, minimum, and maximum values on treatment will be presented. For purposes of analyses, laboratory results based upon standardized units and/or conventional units as appropriate will be used.

Absolute values and change from baseline for all continuous haematology and clinical chemistry parameters will be summarized by visit.

All laboratory values will be classified as low, normal, or high based on normal ranges supplied by the central laboratory. Baseline versus treatment emergent maximum and minimum values shift table will be provided.

Box plots of absolute values by scheduled visit, and box plots of change from baseline by visit, may be presented for certain parameters if warranted after data review.

Additionally, participant listings of all haematology and chemistry will be presented.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Refer to section 4.6.3.1 for the definitions.

4.6.4.2 Presentations

The clinical urinalysis parameters will be summarized based on central laboratory. Local laboratory results will only be listed in the listings.

Absolute values and change from baseline for all continuous urinalysis will be summarized by visit. Urinalysis baseline versus treatment emergent maximum and minimum values shift table will also be provided.

For categorical urinalysis parameters, results will be categorized as positive, negative, trace, +1, +2, +3, etc., the number and percentage of participants with each result will be summarized.

Additionally, participant listing of urinalysis parameters will be presented.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Pregnancy data from all women of childbearing potential (WOCBP) will be collected at the protocol-specified timepoints in the SoA (CSP section 1.3).

WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry will be recorded at the timepoints specified in the SoA (CSP section 1.3).

4.6.5.2 Presentations

Pregnancy data will be listed only, no summary tables will be produced.

Absolute values and change from baseline for PNH clone size assessments will be summarized for the scheduled visits. Corresponding listing will also be provided.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs will include assessments of systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), temperature (C/F), respiration rate (breaths/min), heart rate (beats/min), and weight (kg).

4.6.6.2 Presentations

Summary statistics for vital signs will be calculated for absolute values and change from baseline to each subsequent planned visit where applicable. For each summary, the number of non-missing observations, mean, median, standard deviation, minimum, and maximum will be presented.

A listing of vital signs will be provided.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

ECG parameters will include ECG mean heart rate (beats/min), QRS duration (msec), PR interval (msec), QT interval (msec), and QTc interval (msec).

QTc interval will be calculated using the Fridericia formula:

$$QTcF = \frac{\mathrm{QT}(msec)}{(RR(msec)/1000)^{1/3}}$$

Where:

1. RR (msec) = (60/HR) * 1000

2. RR = RR interval

3. HR = Heart rate

4.6.7.2 Presentations

Electrocardiograms will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on treatment ECG table will be presented for ECG results. This table will be presented separately for Primary Treatment Period.

Observed values and change from baseline for all ECG parameters will be summarized descriptively at baseline and each postbaseline timepoint.

An ECG listing of participants with overall ECG evaluation will be provided.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Refer to CSP section 8.3.1 for the physical examinations.

4.6.8.2 Presentations

Adverse changes from baseline in physical examination findings will be classified as AEs and analysed accordingly.

5 INTERIM ANALYSIS

An interim efficacy and safety assessment will be conducted as Primary Analysis when all participants have completed 26-week Primary Treatment Period or withdraw from the 26-week Primary Treatment Period following the primary Database Lock. A CSR will be developed based on efficacy and safety data collected through the end of the 26-week Primary Treatment Period after the primary DBL. It will be utilized for the submission of the NDA in China.

6 REFERENCES

Not applicable.

7 APPENDIX

7.1 Appendix A: Disallowed Medications

Disallowed Medicine and Therapy	
Drug category	**Prohibited drug name**
chemotherapy	fludarabine
	cyclophosphamide
	bendamustine
	chlorambucil
	pentostatin
	cytarabine
	cisplatin
	oxaliplatin
	carboplatin
	doxorubicin
	vincristine
	methotrexate
	etoposide
	gemcitabine
	procarbazine
	vinorelbine
	ifosfamide
	lenalidomide
	Thalidomide
	bortezomib
Complement Inhibitor	Eculizumab

Disallowed Medicine and Therapy	
Drug category	**Prohibited drug name**
	Crovalimab
	Iptacopan
	Pegcetacoplan
	CG001
	KP104
	CAN106
	SB12

Signature Page for VV-RIM-07118897 System v4.0
D9289C00008 Statistical Analysis Plan Edition 2

Approve: Document Level Task Verdict: Approved	PPD Content Approval 07-Jul-2025 01:12:12 GMT+0000

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