STATISTICAL ANALYSIS PLAN

Study Code	D7413C00001
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Prospective, Single-Arm, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab in Complement Inhibitor Treatment-Naïve Pediatric and Adult Subjects with Atypical Hemolytic Uremic Syndrome (aHUS) in China

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
ADA	Antidrug Antibody
ADAMTS-13	A Disintegrin and Metalloproteinase with a Thrombospondin Type 1 Motif
AE	Adverse event
aHUS	Atypical Hemolytic Uremic Syndrome
ATC	Anatomic-Therapeutic-Chemical
CDF	Cumulative Distribution Function
CDL	Clinical Database Lock
CI	Confidence Interval
CKD	Chronic Kidney Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminnology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ER	Emergency Room
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act of 2007
ICE	Intercurrent Events
IPD	Important Protocol Deviation
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred Term
PTAEs	Pretreatment Adverse Events
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class

Abbreviation or Specialized Term	Definition
SOP	Standard Operating Procedure
SS	Safety Set
TE	Treatment Emergent
TMA	Thrombotic Microangiopathy
ULN	Upper Limit of Normal
WHO-DRUG	World Health Organization Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	5/12/2025	In section 3.3 and 4.1.2.2, clarify the criteria on which analysis set(s) to use	Yes, version 2	Tables specified for multiple analysis sets will be generated separately or not depending on whether the analysis sets are the same
Data presentation	5/12/2025	In section 3.3, added specification on maximum number of decimal places for summary statistics	Yes, version 2	To improve readability of summary data.
Data presentation	5/12/2025	In section 3.3.1, added definition on baseline value for categorical variables	Yes, version 2	To improve clarity.
Data presentation	5/12/2025	In section 3.3.1, removed the separate definition of baseline for serum creatinine	Yes, version 2	To synergize with amendment in section 4.2.1.4
Data presentation	11/12/2024	In section 3.3.5, removed the exclusion of serum creatinine from analyses under concurrent dialysis.	Yes, version 2	To account for population with regular dialysis up to 3 months upon enrollment
Data presentation	11/12/2024	In section 3.3.5, added description for handling of clinical laboratory data that are BLQ	Yes, version 2	To improve clarity for programming.
Data presentation	11/12/2024	In section 4.1.3.2, updated the analysis set for IPD to FAS	Yes, version 2	FAS is the main focus of assessment
Data presentation	11/12/2024	In section 4.1.6.1, defined summary categories for ADAMTS-13	Yes, version 2	To improve clarity for programming

Data presentation	11/12/2024	In section 4.1.6.1, added imputation rule for the missing date of aHUS symptom and diagnosis	Yes, version 2	To improve clarity for programming
Data presentation	11/12/2024	In section 4.1.7.1, added derivation rules for ICU stays, and clarified variable types (yes / no) for ER and hospitalization variables	Yes, version 2	To improve clarity for programming
Data presentation	05/20/2025	In section 4.1.8.2, added specification for prior and concomitant vaccination and antibiotic prophylaxis.	Yes, version 2	To provide instruction on the data presentation of vaccination and antibiotic prophylaxis
Data presentation	11/12/2024	In section 4.1.9, removed the summary for “number of infusions”	Yes, version 2	This summary provides limited value
Data presentation	04/29/2025	In section 4.1.9, clarified the definition for “percentage of the number of infusions”.	Yes, version 2	To improve clarity for programming.
Derivation of primary endpoint(s)	11/12/2024	In section 4.2.1.1, updated the details for TMA response during 26 week treatment period	Yes, version 2	To improve clarity for programming
Statistical analysis methods for primary endpoint(s)	04/29/2025	In section 4.2.1.3, updated the specification for LOCF rule.	Yes, version 2	To improve clarity for programming.
Statistical analysis methods for primary endpoint(s)	04/29/2025	In section 4.2.1.6,updated the description for supplemental analyses.	Yes, version 2	To improve the interpretability of the analysis

Statistical analysis methods for primary endpoint(s)	11/13/2024	In section 4.2.1.7 added details for subgroup of patients with dialysis	Yes, version 2	To account for difference between acute and chronic (regular) dialysis
Statistical analysis method for secondary endpoint(s)	04/29/2025	In section 4.2.2.4, removed the MMRM model analysis and the plots for eGFR and hematologic parameters	Yes, version 2	The descriptive statistics suffice for the assessment
Statistical analysis method for secondary endpoint(s)	11/13/2024	In section 4.2.2.5, removed the over time analysis for complete TMA response	Yes, version 2	Some of the contents are overlapped with section 4.2.2.4.
Pharmacodynamic endpoint	11/13/2024	In section 4.3.2, updated the specification for C5 complement analysis	Yes, version 2	To improve clarity of assessment
Pharmacokinetic endpoints	11/13/2024	In section 4.4, updated the analysis specification for PK analysis	Yes, version 2	To improve clarity of assessment
Immunogenicity	11/13/2024	In section 4.5, updated the analysis specification for immunogenicity analysis	Yes, version 2	To improve clarity of assessment
Safety Analyses	11/13/2024	In section 4.6.1, distinguished the definition between treatment duration and exposure duration	Yes, version 2	To improve clarity of assessment

1 INTRODUCTION

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D7413C00001 (also referred to as ECU-aHUS-302) supporting the clinical study report. The reader is referred to the protocol amendment 1 of CSP and the case report form for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

There is no change to protocol planned analyses.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The final analysis will be performed after clinical database lock (CDL) and the results will be provided in the CSR.

3.2 Analysis Populations

The following analysis populations are as defined in CSP section 9.3:

Full Analysis Set (FAS): All subjects who receive at least 1 dose of study intervention and have at least 1 efficacy assessment post first dose.

Safety Set (SS): All subjects who receive at least 1 dose of study intervention.

Pharmacokinetic Analysis Set (PK Analysis Set): All subjects who receive at least 1 dose of study intervention and have evaluable pharmacokinetic data.

Pharmacodynamic Analysis Set (PD Analysis Set): All subjects who receive at least 1 dose of study intervention and have evaluable pharmacodynamic data.

In addition, define the following analysis populations:

All Subject Analysis Set: All enrolled subjects who signed the informed consent form, including screening failures.

Per-Protocol Set (PP set): All subjects in the FAS who receive any amount of Investigational Product and have no important protocol deviations that are likely to impact efficacy during the treatment period. The PP set will be decided based on the discussion before clinical data lock in a separate document named subject evaluability criteria & subject classification.

3.3 General Considerations

The following general principles will be followed throughout the study:

If an analysis is specified on both FAS and SS, and the two sets are equal based on final data, then the following criteria apply:

- If the analysis is in the section of study population or efficacy, it will only be presented on FAS and no duplication on SS will be produced.

- If the analysis is in the safety section, it will only be presented on SS and no duplication on FAS will be produced.

Descriptive statistics will be used as appropriate.

- Continuous variables will be summarized in the following order: number of observations (n), mean, SD, minimum, Q1 (optional), median, Q3 (optional), and maximum as appropriate. The statistics above will be aligned with the decimal point. Mean, SD, median, as well as Q1 and Q3 (if applicable) have one more decimal place as compared to min and max but not exceeding 3 decimal places, while min and max are summarized as precise as the data are reported but not exceeding 2 decimal places. For the calculation of summary statistics, only subjects with non-missing data at the relevant timepoint will be included.

- Categorical variables will be summarized by frequency counts and percentages for each category. The frequency counts will be right aligned. The percentages will reserve the precision of 1 decimal place except 0 and 100%, for percentage below 1.0%, present with leading 0 (eg, “0.6” instead of “.6”) and percentage below 0.05 is presented as 0.0; the case of 0 count will be presented as “0” with no value of percentage, and the case of 100 percent will be presented as 100 instead of 100.0 (without decimal); all percentages are to be aligned with decimal place and presented within round parenthesis with no space between bracket and percentage.

All statistical computations will be performed using SAS® version 9.4, or higher.

3.3.1 General Study Level Definitions

This section describes the definitions and conventions that are applicable to more than one domain.

Study Day:

If the actual date of assessment is prior to the date of first study treatment, then the study day is calculated as: date of assessment - date of first study treatment.

If the actual date of assessment is on or after the date of first study treatment, then the study day is calculated as: date of assessment - date of first study treatment + 1.

Study Periods:

Screening Period is from the informed consent date until day -1.

Treatment period: For subjects who have not discontinued the study treatment, treatment period is from day 1 (date of first study treatment) to the final scheduled visit which is the visit after the final scheduled dose; for subjects who have discontinued the treatment but have remained in the study, treatment period is from day 1 to the final scheduled visit; for subjects who have discontinued from the study, treatment period is from day 1 to the early discontinuation visit.

Follow-up period: A single Safety Follow-up Phone Call is scheduled for subjects who either have discontinued study treatment early or will not receive continued access to study treatment after the study. The Safety Follow-up Phone Call is scheduled 8 weeks after the last dose.

Baseline:
For the analysis, the baseline value of continuous variables is defined as the average of the values from the assessments performed prior to the first study drug infusion (these can include results from Screening and the Day 1 visit), while the baseline value of categorical variables is defined as the last assessment performed prior to the first study drug infusion.

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 (see Section 3.3.5), then a change from baseline will not be calculated. If needed, the percentage change from baseline will also be summarized as appropriate.

Derivation of Durations

Time from first study treatment to AE onset (days) will be calculated as date of AE onset minus date of first study treatment plus one. This will be calculated for AEs with an onset date >= date of the first infusion.

Time from first study treatment to death (days) will be calculated as date of death minus date of first study treatment plus one.

3.3.2 Visit Window, Analysis Visits and Analysis Value

Summaries over postbaseline time points or analyses at specific postbaseline timepoints will be performed based on the list of visits described in the schedule of activities of the protocol. For all assessments, the study day will be calculated based on description in Section 3.3.1.

The analysis visit assignment for a specific assessment will be based on **visit windows** around each scheduled visit for that specific assessment.

For the definition of the visit windows:

- The lower limit of each visit window will be the midpoint (in days, rounded up to the nearest integer if possible and inclusive) between the current visit and the previous scheduled visit.

- The upper limit of each visit window will be the midpoint (in days, rounded up to the nearest integer if possible and exclusive) between the current visit and the subsequent scheduled visit.

A visit is considered to be a scheduled visit as long as at least one weight cohort has a schedule visit at the target day.

The value being considered for analysis at a specific postbaseline time point will be based on the analysis visit assigned to that value. If there is more than one non-missing value for a specific assessment with the same analysis visit, the value used for analysis will be the one for which the calculated number of days from baseline is closest to the scheduled visit day. If two values have the same analysis visit and are the same distance away from the scheduled visit day, the earlier of the 2 values will be used for analysis.

Note: Assessment values from early discontinuation visit will be considered as falling into the visit window of the scheduled visit right before the early discontinuation visit.

3.3.3 Handling of Unscheduled Visits

Any data collected at unscheduled assessments will be listed and will be included in baseline definitions (see Section 3.3.1), and in any definitions of maximum value and minimum value.

Measurements collected from unscheduled visits or early study discontinuation visits may also be considered in the analysis visit window (see Section 3.3.2). In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled

assessment within the same visit window, the non-missing value at the unscheduled assessment will be used.

3.3.4 Multiplicity/Multiple Comparisons

No formal statistical hypothesis will be tested and hence no correction for multiplicity will be used.

3.3.5 Handling of Missing Data

For the handling of missing date to decide whether a medication or procedure is prior or concomitant, see Section 4.1.8.1.

For the handling of missing date to decide whether an adverse event is treatment-emergent or not, see Section 4.6.2.1.

For the handling of missing data in the efficacy analyses, see Section 4.2.1.3 and Section 4.2.2.3.

For the safety analyses of results from clinical laboratory (blood samples and urinalysis), missing data will not be imputed and only observed results are reported in the summary tables and listings. However, safety assessment values of the form <x (i.e., below the LLOQ) or >x (i.e., above the upper limit of quantification) are imputed as x in the calculation of summary statistics but displayed as <x or >x in the listings.

The following rules apply throughout the whole analysis plan unless otherwise stated:

- Serum creatinine measurements are not reliable with concurrent dialysis. Therefore, all eGFR will be imputed with a value of 10 (in mL/min/1.73 m^2) while a subject is on dialysis. A subject will be considered on dialysis from the first day of dialysis through 5 days (inclusive) after the end of dialysis.

- Platelet and hemoglobin measurements are not reliable with concurrent blood transfusions. Therefore, platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion will be excluded from all analyses. Hemoglobin values obtained from the day of blood transfusion of either whole blood or packed red blood cells through 7 days after the transfusion will be excluded from all analyses. This rule will only be applied to postbaseline assessments of platelets and hemoglobin.

3.3.6 Handling of Protocol Deviations in Study Analysis

Important protocol deviations will be determined per the standard operating procedure (SOP) “Protocol Deviation Management and Reporting” (SOP-0066828). A final review of the IPD

list will be conducted before the clinical data lock to identify IPDs that may impact data analyses.

More details will be introduced in a separate document named “Protocol Deviation Plan”.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

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

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

The following disposition items will be summarized and presented:

Subjects screened: those who have signed informed consent.

Subjects assigned: those who pass screening and are eligible for the study.

Subjects assigned, not treated: those who are assigned to the study but are not treated towards end of study.

Subjects started treatment: those who receive at least one dose of the study treatment.

Subjects completed treatment: those who complete the treatment period without permanently discontinuing study treatment.

Subjects discontinued from treatment: those who discontinue the study treatment permanently.

Subjects withdrawn from study: those who have terminated early from the study as defined in CSP 4.4, which are those subjects whose status is not "Completed" or "Screen failure" in the DS form of eCRF.

Subjects completed study: those who completed the study as defined in CSP 4.4.

4.1.1.2 Presentation

The summary of "Subjects screened", "Subjects assigned", "Subjects assigned, not treated" will be applied on "All Subject Analysis Set", and only frequency count will be presented, and no percentage will be calculated. For "Subjects screened", the reasons for screen failure will be presented for those who are not eligible for the study.

The rest of the disposition items rather than those mentioned above will be summarized by frequency count and percentage on the safety set. The denominator used to calculate the percentage is the number of subjects who started the treatment. For "Subjects discontinued from treatment" and "Subjects discontinued from study", the reasons will be presented as well.

Separate listings including all standardized disposition terms will also be provided for subjects who were withdrawn from the study as well as for subjects who completed the study.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definition of each analysis set is given in Section 3.2

4.1.2.2 Presentation

The frequency count of subjects belonging to each analysis set will be presented in a summary table. The table will be based on "All Subject Analysis Set".

Listings of all subjects excluded from any analysis set and reason for exclusion from respective analysis set will also be provided.

For analyses specified to be performed on multiple analysis sets, the rule specified in Section 3.3 applies.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

For the determination of potential important protocol deviations, see Section 3.3.6.

4.1.3.2 Presentation

The frequency count and percentage of specific important protocol deviations based on FAS will be presented in a summary table.

A by-subject listing of important protocol deviations will be presented, separately.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The demographic variables to be summarized include (and may not be limited to):

- Age (years) at first infusion
- Age group at first infusion: < 18 years and ≥ 18 years
- Sex
- Race
- Ethnicity

4.1.4.2 Presentation

The demographic variables will be summarized for FAS and Safety Set. The descriptive statistics will be presented in a summary table following the specification in Section 3.3.

A by-subject listing of demographics for Safety Set will also be generated.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

The variables in baseline characteristics include:

- Weight at first infusion
- Height at first infusion

4.1.5.2 Presentation

The baseline characteristics will be summarized for FAS and Safety Set. The descriptive statistics will be presented in a summary table following the specification in Section 3.3.

A by-subject listing of baseline characteristics for safety set will also be generated.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The variables for disease characteristics include:

- Age at first aHUS symptoms
- Age at aHUS diagnosis

- A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) activity categorized as >= 5% or < 5%

If the date of aHUS symptoms / diagnosis is completely missing, then the participant will be excluded from the analysis for age at first aHUS symptoms / diagnosis. If the date of aHUS symptoms / diagnosis has non-missing year, then the month (if missing) will be imputed as January, and the day (if missing) will be imputed as 1st of the month.

4.1.6.2 Presentation

The disease characteristics will be summarized for FAS. The descriptive statistics will be presented in a summary table following the specification in Section 3.3.

A by-subject listing of baseline characteristics for safety set will also be generated.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history will be coded in Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher. The terms to be presented are the "System Organ Classes" (SOCs) and Preferred Terms (PTs).

The variables for **history of emergency room visits and hospitalizations due to aHUS** include:

- Any emergency room (ER) visits or hospitalizations due to aHUS prior to start of screening (yes or no)
- If the response to the last bullet point is "Yes", then further derive the following variables:
    - Any ER visit (yes or no)
    - Any hospitalizations (yes or no)
    - ICU level of care (yes or no)
    - Number of days of ICU stay.

The number of days of ICU stay for a participant is the sum of number of days in all reported ICU stays.

The variables for **kidney transplant history** include:

- Any kidney transplant prior to entering the study (yes or no)
- Was the kindey transplant related to aHUS (yes or no)
- Cause of end-stage kidney disease leading to the kidney transplant when not related to aHUS

4.1.7.2 Presentation

Medical history will be summarized for **FAS** and **Safety Set**. The descriptive statistics will be presented in a summary table following the specification in Section 3.3. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted in international order for SOC and in alphabetical order for PT.

The presentation of **surgical history** will follow the same practice as medical history.

The **history of emergency room visits and hospitalizations due to aHUS** will be summarized for **FAS** and **Safety Set**. The descriptive statistics will be presented in a summary table following the specification in Section 3.3. The percentage of subjects with ER visits or hospitalizations due to aHUS prior to start of screening is based on the number of patients in the specified analysis sets; the percentages of subjects in separate categories (ER visit / hospitalizations / ICU level of care) will be based on the number of patients in those who answered 'Yes' for ER visits or hospitalizations due to aHUS prior to start of screening.

The **kidney transplant history** will be summarized for **FAS** and **Safety Set**. The descriptive statistics will be presented in a summary table following the specification in Section 3.3.

By-subject listings will also be generated for data summarized in this section.

4.1.8 Prior and Concomitant Medications / Procedures

4.1.8.1 Definitions and Derivations

Prior and concomitant medications (including vitamins and herbal preparations) will be coded using the World Health Organization Drug Dictionary (WHO-DRUG) Global March 2023 or later, while prior and concomitant nonpharmacologic therapies and procedures will be coded using MedDRA version 26.0 or higher.

Prior medications are defined as any non-study medications that were started, and were stopped, prior to the date of first infusion.

Concomitant medications are defined as any non-study medications that were taken or occurred while the subjects also received study medication. A medication will be considered

concomitant if the start date is on or after the date of the first study drug infusion, or if the start date is before the first infusion date and the end (stop) date is after the first infusion date.

Disallowed concomitant medications are defined as concomitant medications that include the following:

- All the complement inhibitors
- Rituximab
- IVIg

A procedure is defined as either prior or concomitant in the same way as the medications.

If the start date of a medication / therapy is partially or completely missing and the end (stop) date of a medication / therapy does not indicate that it ends prior to first infusion, then the determination of the concomitant status will be based on the following:

- If the start year is after the year of the first study drug infusion, then the medication/therapy is concomitant; else,
- If the start year is the same as the year of the first study drug infusion and
    - the start month is missing, then the medication/therapy is concomitant; else if
    - the start month is present and is the same or after the month of the first study drug infusion, then the medication / therapy is concomitant; else,
- If the start date is completely missing, then the medication / therapy is concomitant.

All other medications / therapies are considered as Prior Medications / Therapies.

For **pre-treatment plasma exchange / infusion** and **pre-treatment kidney dialysis**, the variables to be summarized are:

- For pre-treatment plasma exchange/infusion:

1) Definition:

Whether a subject is with plasma exchange / infusion that is related to the current TMA and prior to the first dose of study drug

2) Interested information:

The type of the plasma exchange / infusion (plasmapheresis, plasma exchange and / or plasma infusion)

The type of infusion or plasma exchange replacement fluid (albumin, plasma, or a combination of the two)

- For pre-treatment kidney dialysis:

1) Definition:

Whether a subject is with kidney dialysis within 5 days prior to the first dose of study drug,

2) Interested information:

whether the dialysis is of regular or not

what is the type of the dialysis (hemodialysis or peritoneal dialysis)

whether it is related to the kidney failure caused by aHUS

whether it is related to the current TMA

For **concomitant kidney dialysis**, it is defined as kidney dialysis that occurred any time after the first dose, and the variables to be summarized are:

- Whether a subject is with concomitant kidney dialysis
- What is the type of the dialysis (hemodialysis or peritoneal dialysis)

Whether the dialysis is related to kidney failure caused by aHUS

4.1.8.2 Presentation

Prior and concomitant summaries will be presented separately.

Medications will be summarized by Anatomic-Therapeutic-Chemical (ATC) code and generic drug name using frequency counts and percentages of subjects for FAS.

Separate summaries will be made for prior and concomitant vaccines.

Separate summaries will be made for prior and concomitant antibiotic prophylaxis.

A separate summary for disallowed concomitant medication will also be generated for FAS.

Procedures will be summarized similarly, but by MedDRA Class and preferred term.

A table summarizing pretreatment plasma exchanges and plasma infusion as well as kidney dialysis will be generated. A similar table will summarize concomitant kidney dialysis. The descriptive statistics will be presented following the specification in Section 3.3.

In the event a subject receives a prohibited/disallowed medication or undergoes a prohibited procedure, this will be reported as a protocol deviation as described in Section 3.3.6

By-subject listings will also be generated for data summarized in this section.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

The variables for study drug compliance are defined as:

- percentage of actual number of infusions among the number of planned infusions (compliance percentage). The number of planned infusions is calculated based on the assigned weight cohort at baseline. The planned dose after drug discontinuation will not be taken into consideration.

- categories for the above defined infusion percentages: < 80%, >= 80% to <=125%, and > 125%

4.1.9.2 Presentation

The study drug compliance will be summarized for FAS and Safety Set.

The infusion percentage will be treated as a continuous variable and summarized with descriptive statistics as specified in Section 3.3

The categories for the above defined infusion percentages will be treated as categorical variables and summarized with numbers and percentages of subjects among the specified analysis sets.

A by-subject listing of study drug compliance will also be generated.

4.2 Endpoint Analyses

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

All estimands have a common **population** of Chinese subjects with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria, with a common **treatment** of IV administration with eculizumab.

Other attributes (endpoint, strategy for ICE, and population-level summary) for each of the estimand is summarized as follows.

Note: The ICEs under considerations are: 1) premature discontinuation of study intervention; and 2) initiation of disallowed therapy or medicine.

Statistical category	Endpoint	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Objective:				
Primary Analysis (FAS)	Complete TMA Response during the 26-week Treatment Period	Composite strategy	The proportion of complete TMA responders overall along with 95% CIs	4.2.1.1
Sensitivity Analysis (PP)	Same as in "Primary Analysis"	Composite Strategy	Same as in "Primary Analysis"	4.2.1.5
Supplementary Analyses (FAS)	Modified Complete TMA Response during the 26-week Treatment Period	Composite strategy	The proportion of modified Complete TMA Responders overall along with 95% CIs	4.2.1.6
Supplementary Analyses (FAS)	Complete TMA response status over time	Composite strategy	The proportion of complete TMA responders over time	4.2.1.6
Supplementary Analyses (FAS)	Modified complete TMA response status over time	Composite strategy	The proportion of modified complete TMA responders over time	4.2.1.6
Subgroup Analyses (FAS)	Same as in "Primary Analysis"	Composite Strategy	Same as in "Primary Analysis"	4.2.1.7
Secondary Objective 1:				
Primary Analysis (FAS)	Time to Complete TMA Response	Composite strategy	Estimate of cumulative distribution function (CDF) of time to complete TMA response	4.2.2.1
Secondary Objective 2:				
Primary Analysis (FAS)	Hemoglobin response during the 26 week treatment period	Treatment policy	The proportion of hemoglobin responders during the 26 week treatment period	4.2.2.4
Supplementary Analysis (FAS)	Hemoglobin response over time	Treatment policy	The proportion of hemoglobin responders over time	4.2.2.6
Secondary Objective 3:				

Statistical category	Endpoint	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Analysis (FAS)	Dialysis requirement status over time	Treatment policy	The proportion of subjects whose dialysis requirement status is "Yes"	4.2.2.4
Secondary Objective 4:				
Primary Analysis (FAS)	Observed values and change from baseline in estimated glomerular filtration rate **(eGFR)** at each scheduled visit	Treatment policy	The mean and mean change from baseline in eGFR at each scheduled visit	4.2.2.4
Sensitivity Analysis (PP)	Same as in "Primary Analysis"	Treatment policy	Same as in "Primary Analysis"	4.2.2.5
Subgroup Analysis (FAS)	Same as in "Primary Analysis"	Treatment policy	Same as in "Primary Analysis"	4.2.2.7
Secondary Objective 5:				
Primary Analysis (FAS)	Chronic kidney disease (CKD) stage shift categorized as "improved", "stable" or "worsened" at each scheduled visit compared to baseline	Treatment Policy	proportion of subjects whose CKD stage has improved, worsened, or have stayed the same	4.2.2.4
Supplementary Analysis (FAS)	Chronic kidney disease (CKD) stage shift of actual stage at each scheduled visit compared to baseline	Treatment Policy	Proportion of subjects under each CKD stage shift category	4.2.2.6
Subgroup Analysis (FAS)	Same as in "Primary Analysis"	Treatment Policy	Same as in "Primary Analysis"	4.2.2.7
Secondary Objective 6:				
Primary Analysis (FAS)	Observed value and change from baseline in specified hematologic parameters over time	Treatment Policy	mean and mean change from baseline in the hematologic parameters over time	4.2.2.4
Sensitivity Analysis (PP)	Same as in "Primary Analysis"	Treatment Policy	Same as in "Primary Analysis"	4.2.2.5

4.2.1 Primary Endpoint

The purpose of this section is to describe in detail analyses for the primary endpoint.

4.2.1.1 Definition

The primary objective of the study is to assess the efficacy of eculizumab in the treatment of subjects with aHUS in China and the **estimand for primary analysis** has the following attributes:

- **Population**: treatment-naïve pediatric and adult subjects with aHUS in China, and those who also meet the requirement of inclusion and exclusion criteria.
- **Endpoint**: **complete TMA response** which is defined as:
  - Normalization of platelet count (defined as platelet count $\geq 150000/\ \mu L$),
  - Normalization of LDH (defined as LDH $\leq$ ULN),
  - $\geq 25\%$ improvement in serum creatinine from baseline.
- **Treatment**: IV administration of eculizumab with a weight-based dose regimen
- **Intercurrent event** and corresponding strategies:
  - **intercurrent events** (ICE): 1) premature discontinuation of study intervention; 2) initation of disallowed therapy or medicine,
  - **strategy**: composite strategy (i.e. All subjects who meet response criteria after either of the ICEs will be considered as non-responders thereafter).
- **Population-level Summary**: the proportion of subjects who achieve complete TMA response during the 26-week treatment period.

Note: the definition of "achieving **complete TMA response during the 26-week treatment period**" is as following:

- Criteria for each component needs to be met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and at any measurement in between.
- There is overlap of the three different time intervals, each defined by the 2 separate assessments (at least 4 weeks apart) for the corresponding component, and the earliest overlapping time is defined to be the **first time to complete TMA response during the 26-week treatment period**.

4.2.1.2 Derivations

The details will be presented in section 4.2.1.4.

4.2.1.3 Handling of Dropouts and Missing Data

For evaluation of complete TMA response during the 26-week treatment period, subjects missing an efficacy assessment that is part of the definition of complete TMA response while still on-study will have their last observation carried forward (LOCF). If a missing value occurs post-first-dose and the previous (last) observation is prior to the first dose, the LOCF method does not apply, and the data should remain missing. If there are two non-missing observations that are at least 28 days apart, then all the missing observations in between can be imputed by LOCF. Otherwise, LOCF will not be applicable if the last observation itself is imputed or missing. For subjects who will have discontinued from the study prior to week 26, their data up to the time of discontinuation will be used to assess complete TMA response.

The handling of the platelet and serum creatinine data as parameters in the complete TMA response definition will follow the specification in Section 3.3.5.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary analysis will be performed on the FAS. It will consist in estimating the population-level summary as specified in Section 4.2.1.1, and this will be performed by calculating the number of responders, the point estimate of the proportion and a 2-sided 95% confidence interval (CI).

The numerator of the point estimate will be the number of subjects in the FAS that complete TMA response during the 26-week treatment period (as defined in section 4.2.1.1). The denominator will be the number of subjects in the FAS. The CI will be based on the exact confidence limits using the Clopper-Pearson method.

The number of responders, the point estimate of proportion and 95% CI based on the Clopper-Pearson method will also be presented for the following components during the 26-week treatment period:

- Platelet count normalization
- LDH normalization
- 25% improvement in serum creatinine from baseline
- Hematologic normalization (normalization of both platelet and LDH):

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

The primary endpoint will be analysed based on the PP set.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The estimands for supplementary analyses in this section (section 4.2.1.6) have the common attributes on population, treatment and ICE and their strategy is the same as the primary analysis. The endpoints and population-level summary will be defined as appropriate.

Supplementary Analysis 1: modified complete TMA response during the 26-week treatment period.

A modified version of complete TMA response will be evaluated. The modification will only affect subjects considered to be on dialysis at baseline (see definition in Section 3.3.1and 4.2.2.1). For these subjects, the criterion requiring an improvement from baseline of 25% or more in serum creatinine will be replaced by a postbaseline change in dialysis status (from requiring dialysis at baseline to no longer requiring dialysis) that is maintained for at least 4 weeks.

The summaries will be tabulated on FAS and are similar to the specification in primary analysis, except that:

The estimand attributes endpoint and population-level summary are defined as:

- **Endpoint**: **Modified complete TMA response** which is defined as:
    - Normalization of platelet count (defined as platelet count $\geq 150000/\ \mu L$),
    - Normalization of LDH (defined as LDH $\leq$ ULN),
    - 1) $\geq 25\%$ improvement in serum creatinine from baseline if the subject is not on dialysis at baseline, OR 2) the subject went from being "on dialysis" at baseline to "not requiring dialysis"
- **Population-level Summary:** the proportion of subjects who achieve **modified complete TMA response** during the 26-week treatment period.

Note: the definition of "achieving modified complete TMA response during the 26-week treatment period" is similar to the one for complete TMA response during the 26-week treatment period.

Another version of modified complete TMA response will also be assessed. The modification will only affect subjects considered to be on regular dialysis at baseline based on eCRF.

Supplementary Analysis 2: complete TMA response status over time.

The estimand attributes on endpoint and population-level summary are defined as:

- **Endpoint**: complete TMA response at scheduled visits
- **Population-level Summary:** the proportion of subjects who achieve **complete TMA response** at scheduled visits:
    - Include a subject in the denominator of the proportion as long as the result is available for at least one component at that visit for that subject.
    - Include a subject in the numerator of the proportion as long as the result meets the complete TMA response criteria at that visit.

Complete TMA response will be summarized over time by presenting the number (in the format of fraction) and proportion of responders along with a 2-sided 95% CI for each postbaseline time point, which will be based on exact confidence limits using the Clopper-Pearson method. The analysis will be applied on FAS.

This summary will be accompanied by a similar presentation for the components of complete TMA response. The list of components to be summarized are the same as is described in Section 4.2.1.4. For missing data, if the prior (last) visit is not missing or imputed, then LOCF will be applied component-wise. The post-dose missing data can not be imputed via LOCF from the baseline value.

These tabular summaries will be accompanied by a line chart displaying for each time point the proportion of complete TMA response and proportions of response for each component in its definition, connected with line segment between neighboured time points.

Supplementary Analysis 3: Modified complete TMA response status at a specific time point over time.

A summary similar to “Supplementary Analysis 2” as in section 4.2.1.6 will be tabulated on FAS except that:

The estimand attributes on endpoint and population-level summary are defined as:

- **Endpoint**: status of meeting the criteria of modified complete TMA response at a specific time point (with no need to be confirmed) at all scheduled visits
- **Population-level Summary:** the proportion of subjects who achieve modified complete TMA response status at a specific time point at all scheduled visits.

4.2.1.7 Subgroup Analyses

The primary efficacy analysis will be conducted by the following subgroups on FAS if it is deemed appropriate:

- age (< 18 years, ≥ 18 years)
- sex (male, female)
- kidney transplant history (yes, no)
- immunogenicity status (ever positive, always negative)
- dialysis within 5 days prior to treatment initiation (yes and regular, yes and not regular, no)

4.2.2 Secondary Endpoints

This section describes analysis details for **secondary endpoints** related to **efficacy**. For the rest of the secondary endpoints, see Section 4.6.2 for the analysis plan for adverse events (safety and tolerability), see Section 4.3 for the analysis plan for pharmacodynamics, see Section 4.4 for the analysis plan for pharmacokinetics, see Section 4.5 for the analysis plan for immunogenicity, see Section 4.6.1 (Exposure), Section 4.6.3 (Chemistry and Hematology), Section 4.6.4 (Urinalysis), Section 4.6.5 (Vita Signs) and Section 4.6.6 (Electrocardiogram) for the analysis plan for the additional safety measures.

4.2.2.1 Definition

Under estimand framework, the common attributes of the endpoints in this section are:

- **Population**: treatment-naïve pediatric and adult subjects with aHUS in China, and those who also meet the requirement of inclusion and exclusion criteria.
- **Treatment**: IV administration of eculizumab with a weight-based dose regimen
- **Intercurrent event** and corresponding strategies:
    - **intercurrent events** (ICE): 1) premature discontinuation of study intervention; 2) initation of disallowed therapy or medicine,
    - **strategy**: composite strategy will be applied for any estimand whose **variable** attribute is related to complete TMA response, as is defined in section 4.2.1.1; otherwise, treatment policy will be applied.

The **endpoint** and population-level **summary** are:

For **secondary objective 1**:

- **Variable: time to complete TMA response.** Time from first infusion to the first time point at which all the criteria for complete TMA response are met. The definition of complete TMA response follows the specification in section 4.2.1.1

- **Population-level measure:** estimate of cumulative distribution function (CDF) of time to complete TMA response.

For **secondary objective 2:**

- **Variable: increase in Hemoglobin.** A subject is classified as having achieved the response of increase in hemoglobin of ≥ 20 g/L from baseline through Week 26, if the criteria of increase is met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. See also Section 8.1.3 of CSP.

- **Population-level summary:** proportion of subjects who meet the criteria of responder for increase in hemoglobin.

For **secondary objective 3:**

- **Variable: Dialysis requirement status** over time. A subject will be considered as not requiring dialysis at a specific time point if they have been dialysis free for more than 5 days prior to that time point; the dialysis requirement status will be "Yes" if a subject has been dialysis free for 5 days or less up to that time point.

- **Population-level summary:** proportion of subjects whose dialysis requirement status is "Yes".

For **secondary objective 4:**

- **Variable:** Observed values and change from baseline in estimated glomerular filtration rate **(eGFR)** at all scheduled visits

- **Population-level summary:** mean and mean change from baseline in eGFR

For **secondary objective 5:**

- **Variable:** Chronic kidney disease **(CKD)** stage shift as evaluated by eGFR and classified as improved, stable (no change), or worsened at all scheduled visits compared to baseline. The definition for CKD stage classification and CKD stage shift can be seen in CSP Section 8.1.3.

- **Population-level summary:** proportion of subjects whose CKD stage has improved, worsened, or have stayed the same

For **secondary objective 6:**

- **Variable:** Observed value and change from baseline in below listed **hematologic parameters** at all scheduled visits:
    - platelets
    - LDH
    - Hemoglobin
- **Population-level summary:** mean and mean change from baseline in the hematologic parameters listed above.

4.2.2.2 Derivations

The details are already included in Section 4.2.2.4.

4.2.2.3 Handling of Dropouts and Missing Data

There will be no imputation for missing data. Special considerations are described below for data under concurrent procedures:

The handling of hemoglobin with concurrent transfusions will follow the specification in Section 3.3.5 and applies to the following secondary endpoints:

- Increase in hemoglobin

The handling of platelet measurements with concurrent transfusions, and handling of serum creatinine with concurrent dialysis will follow the specification in Section 3.3.5 and applies to the following secondary endpoints:

- Time to complete TMA response
- Hematologic parameter (platelet)

The handling of eGFR with concurrent dialysis will follow the specification in Section 3.3.5 and applies to the following secondary endpoint:

- eGFR observed value and change from baseline over time
- CKD stage shift

4.2.2.4 Primary Analysis of Secondary Endpoints

The primary analyses for secondary endpoints will be performed on the FAS. Separate by-subject listings will be created for all secondary efficacy analysis parameters.

For **time to complete TMA response**:

Subjects that do not have a response at the time when the analysis is performed will be censored at the date of last visit or study discontinuation.

Kaplan Meier cumulative distribution curves will be generated along with 2-sided 95% CIs. The corresponding summary table will present at each postbaseline time point:

- The cumulative distribution function (CDF) estimate
- The number of subjects at risk
- The number of subjects responding
- The number of subjects censored

The table wil also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to complete response.

For **increase in hemoglobin:**

The number and proportion of subjects that achieved the response of increase in hemoglobin through the 26-week treatment period (as defined in Section 4.2.2.1) will be summarized along with a 2-sided 95% CIs.

For **dialysis requirement status**:

An analysis will present the number and proportion of subjects that are requiring dialysis (see definition in Section 4.2.2.1) over time. A 2-sided 95% CI for the proportion will be provided. The CI will be based on exact confidence limits using the Clopper-Pearson method. The summary will be produced for subjects requiring dialysis at baseline (see definition in Section 3.3.1), not requiring dialysis at baseline, and overall. A by-subject figure showing dialysis status or events over time will be presented.

For **eGFR observed value and change from baseline over time:**

Kidney function evaluated by eGFR will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables as specified in Section 3.3, for

both the observed value and the change from baseline value. A value for eGFR will be imputed for subjects requiring dialysis (see Section 4.2.2.3 for details).

For **CKD stage**:

CKD stage will be summarized over time by presenting the number and proportion of subjects that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 will be considered the worst category, while stage 1 will be considered the best category (see Section 8.1.3 of CSP for details). A 2-sided 95% CI for each proportion will be provided. The CIs will be based on exact confidence limits using the Clopper-Pearson method.

For **hematologic parameters**:

Hematologic parameters (platelets, LDH, hemoglobin) will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoints

For **eGFR observed value and change from baseline over time:**

A sensitivity analysis will be performed on the PP set. The summaries will be similar to the one specified in Section 4.2.2.4

For **hematologic parameters**:

A sensitivity analysis will be performed on PP set. The summaries will be similar to the one specified in Section 4.2.2.4.

4.2.2.6 Supplementary Analyses of the Secondary Endpoints

For **increase in hemoglobin**:

Supplementary analyses will be applied to FAS summarizing the response status of hemoglobin increase over time.

The estimand attribute on variable is either or not meeting the criteria of increase in hemoglobin of ≥ 20 g/L from baseline at each scheduled visit, and the population-level summary is the proportion of responders at each scheduled visit.

For **CKD** stage**:**

A supplementary analysis will be performed on the FAS. A shift table will summarize the CKD stage shift of the actual stages (5 stages in total as defined in CSP 8.1.3) from baseline by each visit.

4.2.2.7 Subgroup Analyses

For both the **eGFR observed value and change from baseline over time** and the **CKD** stage:

A subgroup analysis will be performed on the FAS. The summaries will be similar to the one specified in Section 4.2.2.4 and performed separately on the following subgroups:

- Subjects with kidney transplant history at enrollment
- Subjects without kidney transplant history at enrolment

4.3 Pharmacodynamic Endpoint

This section covers details related to pharmacodynamic endpoints and analyses.

4.3.1 Definitions and Derivations

The estimand attributes for pharmacodynamic endpoint are:

- **Population**: treatment-naïve pediatric and adult subjects with aHUS in China, and those who also meet the requirement of inclusion and exclusion criteria.
- **Variable**: changes in serum free and total C5 concentrations over time
- **Treatment**: IV administration of eculizumab with a weight-based dose regimen
- **Intercurrent event** and corresponding strategies:
    - **intercurrent events** (ICE): 1) premature discontinuation of study intervention; 2) initation of disallowed therapy or medicine,
    - **strategy**: treatment policy (ie. all data after ICE1 or ICE2 will be used)

Population-level summary: the mean changes in serum free and total C5 concentrations at all scheduled visits.

4.3.2 Presentation

Any tabular 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 listed, and summarized with descriptive statistics by timepoints (i.e pre-

dose, post dose or anytime for each scheduled visit), including number of subjects, mean, SD, median, minimum, and maximum. Box plots of observed serum free C5 concentrations versus scheduled visits need to be plotted (semi-log scale) and stratified by pre-dose, post-dose or anytime for each scheduled visit.

4.4 Pharmacokinetics Endpoint

This section covers details related to pharmacokinetics endpoints and analyses.

4.4.1 Definitions and Derivations

The estimand attributes for the pharmacokinetic endpoint are:

- **Population**: treatment-naïve pediatric and adult subjects with aHUS in China, and those who also meet the requirement of inclusion and exclusion criteria.
- **Variable**: serum eculizumab concentrations over time
- **Treatment**: IV administration of eculizumab with a weight-based dose regimen
- **Intercurrent event** and corresponding strategies:
    - **intercurrent events** (ICE): 1) premature discontinuation of study intervention; 2) initation of disallowed therapy or medicine,
    - **strategy**: treatment policy (ie. all data after ICE1 or ICE2 will be used)
- **Population-level summary**: mean serum eculizumab concentrations at all scheduled visits.

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 listed and summarized with descriptive statistics by timepoints (i.e pre-dose, post dose or anytime for each scheduled visit), including number of subjects, mean, SD, geometric mean, geometric CV (%), median, minimum and maximum. Box plots of eculizumab concentrations versus scheduled visits need to be plotted (both linear scale and semi-log scale) and stratified by pre-dose, post-dose or anytime for each scheduled visit. In the above analyses, the BLQ values are defined as serum concentrations that are below LLOQ (lower limit of quantification) and will be imputed as LLOQ / 2). 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 document when needed.

4.5 Immunogenicity

4.5.1 Definition and Derivations

The estimand attributes for immunogenicity are:

- **Population**: treatment-naïve pediatric and adult subjects with aHUS in China, and those who also meet the requirement of inclusion and exclusion criteria.
- **Variable**: ADA response (as categorized by the definitions below)
- **Treatment**: IV administration of eculizumab with a weight-based dose regimen
- **Intercurrent event** and corresponding strategies:
    - **intercurrent events** (ICE): 1) premature discontinuation of study intervention; 2) initation of disallowed therapy or medicine,
    - **strategy**: treatment policy (ie. all data after ICE1 or ICE2 will be used)
- **Population-level summary**: proportion of subjects for each pre-defined ADA response category

ADA response categories:

- ADA negative: collected samples are tested negative at all time points, including baseline and post-baseline.
- ADA positive: collected samples are tested positive at any time during the study, including baseline and/or post-baseline. Subjects 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 response when the baseline ADA result is negative
        - Persistent treatment-emergent responses: treatment induced ADA (subject 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 or a treatment induced ADA detected at the last available assessment.

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

- Transient treatment-emergent responses: at least one treatment induced (subject is ADA negative at baseline) ADA positive measurement, but not fulfilling the conditions for persistently positive or indeterminant.

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

- Neutralizing antibody (NAb) : The presence of neutralizing antibodies (nAb) 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 tabular summary of immunogenicity data will be made on the Safety Set. 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 subjects with at least one ADA result during the study. The number and percentage of patients with different titer categories (including negative) will be summarized by visit. ADA titre results can be presented for individuals as a listing.

4.6 Safety Analyses

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

Tables are provided for the safety set; listings are provided for All subjects or the safety set depending on the availability of data.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

The variables for study drug exposure is defined as:

- Follow-up duration: date of study completion / study discontinuation / last available study visit – date of first dose + 1 day

The "/" means to use either the date of study completion or the date of study discontinuation as indicated by eCRF. If neither is available, then to use the date of last available study visit.

- Treatment duration: date of last dose – date of first dose + 1 day
- Exposure duration: date of last dose – date of first dose + 14 days
- Total dose (in mg) through the 26-week treatment period

4.6.1.2 Presentation

The study drug exposure will be summarized for Safety Set. The durations for study, treatment, and exposure will be converted into weeks and approximated up to one decimal place, and the descriptive statistics will be presented in a summary table following the specification in Section 3.3.

A by-subject listing of study drug exposure will also be generated. The actual kit numbers will be listed for all subjects who have at least one dose of treatment.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

The definition of adverse event (AE) is introduced in CSP 10.3.1.

The following definitions based on onset date and time of an AE will be used:

- Pretreatment adverse events: any AE that starts after providing informed consent, but before the first infusion of study drug.
- Treatment-emergent adverse event (TEAE): any AE that starts during or after the first infusion of study drug.

If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
    - The start month is missing, then the AE is treatment emergent, else if

- The start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else

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

All other AEs are considered Pretreatment Adverse Events (PTAEs).

The variables in the domain of 'Adverse events' that are of interest for analysis are the incidence of the following adverse events:

- TEAE
- TEAE leading to withdrawal from the study.
- TEAE leading to study intervention discontinuation.
- Study intervention related TEAE: see CSP 10.3.3.
- Severe TEAE: see CSP 10.3.3.
- Treatment-emergent serious adverse event (TESAE): see CSP 10.3.2.
- Adverse event of special interest (AESI): Meningococcal infections will be considered as AEs of special interest.
    - To find meningococcal events, the adverse event dataset will be searched for the following MedDRA Preferred Terms: Meningitis meningococcal, Meningococcal bacteraemia, Meningococcal infection, Meningococcal sepsis, Meningococcal carditis, Encephalitis meningococcal, Endocarditis meningococcal, Myocarditis meningococcal, Optic neuritis meningococcal, and Pericarditis meningococcal.

4.6.2.2 Presentation

The AEs will be summarized on Safety Set and the calculation of any percentage will be based on the number of subjects in the Safety Set, or the number of subjects in the relevant subgroup in the Safety Set.

Both **pretreatment AEs** and **TEAEs** will be summarized in **listings**.

Only **TEAEs** will be **tabulated** as described **below**, following the specification for descriptive statistics of categorical variables in Section 3.3.

Overview summary of adverse events:

An overview summary of AEs and SAEs will be presented. The number and percentage of subjects with events (n, %) will be shown for the following sub-categories:

- Any AE
- Any SAE
- Fatal SAE (Any SAE with outcome of death)
- Any AE leading to discontinuation of study intervention
- Any AE resulting in withdrawal from the study
- AEs by relationship to study intervention: related vs not related
- AE by severity as defined by CTCAE v5.0 (see CSP 10.3.3)

Detailed listings of all AEs, SAEs, and related AEs, will be presented. These listings will include severity and relationship to treatment, as well as action taken regarding study treatment, other action taken, and AE outcome.

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

The number and percentage of subjects with events will be presented by SOC and PT. Subjects will be counted once in each SOC and PT.

Adverse events leading to discontinuation of study treatment will also be summarized by SOC and PT.

SAEs will be summarized similarly including:

- SAE with outcome of death by SOC and PT;
- SAE by SOC and PT

Related AEs and SAEs by SOC and PT

The number and percentage of subjects with events will be presented by SOC and PT. If a subject has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the relationship to treatment summary table.

Related SAEs will be summarized similarly.

AEs and SAEs by SOC, PT, and Severity

The number and percentage of patients with events will be presented by SOC, PT and severity. If a patient has more than one occurrence of an AE, the most severe occurrence of the AE will be used in the severity summary table.

SAEs will be summarized similarly.

AEs by PT and Frequency

A summary table will be presented for adverse events sorted by decreasing frequency on PT level.

Adverse Event of Special Interest:

A summary table and a listing of AEs related to meningococcal infections will be provided. See Section 4.6.2.1 for a list of AE preferred terms that will be considered for these summaries of meningococcal infections.

Deaths, Other SAEs, and Other Significant Adverse Events

Individual listings will be presented for AEs leading to study treatment discontinuation, AEs leading to withdrawal from the study, AEs starting during study drug administration, and fatal AEs.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

The variables for the blood sample in the domain of clinical laboratory include:

- Lab parameters from hematology result
- Lab parameters from chemistry result

The measured laboratory variables are listed in Table 14 of study protocol.

4.6.3.2 Presentations

The summaries for blood sample parameters will be performed on the Safety Set.

Observed values and changes from baseline in hematology and clinical chemistry results will be summarized descriptively at baseline, and at each postbaseline time point.

For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

Abnormality status (“normal”, “low”, “high”) of the laboratory values will be derived based on the normal ranges provided by the central laboratory.

All data will be presented in listings, and a specific listing of abnormal results will be provided. For analysis purposes, laboratory results based upon standard units will be used.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

The variables for the urine sample in the domain of clinical laboratory include:

- Lab parameters from urinalysis result

The measured urinalysis variables are listed in Table 14 of study protocol.

4.6.4.2 Presentations

The summaries for urinalysis parameters will be performed on the Safety Set and presented similarly to those specified for blood sample, and the abnormality status will be derived based on the normality ranges provided by the central laboratory.

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

The variables in the domain of vital sign include:

- Blood pressure
- Pulse
- Respiratory rate
- Body temperature
- Weight
- Height

4.6.5.2 Presentations

The summaries for vital signs will be performed on the Safety Set.

Observed values as well as changes from baseline in body weight, height, and the variables for vital signs defined in Section 4.6.5.1 at each time assessment will be summarized descriptively.

A listing of vital signs data will be presented by subject, vital sign, and visit.

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

The variables in the domain of ECG include:

- PR interval
- RR interval
- QT interval
- QTcF: QT interval corrected for heart rate using Fridericia's formula: QTcF = QT/(RR^⅓), where QT is measured in msec and RR is measured in sec.

4.6.6.2 Presentations

The summaries for the ECG variables will be performed on the Safety Set.

Electrocardiograms will be evaluated and summarized as normal, abnormal – not clinically significant, or abnormal – clinically significant. A shift from baseline to worst on-study ECG table will be presented for ECG results.

Observed values and change from baseline in ECG intervals (PR, RR, QT and QTcF) will be summarized descriptively at baseline and each postbaseline time point.

5 INTERIM ANALYSIS

Not applicable.

6 REFERENCES

Not applicable.

7 APPENDIX

Not applicable.

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