STATISTICAL ANALYSIS PLAN	
Study Code	D7414C00001
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Open-Label, Multicenter Study to Assess the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab 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
AESI	adverse event of special interest
C	complement component
C5b-9	terminal complement complex
CDL	Clinical Database Lock
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical Study Report
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
PD	pharmacodynamic(s)
PDAS	Pharmacodynamic analysis set
PK	pharmacokinetic(s)

Abbreviation or Term	Explanation
PKAS	Pharmacokinetic analysis set
PNH	paroxysmal nocturnal hemoglobinuria
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SS	Safety analysis set
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	Table Listing Figure
ULN	upper limit of normal
WOCBP	woman of childbearing potential

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	5/16/2023	Initial approved SAP. In line with CSP version 1.0 (30-Nov-2021).	N/A	N/A
Data presentation	10/30/2024	Section 3.2 Table 1: clarified that different analysis sets will be used for Table and Listing in terms of Study Population.		Provided additional clarification.
Data presentation	10/30/2024	Section 3.3: updated the handling of decimals according to AZ standard output principle.		In line with AZ standards.
Data presentation	10/30/2024	Section 3.3.1: added instruction to handle out of quantification limits data in safety analysis.		Provided imputation rule for out of quantification limits data.
Data presentation	10/30/2024	Section 3.3.1.4: added instruction to impute missing PNH diagnosis dates.		Provided imputation rule for missing PNH diagnosis dates.
Data presentation	10/30/2024	Section 3.3.1.5: added the handling of out of quantification limits data.		Provided the handling of out of quantification limits data.
Statistical analysis method for primary endpoint	10/30/2024	Section 3.3.3 and Section 4.2: modified the terms of mixed model regarding use the absolute LDH instead of natural log scale; added random effect term.		Provided additional clarification and in line with CSP.

Statistical analysis method for primary endpoint	10/30/2024	Section 3.3.3 and Section 4.2.1.4: log-scale is replaced by arithmetic scale in the statistical analysis of LDH		Updated to be consistent with CSP
Data presentation	10/30/2024	Section 3.3.4: clarified the rules of mapping visit windows; added tables for specific parameters; added footnote and safety follow up phone call in the table of visit window.		Provided additional clarification.
Data presentation	10/30/2024	Section 3.3.4: clarified the rules and added footnote and safety follow up phone call in the table of visit window		Provided additional clarification.
Data presentation	10/30/2024	Section 4.1.2.2: removed the reasons for exclusion from each analysis sets.		Removed for simplification and provided clarity for TLFs.
Data presentation	10/30/2024	Section 4.1.4: removed few categories for Race; removed age group in listing for demographics; added unit of LDH.		Removed to be in line with CRF collection. Provided clarity for TLFs.
Data presentation	10/30/2024	Section 4.1.6: added specific formulas to compute age at PNH diagnosis and PNH disease duration; updated the category of PNH clone sizes		Provided additional clarification.

Data presentation	10/30/2024	Section 4.1.7: updated the order of sorting SOC and analysis set to be used for listings; removed date/time of the initial PHN symptom onset.		Provided clarity for TLFs.
Data presentation	10/30/2024	Section 4.1.8: updated the period used in the definition of concomitant medications.		Provided additional clarification.
Data presentation	10/30/2024	Section 4.1.9: provided the calculation for percent compliance of long-term extension period.		Provided additional clarification.
Secondary endpoint(s)	10/30/2024	Section 4.2: added formal definition of transfusion avoidance.	Yes (CSP Amendment 1.0, 6-Nov-2023)	No changes to analyses, provided additional clarification.
Secondary endpoint(s)	10/30/2024	Section 4.2: added one secondary endpoint (Number (%) of participants achieving LDH normalization at Week 12) and corresponding analysis method.	Yes (CSP Amendment 1.0, 6-Nov-2023)	Provided additional clarification.
Statistical analysis method for secondary endpoint(s)	10/30/2024	Section 4.2: updated the description of endpoints, intercurrent event strategy and population level summary.	Yes (CSP Amendment 1.0, 6-Nov-2023)	No changes to analyses, updated the description for clarity.
Statistical analysis method for secondary endpoint(s)	10/30/2024	Section 4.2.1 and Section 4.2.2: updated hypothetical strategy for handling of intercurrent events		Provided additional clarification.

Derivation of secondary endpoint(s)	10/30/2024	Section 4.2.2.2: updated the calculation rule of the Facit-Fatigue score.		Provided additional clarification.
Data presentation	10/30/2024	Section 4.3.2 and Section 4.4.2: added instruction for the summary table and plot of the PD and PK data.		Provided additional clarification.
Data presentation	10/30/2024	Section 4.5.2: clarified that analysis of immunogenicity data will be performed on safety set; updated the definition of TE ADA responses.		Provided additional clarification.
Data presentation	10/30/2024	Section 4.6.1: updated the calculation of exposure duration.		Provided additional clarification to consider half life of the treatment.
Data presentation	10/30/2024	Section 4.6.2.2: clarified only TEAE will be summarized; added the summary table of TEAEs for the Long-term Extension Period; added categories to the overall summary of AEs; added overall summary in terms of event count.	Yes (CSP Amendment 1.0, 6-Nov-2023)	Added supportive analysis for CSR.
Data presentation	10/30/2024	Section 4.6.3 and 4.6.4: clarified the list of parameters for clinical laboratory; clarified the units to be used; updated the categories to be used for urinalysis results.		Provided additional clarification.

Data presentation	10/30/2024	Section 4.6.5: added the summary statistics table of PNH clone size by visit timepoints.		Added supportive analysis for CSR.
Data presentation	10/30/2024	Section 4.6.7: clarified the summary of ECG evaluations; removed the summary related to QTc intervals.		Provided clarity to TLFs.
Other	10/30/2024	Appendix B: updated list of disallowed medications.		Updated to align with the most recent version of Drug Code
Other	10/30/2024	Minor updates for formatting, syntax, grammar and abbreviations.		No changes to content. Updated for clarity and consistency.
Data presentation	5/8/2025	Section 4.2.1 and 4.2.2: updated the figure presentation to line plot/box plot		Provided clarity to TLFs.
Derivation of secondary endpoint(s)	5/8/2025	Section 4.5.1: added definition of treatment-emergent ADA responses		Provided additional clarification.
Data presentation	5/8/2025	Section 4.6.1.1: updated the calculation of intervention duration		Provided additional clarification.

Data presentation	5/8/2025	Appendix: removed Appendix A IPD Master list since it was covered in a separate document (PD plan) and updated list of Disallowed Medications to Appendix A.		No changes to analyses. Simplified the appendix.

1 INTRODUCTION

The purpose of this document is to give details for statistical analysis of study D7414C00001 (ECU-PNH-301) 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 analyses in the CSP for the ECU-PNH-301 study and is based on Amendment 1 of the CSP dated 2023-11-6.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The final analysis will be performed after Clinical Database Lock (CDL).

An interim analysis, if deemed necessary, may be performed after all participants complete or withdraw early from the Primary Treatment Period which will allow for evaluation of the primary endpoint and will be the basis for the initial clinical study report (CSR).

3.2 Analysis Populations

Four main analysis populations are defined of this study, the full analysis set (FAS), the safety analysis set (SS), Pharmacokinetic Analysis Set (PKAS) and Pharmacodynamic Analysis Set (PDAS). Efficacy analyses will be performed on the FAS. Safety analyses will be performed on the SS. PK analyses will be performed on the PKAS. PD analyses will be performed on the PDAS.

3.2.1 Full analysis set

Full analysis set (FAS) will include all participants who receive at least 1 dose of study intervention and have at least 1 efficacy assessment post first dose. All efficacy analyses, unless otherwise specified, will be performed using the FAS.

3.2.2 Safety analysis set

The safety analysis set (SS) will consist of all participants who receive at least 1 dose of study intervention. Safety analysis will be performed based on the SS.

3.2.3 Pharmacokinetic Analysis Set (PKAS)

Pharmacokinetic analysis set (PKAS) will consist of all participants who receive at least 1 dose of study intervention and who have evaluable pharmacokinetic data.

3.2.4 Pharmacodynamic Analysis Set (PDAS)

Pharmacodynamic analysis set (PDAS) will consist of all participants who receive at least 1 dose of study intervention and who have evaluable pharmacodynamic data.

The analysis sets used for each outcome are provided in Table 1.

Table 1 Summary of outcome variables and analysis populations

Outcome variable	Analysis set
Efficacy data	
Primary endpoint/variables	FAS
Secondary endpoints/variables	FAS
Study population[1]	
Demography characteristics	FAS (Table), SS (Listing)
Baseline and disease characteristics	FAS (Table), SS (Listing)
Important protocol deviations	FAS (Table), SS (Listing)
Medical/surgical history	FAS (Table), SS (Listing)
Concomitant medications	FAS (Table), SS (Listing)
Study drug compliance	FAS (Table), SS (Listing)
Safety data	
Exposure	SS
AEs	SS
Laboratory measurements	SS
Vital signs	SS
ECG	SS
Pharmacokinetics	PKAS
Pharmacodynamics	PDAS
Immunogenicity	SS

1. For study population variables, all summary table will be generated based on FAS and all listings will be produced based on SS.

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 timepoint 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) and standard error (SE) 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 two-sided p-value, unless otherwise stated. All p-values will be nominal for this study. 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

Efficacy Baseline

The baseline for LDH is defined as the average of all available assessments prior to the first study intervention.

The baseline for FACIT-Fatigue will be established based on the last available assessment prior to treatment (first study intervention).

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

Safety/PK/PD Baseline

Baseline will be the last non-missing measurement taken prior to first intervention. 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 and there are no pre-specified missing value imputation rules, 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 AE and SAE

AE and SAE are defined in Section 8.3 of the CSP.

3.3.1.3 Definition of Treatment-emergent

Treatment-emergent adverse event (TEAE) is defined as any AE that starts during or after the first infusion of study intervention. Treatment-emergent ADA (TEADA) is defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing.

3.3.1.4 Handling of missing dates

Missing adverse event (AE) and concomitant medication (CM) start and end dates will be imputed as follows:

For 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.

For 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.

Missing PNH diagnosis dates will be imputed by the following rules: impute the 15th of the month for missing day; impute the June 30th for missing day and month; no imputation made for completely missing. If the imputed date of PNH diagnosis is on or after study consent date, then consent date -1 will be used.

3.3.1.5 Handling of out of quantification limits data

For safety analysis 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 Hypotheses

Not applicable.

3.3.3 Mixed Model: Terms and Estimation

The form of the linear mixed effects model employed in the analyses in this study is as follows:

$$Y_{ij} = X_{ij}\beta + Z_i b_i + \varepsilon_{ij}$$

where:

1 Y_{ij} is the j^{th} measurement for the i^{th} participant.

2 X_{ij} is the matrix of fixed effects covariates.

3 β is a vector containing the fixed-effects regression coefficients.

4 Z_i represents the random effects covariates.

5 b_i is a normally distributed random effect parameter.

6 ε_{ij} is a normally distributed random error term.

Variance components will be estimated using a restricted maximum likelihood method (REML) and an unstructured marginal covariance structure will be assumed. If the specified model fails to converge, the final covariance structure will be determined by Akaike's information criteria: Toeplitz, first-order autoregressive and compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For the analysis of primary endpoint, the model will include the percentage change from baseline in LDH at the scheduled visits from Day 8 to Day 85 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.

For the analysis of secondary endpoint: Change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at week 12, the model will include FACIT-Fatigue score change from baseline values at the scheduled visits from Day 8 to Day 85 as dependent variable, the fixed categorical effect of visit, fixed continuous effect of baseline value of FACIT-Fatigue as covariates, and participant as random effect..

3.3.4 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 113 and subsequent scheduled visit Day of 141, the window will start at Day 121 and will go to Day 134.

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 and Table 2. 1, Table 2. 2, Table 2. 3, Table 2. 4 and Table 2. 5.

Table 2 Time windows for allocation of data to visits for statistical analysis

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[3]	11
Day 15 (End of week 2)	15	12	18

Day 22 (End of week 3)	22	19	25
Day 29 (End of week 4)	29	26	36
Day 43 (End of week 6)	43	37	50
Day 57 (End of week 8)	57	51	64
Day 71 (End of week 10)	71	65	78
Day 85 (End of week 12) [2]	85	79	92
Long-term Extension Treatment Period			
Day 99 (End of week 14)	99	93	106
Day 113 (End of week 16)	113	107	120
Day 127 (End of week 18)	127	121	134
…	…	…	…
Day 421 (End of week 60)	421	415	428
Day 435/EOT (End of week 62)	435	429	442
Day 449 (End of week 64)	449	443	456
Safety Follow up Phone Call	Last dose+8 weeks	Last dose+8 weeks-3days	Last dose+8 weeks-3days

1.The baseline starts from screening and lasts up to the date and time of the first dose.
2. Eculizumab administration on Day 85 is considered to be part of the Long-term Extension Period. Any measurements collected after Euclizumab administration Day 85 are considered as measurements in the Long-term Extension Period.
3. Any measurements occur after first dose on Day 1 is also included in this visit window.
4. The footnotes above also apply to Table 2.1, 2.2, 2.3, 2.4 and 2.5.
5. Visit window is not applicable for PK/PD endpoints.

Table 2. 1 Visit window for PNH clone size

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 29 (End of week 4)	29	2	43
Day 57 (End of week 8)	57	44	71
Day 85 (End of week 12)	85	71	176
Long-term Extension Treatment Period			
Day 267 (End of week 38)	267	177	358
Day 449 (End of week 64)	449	359	456

Table 2. 2 Visit window for FACIT-Fatigue

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 8 to Day 71	Same as Table 2		
Day 85 (End of week 12)	85	79	127
Long-term Extension Treatment Period			
Day 169 (End of week 24)	169	128	211
Day 253 (End of week 36)	253	212	295
Day 337 (End of week 48)	337	296	379
Day 421 (End of week 60)	421	380	428
Day 435/EOT (End of week 62)	435	429	442
Day 449 (End of week 64)	449	443	456

Table 2. 3 Visit window for ECG

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 85 (End of week 12)	85	2	134
Long-term Extension Treatment Period			
Day 183 (End of week 26)	183	135	274
Day 365 (End of week 52)	365	275	407
Day 449 (End of week 64)	449	408	456

Table 2. 4 Visit window for chemistry and hematology

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			

Day8 to Day 71	Same as Table 2		
Day 85 (End of week 12)	85	79	127
Long-term Extension Treatment Period			
Day 169 (End of week 24)	169	128	211
Day 253 (End of week 36)	253	212	295
Day 337 (End of week 48)	337	296	379
Day 421 (End of week 60)	421	380	435
Day 449 (End of week 64)	449	436	456

Table 2. 5 Visit window for Urinalysis and urine chemistry

Study Visit (Target Day)	Nominal Target Day	Study Visit Window (Days)	
		Lower	Upper
Baseline	-28 to 1	-28	1
Primary Treatment Period			
Day 85 (End of week 12)	85	2	127
Long-term Extension Treatment Period			
Day 169 (End of week 24)	169	128	211
Day 253 (End of week 36)	253	212	295
Day 337 (End of week 48)	337	296	393
Day 449 (End of week 64)	449	394	456

3.3.5 Handling of Unscheduled Visits

Unscheduled visits are included in the method of assigning data to scheduled visits described in the rules in Section 3.3.4 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.

3.3.6 Multiplicity/Multiple Comparisons

There is no multiplicity comparisons in this study.

3.3.7 Handling of Protocol Deviations in Study Analysis

According to ICH E3 (ICH 1995) guidelines,

“Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of

protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety or well-being."

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 database lock.

4 STATISTICAL ANALYSIS

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

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, disease characteristic, 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:

- Screened participants
- Participants who received treatment
- Participants who do not receive treatment
- Participants who completed primary treatment period
- Participants who completed long-term extension treatment period
- Participants who completed study treatment
- Participants who discontinued treatment (along with the reasons of treatment discontinuation)
- Participants who completed the study
- Participants who withdrew from the primary treatment period (along with the reasons of study discontinuation)
- 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 will be provided. participant disposition and completion status as defined by the categories in section 4.1.1.1 are summarized for all screened participants.

Disposition listings will include participant ID, age, gender and race, and will be presented sorted by participant ID, and date/time of observation.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Refer to Section 3.2.2 for definition of safety analysis sets.

4.1.2.2 Presentation

The number and percentage of participants included in the FAS, SS, PKAS and PDAS will be summarized.

A listing of participants excluded from any analysis set will include participant ID, age, gender and race, and will be presented sorted by participant ID, and date/time of observation.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Refer to section 3.3.7 for definition of protocol deviations.

4.1.3.2 Presentation

The number and percentage of participants with any IPD, as well as the number and percentage of participants experiencing an IPD in a particular category, will be summarized descriptively as categorical variables, as described in Section 3.3.

A listing of participants with any IPD will be presented sorted by participant ID, IPD category and date/time 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 (White, Black or African American, Asian, Other)

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

4.1.4.2 Presentation

Demographics will be summarized and listed for all participants according to Table 1. 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), baseline FACIT-Fatigue and baseline LDH (U/L).

Refer to section 3.3.1.1 for definition of baseline FACIT-Fatigue and baseline LDH.

4.1.5.2 Presentation

Baseline characteristics will be listed and summarized for all participants according to Table 1. This listing will include participant ID, age, gender and race, and will be presented sorted by participant ID.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease related medical will be coded using the latest version MedDRA implemented in the study at the time of database lock. Disease characteristics will be summarized using descriptive statistics for the following parameters: age (year) at PNH diagnosis, PNH disease duration (year), PNH clone sizes (RBC Type I, II and III, Total RBC, granulocyte, monocytes, where Total PNH RBC=RBC Type II+Type III).

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]). Missing date imputation refers to Section 3.3.1.4.

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. INT [(Date of first infusion – Date of PNH diagnosis +1)/365.25]. Missing date imputation refers to section 3.3.1.4.

4.1.6.2 Presentation

Disease characteristics will be listed and summarized for all participants according to Table 1. This listing of Hemoglobin value and PNH clone size from the most recent PNH clone test prior to first dose will be produced.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and PNH history collected at the Screening visit are classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 25.0 or higher).

4.1.7.2 Presentation

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

A listing will be presented sorted by participant ID, SOC category, PT category, reported term and date/time of observation for the SS.

PNH medical history is summarized by Preferred Term (PT) terms for all participants in FAS.

A listing will be presented for all participants in SS. This listing will be presented sorted by participant ID.

4.1.8 Prior, Concomitant Medications and Procedure

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. 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 studyso there is at least one day in common with the study period from first infusion of study treatment through last study visit .

Prior and concomitant medications will be summarized for all participants in FAS. Prior and concomitant medications will be classified according to the latest version of the WHO Drug coding dictionary. Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (CSP Section 5.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the participant takes or undergoes within 28 days prior to the start of Screening until the first dose of study intervention. Concomitant medications will be recorded from the first infusion of study intervention 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 3.3.1.4.

For the definition of disallowed medications and therapy, see Appendix A.

Prior and concomitant procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) that the participant takes or undergoes within 28 days before the start of Screening or during the Screening Period before the first dose of eculizumab, as well as any meningococcal vaccine administered, will be recorded in the participant's eCRF.

4.1.8.2 Presentation

Prior, concomitant medications and disallowed medications listed in Section 6.5 of the CSP will be summarized separately in a descriptive manner by chemical subgroup (ATC 4th level) and preferred WHO name respectively for the FAS by presenting the number and percentage of participants receiving the medication by ATC classification and generic drug name. Participants with the same concomitant medication multiple times will be counted once per medication. A medication that can be classified into more than one (chemical) subgroup will be presented in each subgroup. A medical review may also be done.

Prior and concomitant procedure will be summarized by System Organ Class (SOC) and Preferred Term (PT) which will be coded by MedDRA(version 25.0 or higher) and sorted by international order for system organ class and in alphabetical order for preferred term.

Prior and concomitant medications and Therapy (allowed and disallowed) and procedures will be listed respectively for all participants in the SS, and will be presented sorted by participant ID.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Percent compliance of primary treatment period =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*100%.

Percent compliance of long-term extension period = Total number of infusions taken during long-term extension period / Total number of expected infusions during long-term extension period*100%.

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

Compliance will be analysed as a continuous variable, as well as a 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 3.3.1. Treatment compliance will be summarized separately for primary treatment period and overall study.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Table 3 Summary of endpoint analyses

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)
Primary objective: To assess efficacy of eculizumab in participants with PNH at Week 12				
Primary	Percentage change from baseline in LDH at Week 12	FAS	Hypothetical strategy for handling of intercurrent events: the measurements from a participant using disallowed therapy or medicine are excluded from the analysis, and the measurements after premature discontinuation of study intervention will be included till last dose+14 days.	Percentage change from baseline in LDH values at Week 12, estimated using a longitudinal mixed model.
Supplementary	Percentage change from baseline in LDH at Week 12	FAS	Treatment policy: intercurrent events ignored	Percentage change from baseline in LDH values at Week 12 , estimated using a longitudinal mixed model.
Secondary objective: To evaluate the efficacy of eculizumab in participants with PNH by additional measures				
Secondary	Change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at week 12.	FAS	Hypothetical strategy for handing of intercurrent events: the measurements from a participant using disallowed therapy or medicine are excluded from the analysis, and the measurements after premature discontinuation of study intervention will be included till last dose+14 days.	Change from baseline in FACIT-Fatigue values at Week 12, estimated using a longitudinal mixed model.
Supplementary	Change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at week 12.	FAS	Treatment policy: intercurrent events ignored.	Change from baseline in FACIT-Fatigue values at Week 12 , estimated using a longitudinal mixed model.
Secondary	Proportion of participants with breakthrough hemolysis during	FAS	Composite strategy: Intercurrent event (use of disallowed medication and	Proportion of participants with breakthrough hemolysis during the Primary

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)
	the Primary Treatment Period.		premature discontinuation of study intervention) is included as part of a composite endpoint.	Treatment Period, estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary	Number (%) of participants achieving LDH normalization at Week 12.	FAS	Treatment policy: intercurrent events ignored.	Proportion of participants achieving LDN normalization at Week 12, estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary	Proportion of participants achieving transfusion avoidance during the Primary Treatment Period, where transfusion avoidance is defined as remaining transfusion free (i.e. participants have not received any blood transfusion) and not requiring transfusion as per protocol-specified guidelines (CSP Section 8.1.5). .	FAS	Treatment policy: intercurrent events ignored.	Proportion of participants achieving transfusion avoidance during the Primary Treatment Period,estimated with 95% two-sided Clopper-Pearson exact CIs.
Secondary	Proportion (%) of participants achieving LDH≤ 1.5 × ULN at Week 12.	FAS	Treatment policy: intercurrent events ignored.	Proportion of participants achieving LDN≤ 1.5 × ULN at Week 12, estimated with 95% two-sided Clopper-Pearson exact CIs.

4.2.1 Primary Endpoint

The primary endpoint is reduction in hemolysis as evaluated by percentage change from baseline in LDH at Week 12. Descriptive statistics will be presented for LDH values by visits from Screening (prior to Day 1) to the Week 12. Percentage change from baseline will be summarized. In addition, a line plot of LDH values and percent change from baseline by visit will be presented.

4.2.1.1 Definition

The primary endpoint is reduction in hemolysis as evaluated by percentage change from baseline in LDH at Week 12. For the main analysis of the primary endpoint, a hypothetical strategy will be used to handle intercurrent events, where all LDH measurements from 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+14 days, 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 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. It will be imputed by primary analysis method 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 model will include the percentage change from baseline in LDH at the scheduled visits from Day 8 to Day 85 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. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion; first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The estimated mean percentage change from baseline in LDH values will be provided along with accompanying 2-sided 95% confidence intervals.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

Not applicable.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

Intercurrent events will be ignored. The statistical analysis method should keep the same as primary endpoint.

4.2.1.7 Subgroup Analyses

Not applicable.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

The secondary efficacy endpoints will include the following:

- Change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 12.
- Proportion of participants with breakthrough hemolysis during the Primary Treatment Period.
- Number (%) of participants achieving LDH normalization at Week 12.
- Proportion of participants achieving transfusion avoidance during the Primary Treatment Period, where transfusion avoidance is defined as remaining transfusion free (i.e. participants have not received any blood transfusion) and not requiring transfusion as per protocol-specified guidelines (CSP Section 8.1.5).
- Number (%) of participants achieving LDH ≤ 1.5 × ULN at Week 12.

4.2.2.2 Derivations

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.

Participant with breakthrough hemolysis is defined as at least one new or worsening symptom or sign of intravascular 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.

LDH normalization defined as participant whose LDH ≤ ULN.

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 (CSP Section 1.3).

4.2.2.3 Handling of Dropouts and Missing Data

For the secondary endpoint, change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at all scheduled visits, missing FACIT-Fatigue for a particular participant at a particular visit will not be imputed.

For the secondary endpoint of proportion of participants with breakthrough hemolysis,missing breakthrough hemolysis for a particular participant at a particular visit will not be imputed.

For the secondary endpoint of number (%) of participants achieving LDH normalization at all scheduled visits., missing assessments of LDH for a particular patient at a particular visit will not be imputed.

For the secondary endpoint of proportion of participants achieving transfusion avoidance , participants who withdraw from the study due to lack of efficacy during the study will be considered as non-responders and will be counted in the group requiring transfusions.

For the secondary endpoint of participants achieving LDH ≤ 1.5 × ULN at all scheduled visits, missing assessments of LDH for a particular patient at a particular visit will not be imputed.

4.2.2.4 Primary Analysis of Secondary Endpoint

Change from baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 12.

Change in FACIT-Fatigue from Baseline to at Week 12 will be analyzed using a mixed model for repeated measures , with fixed categorical effect of study visit and fixed covariates of baseline FACIT-Fatigue. Participant is random effect. Change form baseline of FACIT-Fatigue will be summarized by scheduled visits.

An unstructured covariance matrix will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion; first order autoregressive, compound symmetry and Toeplitz method.

The nominal p-value from REML (two-sided) will be provided to compare change in FACIT-Fatigue values at week 12 with zero. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. For the analysis of this secondary endpoint, a hypothetical policy strategy will be used to handle intercurrent events, where all FACIT-

Fatigue measurements from a participant using disallowed therapy or medicine are excluded from the analysis and the FACIT-Fatigue measurements after premature discontinuation of study intervention are included till last dose+14 days, 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).

In addition, a line plot of absolute values and change from baseline by visit will be presented.

Proportion of participants with breakthrough hemolysis during the Primary Treatment Period.
The observed proportions of participants with breakthrough hemolysis during the Primary Treatment Period and Long-term Extension Period will be provided along with 95% two-sided Clopper-Pearson exact CIs. A composite strategy will be applied for this secondary analysis in which intercurrent events (use of disallowed medication and premature discontinuation of study intervention) are included as part of a composite endpoint, where participants who withdraw from the study early during will be considered as not achieving the criterion.

Number (%) of participants achieving LDH normalization at Week 12.
Summary statistics will be presented for LDH normalization for each scheduled visit, as well as LDH baseline. The statistics will include the number and percentage of participants achieving LDH normalization for each scheduled visits. The observed proportions of participants achieving LDH normalization at the end of Primary Treatment Period and Long-term Extension Period will be provided along with 95% two-sided Clopper-Pearson exact CIs. In addition, a box plot of numbers (percentage) of LDH normalization values by visit will be presented. A treatment policy strategy will be applied for this secondary analysis aiming at evaluating the impact of efficacy ignoring intercurrent events.

Number (%) of participants achieving transfusion avoidance during the Primary Treatment Period .
The observed proportions of participants achieving transfusion avoidance during the Primary Treatment Period and Long-term Extension Period will be provided along with 95% two-sided Clopper-Pearson exact CIs. A treatment policy strategy will be applied for this secondary analysis aiming at evaluating the impact of efficacy ignoring intercurrent events.

Number (%) of participants achieving LDH ≤ 1.5 × ULN at Week 12.
Summary statistics will be presented for LDH ≤ 1.5 × ULN for each scheduled visit. The statistics will include the number and percentage of participants achieving LDH ≤ 1.5 × ULN for each scheduled visits. The observed proportions of participants achieving LDH ≤ 1.5 × ULN at the end of Primary Treatment Period and Long-term Extension Period will be provided along with 95% two-sided Clopper-Pearson exact CIs. In addition, a box plot of numbers (percentage) of LDH ≤ 1.5 × ULN by visit will be presented. A treatment policy strategy will be applied for this 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 endpoint Change in FACIT-Fatigue from Baseline at Week 12 will also be conducted. A treatment policy strategy will be applied for this supplementary analysis aiming at evaluating the impact of efficacy ignoring intercurrent events The statistical analysis method should keep the same as primary analysis.

4.2.2.7 Subgroup Analyses

Not applicable.

4.3 Pharmacodynamic Endpoint(s)

This section covers details related to pharmacodynamic endpoints and analyses.

4.3.1 Definitions and Derivations

The variables and derivations for pharmacodynamic endpoints include:

- Serum free and total complement component 5 concentrations over time
- Changes in concentration from baseline, and percent change from baseline at all scheduled visit

4.3.2 Presentation

Any summary of pharmacodynamic data will be made on the PD Analysis Set. Individual serum free and total C5 concentrations, change from baseline, percent of change from baseline will be summarized with descriptive statistics, including number of participants, mean, SD, CV, median, minimum and maximum by timepoints (pre-dose or post-dose) in each scheduled visit. Mean (SD) of serum free and total C5 concentrations (linear scale and semi-log scale), change from baseline and percent of change from baseline will be graphically demonstrated in boxplots over study days based on the timepoints (pre-dose or post-dose) in each scheduled visit.

4.4 Pharmacokinetics

4.4.1 Definitions and Derivations

The variables for pharmacokinetic endpoint include:
• Serum eculizumab concentrations over time.

4.4.2 Presentation

Any tabular summary of pharmacokinetic (PK) data will be made on the PK Analysis Set. Individual eculizumab concentration data will be summarized with descriptive statistics, including number of participants, mean, SD, CV (%), geometric mean, geometric CV (%), median, minimum and maximum by timepoints (pre-dose or post-dose) in each scheduled visit. Mean (SD) of eculizumab (linear scale and semi-log scale) will be graphically demonstrated in boxplots over study days based on the timepoints (pre-dose or post-dose) in each scheduled visit. The PK data in this study might be pooled with other studies to conduct a population-PK modelling analysis and the exposure-response relationship might be explored, which would be described in a separate SAP when needed.

4.5 Immunogenicity

4.5.1 Definitions and Derivations

The variables for immunogenicity endpoint include ADA response category incidence and titer over the duration of the study as follows:

ADA response categories

- ADA negative: collected samples are tested negative at all time points, including baseline and post-baseline.
- ADA positive: collected sample is tested positive at any time during the study, including baseline and/or post-baseline

Participants that are ADA positive will be categorized as follows:

- Pre-existing immuno-reactivity: ADA positive at baseline
- Treatment-emergent ADA responses: any post-treatment positive ADA assay response when the baseline ADA result is negative or missing.

  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.

- Treatment-boosted ADA responses: post-baseline increase in pre-existing baseline ADA titres by ≥4-fold during the study period
- Neutralizing antibody (NAb) positive: The presence of neutralizing antibodies will be tested in all ADA-positive samples using a ligand binding assay. The following variables will be evaluated:
  - NAb negative: NAb-negative at *all* time points, including baseline and/or post-baseline
  - NAb positive: NAb-positive at *any* time during the study, including baseline and/or post-baseline

4.5.2 Presentation

Any summary of immunogenicity data will be made on the safety analysis set (SS). The number and percentage of patients developing ADA, and anti-drug nAb as described in Section 4.5.1, will be presented. For the summary of overall ADA categories (e.g., ADA positive at any time), percentages will be based on participants with at least one ADA result during the study. ADA titre results can be presented for individuals as a listing.

4.6 Safety Analyses (if not already covered as endpoint variables)

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

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 from the Primary Treatment Period (i.e intervention duration = last study intervention date from the Primary Treatment Period+14 -first study intervention date). Note that intervention on Day 85 is the start of the Extension Period and will not be included in these calculations.

Exposure duration of long-term extension 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 long-term extension period (i.e intervention duration = last study intervention date from the long-term extension period+14-first study intervention date from the long-term extension period).Exposure duration of overall 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+14- first study intervention date).

4.6.1.2 Presentation

Two summary tables of the extent of exposure will be presented. The duration on treatment (in days) and the number of infusions 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 8.3.

TEAE is defined as any AE that starts during or after the first infusion of study intervention.

The derivations for the following parameters will be the difference between the two dates stated below + 1 day.

- Time from first dose to onset of AE (days)
- Time from last dose to death (days)
- Time from first dose to death (days)
- Time from first dose to AE becoming serious (days)
- Time from first dose to discontinuation of investigational product (due to adverse event) (days).

MedDRA (using the latest or current version) is used to code AEs apart from transfusion. The identified risk of transfusion is defined by laboratory values and not by specific MedDRA terms.

4.6.2.2 Presentation

Adverse Events will be presented separately for the primary treatment period, the long-term extension period and overall study. All AEs, including those considered pretreatment AEs, will be included in safety listings. Only TEAEs will be included in summary table.

The onset date of the AE determines the phase in which the AE will be summarized. This is in order to have a consistent “worst case” allocation of AEs, because it will not be possible to distinguish AEs occurring before or after the actual intake of study intervention.

Overall Summary of Adverse Events

AEs will be summarised and will include the following:

- the number and percentage of participants experiencing an AE
- the number and percentage of participants experiencing an AE with an outcome of death

- the number and percentage of participants experiencing a SAE
- the number and percentage of participants experiencing an AE leading to discontinuation of investigational product
- the number and percentage of participants experiencing a possibly related AE
- the number and percentage of participants experiencing a possibly related SAE
- the number and percentage of participants experiencing an AE grouped by the severity (defined by CTCAE v5.0) of AE
- the number and percentage of participants experiencing an AESI

This table will be done both treatment-emergent and using all AEs that occurred during Primary Treatment Period and overall study.

In addition to presentations of the number of patients with event, the total number of events counting multiple events per subject will be presented.

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

The number and percentage of participants with AEs and SAEs will be summarised by SOC and PT. A participant with more than one type of AE in a particular SOC will be counted only once in the total of participants experiencing AEs in that particular SOC. Since a participant could have more than one type of AE within a particular SOC, the sum of participants experiencing different AEs within the SOC could be larger than the total number of participants experiencing AEs in that SOC. Similarly, a participant who has experienced an AE in more than one SOC will be counted only once in the total number of participants experiencing AEs in all SOCs.

AEs by PT and frequency

The number and percentage of participants with AEs will be summarised by PT and sorted by descending frequency on PT level.

Possibly related AEs and SAEs by SOC and PT

The number and percentage of participants with possibly related AEs and SAEs will be summarised by SOC and PT.

AE of special intertest by SOC and PT

The number and percentage of participants with AEs of special interest will be summarised by SOC and PT.

AEs by SOC, PT, and maximum severity

The number and percentage of participants with AEs will be summarised by SOC, PT and maximum intensity.

Deaths

The number and percentage of participants with SAEs or AEs with outcome of death will be summarised by SOC, PT. Participant listings of all deaths and their causes will be provided.

AE leading to discontinuation of IP by SOC and PT

The number and percentage of participants with AE leading to discontinuation of IP will be summarised by SOC and PT.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

A full list of parameters (including other) is provided in Table 8 in the CSP.

These will be evaluated fasting at Screening, every visit during Primary Treatment Period and day 169, day 253, day 337, day 421, day 449 and ED.

The date, time of collection and results (values, units and reference ranges) will be recorded in the appropriate eCRF module.

The clinical chemistry and hematology will be performed at a central laboratory and summarized based on central laboratory. Local laboratory results will only be listed in the listings as appropriate.

4.6.3.2 Presentations

Descriptive statistics by time of assessment will be presented for each laboratory parameter including other serum electrolytes. All laboratory values will be classified as low, normal, or high based on normal ranges supplied by the central laboratory. For purposes of analyses, laboratory results based upon standardized units will be used.

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 hematology and clinical chemistry parameters will be summarized for scheduled visit.

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.

Any treatment-emergent laboratory data reported as abnormal according to reference values as well as individuals with treatment-emergent, abnormal serum laboratory values will be summarized and listed for the relevant safety analysis set.

Additionally, participant listings and summary of all on-treatment hematology and chemistry changes will be presented.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

A full list of the urinalysis parameters for this study (including other electrolytes) is provided in Table 8 in the CSP.

The urinalysis will be performed at a central laboratory.

4.6.4.2 Presentations

Absolute values and change from baseline for all continuous urinalysis will be summarized by visit.

Urinalysis baseline versus maximum and minimum value on treatment shift table will be provided for categorical urinalysis parameters.

The urinalysis results will be categorized as negative ,trace, +1,+2,+3 in a shift table. For purposes of analyses and where applicable, possible values provided by the central laboratory of 'normal' and 'unconfirmed positive' will be treated as negative and trace resepectively.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Pregnancy data from female participants of childbearing potential and female spouses/partners of male participants will be collected from the first dose of study intervention and at the timepoints specified in the SoA (CSP Section 1.3)

For PNH clone size assessments, white blood cell (WBC; granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry will be collected 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 scheduled visit.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs will include assessments of systolic and diastolic blood pressure (BP), pulse rate, temperature, respiration rate (RR). Systolic and diastolic BPs will be documented in millimeters of mercury. Temperature will be obtained in degrees Celsius or Fahrenheit. Respiration rate will be documented in breaths per minute. Pulse rate will be documented in beats per minute.

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.

Baseline versus maximum and minimum values on treatment shift table will be provided for all vital sign parameters.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Descriptive statistics by visit will be presented for each ECG parameter (including heart rate, PR, QRS, QT, and QTc intervals) values and for change from baseline values.

QTc intervals

QTc intervals will be calculated using the Fridericia formula:

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

Where:

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

2 RR = RR interval

3 HR = Heart rate.

4.6.7.2 Presentations

Overall ECG evaluations will be presented in a summary table by visit.

The following ECG variables will be descriptively summarized by visit to include change from baseline to each subsequent visit: ECG mean heart rate, PR interval aggregate, QRS duration aggregate, QT interval aggregate and QTcF interval aggregate.

A listing of participants with overall ECG evaluation reported as abnormal or borderline abnormal will also be provided.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Not applicable.

4.6.8.2 Presentations

Not applicable.

5 INTERIM ANALYSIS

An interim analysis, if deemed necessary, may be performed after all participants complete or withdraw early from the Primary Treatment Period.

6 REFERENCES

This Statistical Analysis Plan (SAP) is based on ECU-PNH-301 Protocol Version 1.0, dated 30 Nov 2021.

SAS/STAT® 9.3 User's Guide. The FREQ Procedure: Odds Ratio and Relative Risks for 2 x 2 Tables, viewed Jan 2019, https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_freq_a0000000565.htm

7 APPENDIX

Deviation Code	Deviation	CSP version & date	Identification method	Source for identification
1	**Inclusion Criteria Deviations** (Participants who entered treatment period but did not meet critical inclusion criteria)			
1.1	Inc#1: Must be ≥ 18 years of age at the time of signing the informed consent form (ICF).	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management	• Source data • Rave data (DM)
1.2	Inc#2: Documented diagnosis of PNH, confirmed by flow cytometry evaluation of white blood cells and RBCs, with granulocyte or monocyte clone size of ≥ 10% at Screening.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management (Documented diagnosis of PNH, confirmed by flow cytometry evaluation.) • TPV alerts	• Source data • Rave data(PNHMH) • TPV(Lablink)
1.3	Inc#3: LDH level ≥ 1.5 × the upper limit of normal (ULN) at Screening (central laboratory test result).	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • TPV alerts	• Source data • TPV(Clab)
1.4	Inc#4: To reduce the risk of meningococcal infection (N meningitidis), all participants must be vaccinated against N meningitidis if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer. Participants must be vaccinated at least 14 days prior to receiving the first dose of eculizumab or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management	• Source data • Rave data (CM1)
1.5	Inc#5: Male and/or female.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
1.6	Inc#6: Female participants of childbearing potential and	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and	• Source data

	male participants must follow protocol-specified contraception guidance as described in Section.		Verifications - SDR and SDV). • EDC Automatic Check/ Data Management (check preg for female) • TPV alert	• Rave data (PREG, PREGREP) • TPV(Lablink)
1.7	Inc#7: Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
2	**Exclusion Criteria Deviations** (Participants who entered treatment period but did not meet critical exclusion criteria)			
2.1	Exclu#1：History of N meningitidis infection or unresolved meningococcal disease.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (MH)
2.2	Exclu#2：Active systemic bacterial, viral, or fungal infection within 7 days prior to Screening.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (MH)
2.3	Exclu#3：Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study intervention administration on Day 1.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management	• Source data • Rave data (VS, MH)
2.4	Exclu#4：History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (MH)
2.5	Exclu#5：History of or ongoing major cardiac, pulmonary, renal, endocrine, hepatic disease (eg, active hepatitis), coexisting chronic anaemia unrelated to PNH or anticipated need for major surgery within 6 months of study entry, that	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (MH)

	in the opinion of the Investigator or Alexion, precludes the participant's participation in an investigational clinical study.			
2.6	Exclu#6：Has received eculizumab or other complement inhibitor treatment previously.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management (to check if eculizumab is used) • GPR to support clinical manual review	• Source data • Rave data (DM)
2.7	Exclu#7：History of hematopoietic stem cell transplantation.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (MH)
2.8	Exclu#8：Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • SAS listing for clinical review/Data Management	• Source data • Rave data (CM)
2.9	Exclu#9：Has participated in any other investigational drug study or was exposed to an investigational drug or device within 28 days or 5 half-lives (whichever is longer) of Screening.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
2.10	Exclu#10：Absolute neutrophil count ≤ 500/μL at Screening.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • TPV alert	• Source data • TPV
2.11	Exclu#11：Platelet count < 30000/mm3 at Screening.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • TPV alert	• Source data • • TPV
2.12	Exclu#12：Hypersensitivity to murine proteins or to one of the excipients of eculizumab.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data

			• GPR to support clinical manual review	
2.13	Exclu#13：Pregnant, breastfeeding, or intending to conceive during the course of the study.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management	• Source data • Rave data (PREG, PREGREP) • Central Lab data • TPV
2.14	Exclu#14：Any medical condition that, in the opinion of the Investigator, might interfere with the participant's participation in the study, poses an added risk for the participant, or confounds the assessment of the participant.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
3	**Discontinuation Criteria for study product met but participant not withdrawn from study treatment**			
3.1	Discontinuation Criteria for study product met but participant not withdrawn from study treatment • Serious hypersensitivity reaction • Severe uncontrolled infection	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical manual review	• Source data • Rave data (DOSDISC, AE, DS)
3.2	• Alexion or Investigator deems it necessary for the participant	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
3.3	• Other safety criteria (eg, AE, PK criteria)	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data (AE, etc.)
3.4	• Pregnancy or planned pregnancy (Section 10.4.3)	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • EDC Automatic Check/ Data Management	• Source data • Rave data (PREG, PREGREP)
3.5	• Use of disallowed medication (defined in Section 6.5.2)	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV). • GPR to support clinical review	• Source data • Rave data (CM)

4	**Discontinuation Criteria for overall study withdrawal met but participant not withdrawn from study**			
4.1	Patient decides to withdraw his/her consent for the study but procedures not followed correctly as per CSP requirement	NA	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data
5	**Investigational Product (IP) Deviation**			
5.1	• IP dosing error that may significantly impact efficacy and safety assessment (e.g., Incorrect dosing level, patient enrolled but not received treatment, etc.)	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • EDC Automatic Check/ Data Management	• Source data • Rave data (EC, OVERDOSE)
5.2	Patient uses expired IP during study	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • EDC Automatic Check/ Data Management	• Source data • Rave data (MER)
5.3	Other situations that may impact the study assessment, such as Administer IP prepared not compliant with the requirement listed in pharmacy manual (e.g., Incorrect volume/type of dilution ,dose expired after preparation under specific environment)	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • EDC Automatic Check/ Data Management	• Source data • Rave data (MER)
5.4	• Administration of IP with temperature excursion confirmed not fit for use	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • EDC Automatic Check/ Data Management	• Source data • Rave data (MER)
6	**Excluded Medications or therapy taken**			
6.1	Participant received concomitant medication defined as prohibited in the CSP **(corporate IPD)**	Version 1.0 30Nov2021	• EDC Automatic Check/ Data Management	• Source data • Rave data (TRANSF1)

	• Whole blood		• Monitoring activities (Source Data Review and Verifications -SDR and SDV)	
6.2	•Participant tookTraditional Chinese herbal preparations that in the opinion of the Investigator or Alexion might confound the assessment of the participant	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • GPR to support clinical review	• Source data • Rave data (CM)
6.3	• Participant took Chemotherapy	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • GPR to support clinical review	• Source data • Rave data (CM)
6.4	• Participant took any other investigational drug or device	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications -SDR and SDV) • GPR to support clinical review	• Source data
7.	**Deviations to study procedure**			
7.1	Any participant who completes study treatment in either the Primary Treatment Period or Long-term Extension Period but who will not receive continued access to Eculizumab after study participation (Procedures not done in full, or not follow the protocol, that are related to eligibility, study objectives, primary and key secondary endpoints, missed dose, missed pregnancy test at Screening). Note: Not recording symptoms associated with the participant's need for transfusion on eCRF is NIPD	Version PA1 06Nov2023	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data(1. EC, DOSDISC, VISIT, CONTACT; 2. DOSDISC, VISIT, CONTACT; 3, ASMPERF; 4. ASMPERF, SPCPKB) • TPV
7.2	PK/PD/ADA samples were not collected and processed per CSP and the related requirement	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data(1. EC, DOSDISC,

				VISIT, CONTACT; 2. DOSDISC, VISIT, CONTACT; 3, ASMPERF; 4. ASMPERF, SPCPKB) • TPV
7.3	Any participant who completes study treatment in either the Primary Treatment Period or Long-term Extension Period but who will not receive continued access to	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data(1. EC, DOSDISC, VISIT, CONTACT; 2. DOSDISC, VISIT, CONTACT; 3, ASMPERF; 4. ASMPERF, SPCPKB) • TPV
7.4	Baseline and week 12 LDH samples were not collected and processed per CSP and the related requirement, which lead to the data missing	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data(1. EC, DOSDISC, VISIT, CONTACT; 2. DOSDISC, VISIT, CONTACT; 3, ASMPERF; 4. ASMPERF, SPCPKB) • TPV
8	**Other Important Protocol Deviations**			
8.1	Any deviation considered important that was not predicted or prespecified.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data • TPV
8.2	Add study specific IPDs that are not covered by any category above.	Version 1.0 30Nov2021	• Monitoring activities (Source Data Review and Verifications - SDR and SDV).	• Source data • Rave data • TPV

7.1 Appendix A: Disallowed Medications

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
chemotherapy	fludarabine	L01BB	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B ANTIMETABOLITES L01BB Purine analogues		010046 01 001
	cyclophosphamide	L01AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01A ALKYLATING AGENTS L01AA Nitrogen mustard analogues		000211 01 001
	bendamustine	L01AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01A ALKYLATING AGENTS L01AA Nitrogen mustard analogues		012633 01 001
	chlorambucil	L01AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01A ALKYLATING AGENTS L01AA Nitrogen mustard analogues		000803 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
	pentostatin	L01XX	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01XX Other antineoplastic agents		006019 01 001
	cytarabine	L01BC	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B ANTIMETABOLITES L0BC Pyrimidine analogues		001462 01 001
	cisplatin	L01XA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B OTHER ANTINEOPLASTIC AGENTS L01XA Platinum compounds		004121 01 001
	oxaliplatin	L01XA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B OTHER ANTINEOPLASTIC AGENTS L01XA Platinum compounds		013188 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
	carboplatin	L01XA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B OTHER ANTINEOPLASTIC AGENTS L01XA Platinum compounds		007409 01 001
	doxorubicin	L01DB	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01D CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES L01DB Anthracyclines and related substances		003309 01 001
	vincristine	L01CA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01C PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS L01CA Vinca alkaloids and analogues		000788 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
	methotrexate	G02CX, L01BA, L04AX (primary ATC)	G GENITO URINARY SYSTEM AND SEX HORMONES G02 OTHER GYNECOLOGICALS G02C OTHER GYNECOLOGICALS G02CX Other gynecologicals L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B ANTIMETABOLITES L01BA Folic acid analogues L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AX Other immunosuppressants		001138 01 001
	etoposide	L01CB	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01CB Methylhydrazines		005119 01 001
	gemcitabine	L01BC	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01B ANTIMETABOLITES L0BC Pyrimidine analogues		012157 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
	procarbazine	L01XB	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01XB Methylhydrazines		000917 01 001
	vinorelbine	L01CA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01C PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS L01CA Vinca alkaloids and analogues		009885 01 001
	ifosfamide	L01AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01A ALKYLATING AGENTS L01AA Nitrogen mustard analogues		003107 01 001
	lenalidomide	L01XX, L04AX (primary ATC)	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AX OTHER IMMUNOSUPPRESSANTS L ANTINEOPLASTIC AND IMMUNOMODULATING		016801 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
			AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01XX Other antineoplastic agents		
	Thalidomide	L01XX, L04AX (primary ATC)	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AX OTHER IMMUNOSUPPRESSANTS L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01XX Other antineoplastic agents		000774 01 001
	bortezomib	L01XG	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L01 ANTINEOPLASTIC AGENTS L01X OTHER ANTINEOPLASTIC AGENTS L01XG Proteasome inhibitors		016118 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
Complement Inhibitor	Crovalimab	L04AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AA SELECTIVE IMMUNOSUPPRESSANTS		152047 01 001
	Iptacopan	NA	V VARIOUS V98 INVESTIGATIONAL DRUG PRODUCT 152226 01 001 IPTACOPAN;		152226 01 001
	Ravulizumab	L04AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AA SELECTIVE IMMUNOSUPPRESSANTS		145484 01 001
	Pegcetacoplan	L04AA	L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L04 IMMUNOSUPPRESSANTS L04A IMMUNOSUPPRESSANTS L04AA SELECTIVE IMMUNOSUPPRESSANTS		157281 01 001
	CG001	NA	V VARIOUS V98 INVESTIGATIONAL DRUG	Investigational drug	999997 01 001

Disallowed Medicine and Therapy					
Drug category	**Prohibited drug name**	**Drug Code in WHODD Sep 2024**	**corresponding ATC Description in WHODD Sep 2024**	**note**	Drug Code
	KP104	NA	V VARIOUS V98 INVESTIGATIONAL DRUG	Investigational drug	999997 01 001
	CAN106	NA	V VARIOUS V98 INVESTIGATIONAL DRUG	Investigational drug	999997 01 001
	SB12	NA	V VARIOUS V98 INVESTIGATIONAL DRUG	Investigational drug	999997 01 001