STATISTICAL ANALYSIS PLAN

A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age

Study Number:	CSL312_3003
Study Product:	CSL312 (Garadacimab; Factor XIIa inhibitor monoclonal antibody)
Development Phase:	Phase 3
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Version:	3.0
Version Date:	5 Mar 2025
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

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Modification History

Version	Effective Date	Author of Modification	Summary of Change
1.0	1 August 2023		Not applicable (original version)
2.0	1 July 2024	Sabine Gerstmayr	• Changes due to protocol amendments 1 and 2: o Sample size. o Minor word modifications in the definitions of the Safety Analysis Set and the Per-protocol Analysis Set. • CRF version updated. • List of IDMC outputs added. • EoT Visit date will be set to last IP administration + 30 days or +60 days for Q1M or Q2M, respectively, if the EoT Visit of a subject is delayed by more than the treatment time window relative to the last IP administration. • AESI by SMQ search (hypersensitivity) renamed to TEAEs by SMQ search (hypersensitivity).
3.0	5 March 2025	Sabine Gerstmayr	• Implementation of protocol amendment 3: o Subjects can complete the study without Follow-up after the End of Treatment visit. • Description of time windows for efficacy and adverse events added as per TLF shells. • Term "Data Review" renamed to "Planned Analysis Review" following Parexel SOP update.

Version	Effective Date	Author of Modification	Summary of Change
			• SMQ search renamed to "hypersensitivity including anaphylaxis" for clarification. • Compliance formula for completed subjects in Section 9.6 corrected. • Term "infusion device" modified to "device issues". • Overview table for TEAEs and TEAE table by SOC and PT until Follow-up added. • Minor editorial changes.

1 List of Abbreviations

Abbreviation	Term
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BLQ	Below limit of quantification
BMI	Body mass index
C1-INH	C1-esterase inhibitor
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CPP	CSL Behring Clinical Pharmacology and Pharmacometrics
CSR	Clinical study report
C_{trough}	Trough plasma concentration
CV	Coefficient of variation
CV%	Percent coefficient of variation
DBL	Database lock
eCRF	Electronic case report form
EoS	End of study
EoT	End of treatment
ESP	External service provider
FXII	Factor XII
FXIIa	Activated factor XII
HAE	Hereditary angioedema
ICE	Intercurrent event
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IP	Investigational product
ISR	Injection Site Reaction
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MSAP	Modeling and simulation analysis plan

Abbreviation	Term
PARM	Planned Analysis Review Meeting
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
Q1	First quartile
Q3	Third quartile
Q1M	Once monthly
Q2M	Every 2 months
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study Data Tabulation Model
SMQ	Standardised MedDRA Query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLF	Tables, listings, figures
T_{max}	Time to reach maximum plasma concentration
WHO	World Health Organization

2 Purpose

This Statistical Analysis Plan (SAP) provides a detailed and complete description of the planned statistical analyses of the Study CSL312_3003 to support the Clinical Study Report (CSR).

This SAP complies with the International Council for Harmonisation (ICH) E9 'Statistical Principles for Clinical Trials' and E9(R1) 'Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials', and is based upon the following study documents:

- Clinical Study Protocol Amendment 3, dated 9 January 2025
- electronic Case Report Form (eCRF), Version dated 30 Jan 2025

Population pharmacokinetic (PK) analyses are described within the modeling and simulation analysis plan (MSAP) and reported separately.

Mock tables, listings, and figures (TLF) shells are provided in a separate supporting document.

All decisions regarding the final analysis of the study results, as defined in this SAP, have been made before database lock (DBL) of the study data. Deviations from the planned analyses in this SAP will be detailed in the CSR.

3 Study Design

This is a multicenter, open-label, phase 3b pediatric study designed to investigate the safety, PK / pharmacodynamics (PD), and efficacy of subcutaneous (SC) administered CSL312 in the prophylactic treatment of hereditary angioedema (HAE) in children 2 to 11 years of age. The study schematic is shown in Figure 1. The study will enroll a target sample size of approximately 20 subjects to ensure that at least 15 subjects complete 12 months of treatment.

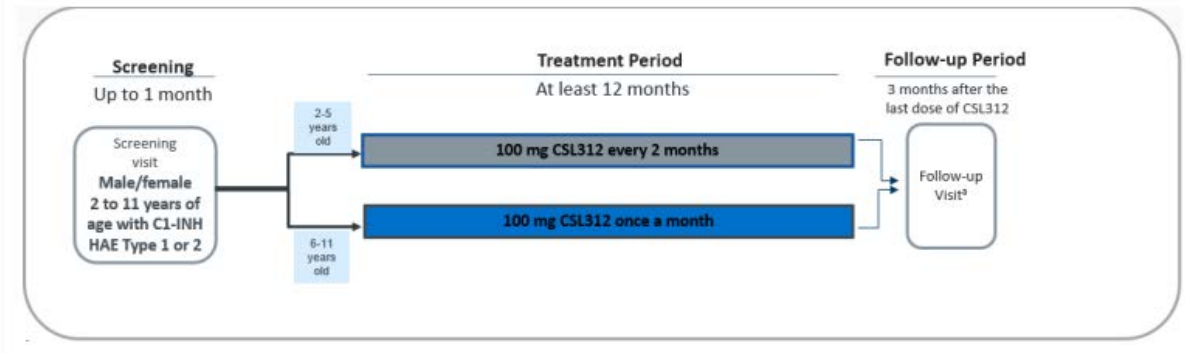
The following subjects will be eligible to participate in this study if they meet all eligibility criteria:

- CSL312-naïve pediatric subjects with C1-esterase inhibitor (C1-INH) HAE type 1 or 2

CSL312 will be administered SC at a dose of 100 mg once monthly (Q1M; subjects 6 to 11 years of age) or every 2 months (Q2M; subjects 2 to 5 years of age) for at least 12 months.

The study will consist of a Screening Period, an open-label Treatment Period, and Follow-up Period. The Follow-up Visit takes place 3 months after last dose of CSL312. Subjects who complete the study have the option to continue treatment with CSL312 or another prophylactic treatment without a scheduled follow-up. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

Figure 1 Overall Study Schema



C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema.
[a] The Follow-up Visit may be conducted via telephone instead of at study site. Assessments / tests may be omitted if the Follow-up Visit is conducted via telephone. The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

3.1 Objectives and Endpoints

Table 1 Primary Study Objectives and Endpoints

Objectives	Endpoints and / or Estimands	Summary Measure(s)
Primary		
The primary objectives of the study are to evaluate the safety and PK of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.	Treatment-emergent adverse events (TEAEs)	Number of subjects, percentage of subjects, and number of events as well as the event rates per injection and per subject year
	PK parameters after SC administration of CSL312 at steady state: • C_{max} • C_{trough} • T_{max}	• Mean (standard deviation [SD]) and geometric mean (geometric coefficient of variation percentage [CV%]) for all PK parameters except for T_{max} • Median (minimum, maximum) for T_{max}

Table 2 Secondary and Exploratory Study Objectives and Endpoints

Objectives	Endpoints and / or Estimands	Summary Measure(s)
Secondary		
The secondary objectives of this study are to evaluate efficacy, PD, and safety of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.	• Time-normalized number of HAE attacks • Time-normalized number of HAE attacks treated with on-demand treatment • Time-normalized number of moderate and / or severe HAE attacks • Percentage reduction in the time-normalized number of HAE attacks	• The time-normalized number (per month and year) of HAE attacks, of HAE attacks treated with on-demand treatment, and of moderate and / or severe attacks on treatment, respectively • The percentage reduction and the number of subjects experiencing at least ≥ 50%, ≥ 70%, ≥ 90%, or equal to 100% (attack-free) reduction in the time-normalized number of HAE attacks on treatment compared to their time-normalized number of HAE attacks documented in medical records
	• Serious adverse events (SAEs) • Deaths • Related TEAEs • TEAEs leading to study discontinuation • TEAEs in each severity category • Anti-CSL312 antibodies	The number and percentage of subjects experiencing the specified safety events on treatment as well as the event rates per injection and per subject year

Objectives	Endpoints and / or Estimands	Summary Measure(s)
	• Laboratory findings reported as adverse events (AEs) • Adverse events of special interest (AESIs) (severe hypersensitivity including anaphylaxis)	
	FXIIa-mediated kallikrein activity at scheduled time points	Descriptive summaries by nominal time point and the percentage of Baseline value
Exploratory		
The exploratory objective of the study is to further evaluate the PD effects of CSL312.	FXII concentration at scheduled time points	Descriptive summaries by nominal time point

C_{max} = maximum plasma concentration; C_{trough} = trough plasma concentration; C1-INH = C1-esterase inhibitor; FXIIa = activated factor XII; HAE = hereditary angioedema; PD=pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous; T_{max} = time to reach maximum plasma concentration.

3.1.1 Primary Study Hypotheses

Not applicable. The study is a single-arm, open-label study, and the primary endpoint of the study is not an efficacy endpoint.

3.2 Study Treatments

Eligible subjects will be assigned to open-label CSL312 with a dosing regimen dependent on their age at the time of consent as follows:

- 2 to 5 years of age: 100 mg Q2M SC administration
- 6 to 11 years of age: 100 mg Q1M SC administration

If a subject turns 6 years of age during the study, the dose regimen will remain unchanged, and the subject will be analyzed in the age group according to the subject's age at the time of consent.

3.3 Randomization Procedures and Blinding

Not applicable. This is a single-arm open-label study with no randomization.

3.4 Determination of the Sample Size

No formal sample size calculation is made, and the sample size is not based on formal statistical considerations. This study will enroll a prespecified number of subjects as agreed with health authorities. See Section 5.2 for definition of "enrolled".

3.5 Planned Interim Analyses

No formal interim analyses or sample size re-estimation are planned for this study.

3.5.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor the efficacy and safety data generated during the study. The IDMC will consist of independent clinical specialists in HAE, who also have experience in clinical trials. The IDMC will review accumulating data from the ongoing study. Based on these reviews, the IDMC will advise on the further conduct of the study. No success or futility thresholds will be set for the IDMC reviews. The Sponsor will continue the study unless a safety issue is confirmed that warrants study termination. The composition, activities, analyses, responsibilities, and timing of meetings of the IDMC will be described in the IDMC charter.

The following outputs are planned for IDMC meeting #2:

1. Tables:
    i. Demographic Characteristics
    ii. HAE History
    iii. Time-normalized Number of HAE Attacks During Various Time Windows of the Treatment Period
    iv. Analysis of Responders
    v. Overview of Treatment-emergent Adverse Events
    vi. Overview of Serious Treatment-emergent Adverse Events
    vii. Treatment-emergent Adverse Events by System Organ Class and Preferred Term

2. Figures:
    i. Subject Profiles for Study Participation, HAE Attacks by Severity, and On-demand Treatment

3. Listings:
    i. HAE Attacks – Investigator Reported
    ii. Derived Efficacy Variables: Time-normalized Number of HAE Attacks and Percent Reduction
    iii. Treatment-emergent Adverse Events

The IDMC mock TLF shells are provided in a separate supporting document.

In subsequent IDMC meetings, outputs may be added or removed including PK concentration listings and summaries.

4 Changes from the Protocol Planned Analyses

No changes to the analyses as presented in the study protocol are currently planned. Any changes in the planned analysis will be described in a new version of the SAP or in the CSR.

5 Study Analysis Sets

5.1 Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent / assent.

5.2 Enrolled Analysis Set

The Enrolled Analysis Set consists of all subjects in the Screened Analysis Set who were enrolled into the study. Subjects are considered "enrolled" in the study when they, or their legally authorized representative, has agreed to participate in the study after completing the informed consent process and Screening. Potential subjects who are screened to determine their eligibility but fail Screening or do not meet all the eligibility criteria, are not considered enrolled.

5.3 Safety Analysis Set

The Safety Analysis Set comprises all subjects in the Enrolled Analysis Set who received at least 1 dose of investigational product (IP). The Safety Analysis Set will be analyzed using the treatment that the subject actually received.

5.4 Per-protocol Analysis Set

The Per-protocol (PP) Analysis Set consists of all subjects in the Enrolled Analysis Set with no major protocol deviation potentially affecting the primary endpoint(s). Protocol deviations resulting in exclusion from the PP Analysis Set will be documented in the planned analysis review meeting (PARM) report before DBL. The PP Analysis Set will be analyzed using the treatment to which the subject was assigned regardless of the treatment that the subject actually received.

5.5 Pharmacokinetic Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set for whom there is at least 1 quantifiable PK concentration of CSL312 after administration.

5.6 Pharmacodynamic Analysis Set

The PD Analysis Set consists of all subjects in the Safety Analysis Set for whom at least one PD measurement was obtained.

6 General Considerations

All analyses will be done by dosing regimen (100 mg Q1M and 100 mg Q2M) and overall (if not stated otherwise).

Datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. Study data will be provided in Study Data Tabulation Model (SDTM) format. Analysis data will be provided in Analysis Data Model (ADaM) format.

SAS version 9.4 or higher will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum and maximum. Other descriptive statistics (e.g., standard error, CV) may be reported when appropriate and will be described in the respective section. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics defined with the analysis in the applicable SAP section.

The by-subject listings will be sorted by dosing regimen, site-subject number, and by visit / date and time, or item number (if applicable).

Generally, only data of scheduled visits will be used in statistical summary tables; data from unscheduled visits will be included in the listings.

Actual, rather than planned, sampling time points will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of plasma concentration data. The planned study visits will also be included in the listing. Planned sampling time points will be used in the descriptive summaries and in mean plots. Concentration-time data will also be listed according to actual sampling time points relative to previous injection.

7 Data Handling Conventions

7.1 Missing Data

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. These data will be indicated using a "blank" in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

The primary safety endpoint is TEAEs and will not be missing. The monitoring of reported AEs is performed throughout the study. If inconsistencies are detected, queries will be generated. If a subject did not report TEAEs, the number of TEAEs will be 0.

As only descriptive statistics will be presented for all PK parameters (primary PK endpoints), missing data will not be imputed.

Missing efficacy data will not be imputed, as there is no formal statistical analysis being done. All subjects who drop out within the first 30 days of the treatment period will be regarded as missing for all efficacy analyses.

The details of handling missing data are presented in the corresponding sections of this SAP for the respective analyses (e.g., efficacy analyses, safety analyses).

7.2 General Derived Variables

7.2.1 Reference Dates and Study Days

Reference dates are used to assign study periods relative to treatment (Section 7.4).

- The efficacy reference date will be the Day 1 Visit date for subjects who did not receive treatment and the date of first IP for treated subjects and will be used to calculate study day for efficacy measures.

- The safety reference date will be the date of first IP and will be used to calculate study day for safety measures.
- The PK reference date will also be the date of first IP and will be used to calculate study day for PK measures.

The respective study day will be calculated as (date of interest - reference date) + 1 if the date of interest occurs on or after the reference date. If the date of interest occurs before the reference date, the study day will be calculated as (date of interest – reference date). There will be no study day 0.

7.2.2 Durations and Time to Event Data

Durations (e.g., the duration of an AE) are calculated in days as:

- event end date – event start date + 1, if end time or start time is not available.
- event end date / time – event start date / time, if both end time and start time are available.

Thus, there will be no duration of 0 if end time or start time are not available. If an AE has missing or partially missing start or end date, no duration will be calculated.

For elapsed time (e.g., the time to event), use:

- event date / time – reference date /time, (if time available).

Thus, an event which happens on the same date as the reference date will have an elapsed time of 0 if event time or reference time are not available.

To transform durations or elapsed times, which are calculated in days into weeks, the number of days will be divided by 7; to report in months, the number of days will be divided by 30.4375; to report in years, the number of days will be divided by 365.25. These algorithms return decimal numbers and ignore the actual number of days in the months or years (the calendar days) between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

7.2.3 Baseline Definition

Baseline is defined as the most recent, non-missing value before the first IP administration (including unscheduled visits) for all assessments unless otherwise stated. For weight, the assessment on Visit Day 1, if available, will be used as Baseline even if it was taken after the first administration of IP. Assessments of weight after Visit Day 1 will not qualify as Baseline value.

7.2.4 Change from Baseline

Change from Baseline is calculated as:

- visit value – Baseline value.

Percentage change from Baseline is calculated as:

- (change from Baseline / Baseline value) * 100.

Percentage Baseline value is calculated as:

- (visit value / Baseline value) * 100.

If either the Baseline or visit value is missing, the change from Baseline, the percentage change from Baseline and the percentage Baseline value is also missing.

7.2.5 Multiple Assessments

All data will be reported according to the nominal visit date for which they were reported (that is, no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the protocol). Unscheduled data will not be included in by-visit summaries, but may contribute to the Baseline value, the End of Study (EoS) value, or best/worst case value (e.g., shift tables) and will appear in listings.

If a laboratory sample was repeated due to technical problems the results from the valid sample(s) for this visit will be used in the analysis. If a laboratory sample was repeated as safety follow-up to monitor abnormal values of the initial sample, the initial sample (revealing the abnormal values) of this visit will be used in the analysis.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

7.2.6 Actual Treatment

All subjects will receive 100 mg CSL312. The subjects' actual dosing regimen is determined by the subject's age at time of consent and will be checked against the exposure data in the eCRF including the actual administered vial numbers. If a subject receives a dosing regimen that is different from the planned regimen for the entire time of treatment, then the actual dosing regimen will be considered the dosing regimen actually received. In case of other deviations from planned treatment, an evaluation of the case, final treatment assignment, and documentation of the decision will be done before DBL during the PARM.

7.3 Stratification

Not applicable.

7.4 Study Periods and Time Windows Relative to Treatment

The following definitions for the periods of efficacy and safety will be used to define the durations used in the denominator of the time-normalized endpoints and safety endpoints such as exposure and subject-years. The definitions of the time windows will be used in the efficacy analyses and the analysis of TEAEs.

Table 3 Overview of Study Periods and Time Windows

Study Period	Start Date	End Date	Duration
Screening Period	Informed Consent date	Day 1 Visit date - 1 if Informed Consent Date is before Day 1 Visit date. Informed Consent date if Informed Consent date is on Day 1 Visit date.	End Date - Start Date + 1 if Informed Consent Date is before Day 1 Visit date. 0 if Informed Consent date is on Day 1 Visit date.
Treatment Period/ Efficacy Evaluation Period	Day 1 Visit date or date of first IP if available	End of Treatment (EoT) Visit date or for premature discontinuations without the EoT Visit the last available visit or event date [whichever occurs later]. If the EoT Visit of a subject is delayed by more than the treatment time window relative to the last IP administration, EoT Visit date will be set to last IP administration + 30 days or + 60 days for Q1M or Q2M, respectively.	End Date - Start Date + 1
Follow-up Period if applicable	EoT Visit date + 1	Follow-up Visit or for premature discontinuations after the EoT Visit the last available visit or last event date [whichever occurs later]	End Date - Start Date + 1
Safety Evaluation Period	Date of first IP	Subjects who choose not to continue to receive CSL312 or another	End Date - Start Date + 1

Study Period	Start Date	End Date	Duration
		prophylactic treatment: Follow-up Visit or for premature discontinuations the last available visit or last event date [whichever occurs later]. Subjects who choose to continue to receive CSL312 or another prophylactic treatment: EoT Visit or for premature discontinuations without the EoT Visit the last available visit or last event date [whichever occurs later].	

Time Window	Start Date	End Date	Duration
Efficacy: Day 1 Until Day 31	Day 1 Visit date or date of first IP if available	Study day 31	End Date – Start Date + 1
Efficacy: First 6 Months	Day 1 Visit date or date of first IP if available	Month 6 (Day 181) Visit Date	End Date – Start Date + 1
Efficacy: Second 6 Months	Month 6 (Day 181) Visit Date + 1 day	Month 12 (Day 361) EoT Visit Date. If the EoT Visit of a subject is delayed by more than the treatment time window relative to the last IP administration, EoT Visit date will be set to last IP administration + 30 days or + 60 days for Q1M or Q2M, respectively.	End Date – Start Date + 1
Safety: First 3 Months	Date of first IP	EoT date if subjects discontinued or date of first IP + 90 if subjects is ongoing	End Date – Start Date + 1
Safety: Second 3 Months	End Date of previous 3-Months' Time Window + 1	EoT date if subjects discontinued or start date + 90 if subjects is ongoing	End Date – Start Date + 1
Safety: Third 3 Months	End Date of previous 3-Months' Time Window + 1	EoT date if subjects discontinued or start date + 90 if subjects is ongoing	End Date – Start Date + 1

Time Window	Start Date	End Date	Duration
Safety: Fourth 3 Months	End Date of previous 3-Months' Time Window + 1	EoT date if subjects discontinued or start date + 90 if subjects is ongoing	End Date – Start Date + 1
Safety: Fifth 3 Months (if applicable)	End Date of previous 3-Months' Time Window + 1	EoT date if subjects discontinued or start date + 90 if subjects is ongoing	End Date – Start Date + 1
. . .			

Note:
The first day of the Treatment Period may occur on the same day as the Screening Visit for subjects meeting the eligibility criteria for the study. In this case, the duration of the Screening Period is 0.

The Follow-up Visit is mandatory in this study unless a subject chooses to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. For these subjects, the Follow-up Period is not applicable.

The length of the month in the 3-Months' Safety time windows is set to 30 days.

8 Study Population

Unless otherwise stated, all tables and listings in this section will be presented by dosing regimen (100 mg Q2M and 100 mg Q1M) and overall.

Subjects who turn 6 years of age during the study will remain on their dosing regimen from study start and will be analyzed for the age group at their date of consent.

8.1 Subject Disposition

The following summary will be provided based on the Screened Analysis Set (see Section 5.1):

- Number and percentage of subjects who provided Informed Consent.
- Number and percentage of subjects screened.
- Number and percentage of subjects not assigned to treatment (screen failures) with reason for screen failure.
- Number and percentage of subjects enrolled, i.e., eligible to enter the study.
- Number and percentage of subjects eligible to enter the study but not treated.
- Number and percentage of subjects who received any dose of IP.

- Number and percentage of subjects who completed treatment per entry on the eCRF 'End of Treatment' ("Did the subject complete the treatment period?" Answer: "Yes").
- Number and percentage of subjects who completed the study per entry on the eCRF 'Conclusion of Subject Participation' ("Did the subject complete the study?" Answer: "Yes").
- Number and percentage of subjects with at least 12 months treatment period (i.e. subjects with reported Month 12 / EoT Visit in eCRF).
- Number and percentage of subjects who completed the Follow-up Visit as required.
- Number and percentage of subjects who did not completed the Follow-up Visit because they continued in the post-study access program or another prophylactic treatment.
- Number and percentage of subjects who prematurely discontinued treatment during the Treatment Period with reason for treatment discontinuation (percentages based on the number who discontinued).
- Number and percentage of subjects who discontinued the study during the Treatment Period with reason for study discontinuation (percentages based on the number who discontinued).
- Number and percentage of subjects who discontinued the study during Follow-up Period with reason for study discontinuation (percentages based on the number who discontinued).
- Number and percentage of subjects in the Screened Analysis Set.
- Number and percentage of subjects in the Enrolled Analysis Set.
- Number and percentage of subjects in the Safety Analysis Set.
- Number and percentage of subjects in the PP Analysis Set.
- Number and percentage of subjects in the PK Analysis Set.
- Number and percentage of subjects in the PD Analysis Set.

Note:
Subjects may discontinue treatment but remain in the study until the Follow-up Visit. These subjects will be reported for treatment discontinuation, but not for study discontinuation. Other subjects may discontinue treatment and discontinue the study during the treatment period. These subjects will be reported for treatment and study discontinuation. Subjects who choose not to continue to receive CSL312 or another prophylactic treatment after this study may complete treatment and discontinue from the study during follow-up. These subjects will be reported for study discontinuation but not for treatment discontinuation. Subjects who choose to continue to receive CSL312 or another prophylactic treatment after this study will be reported as study completer if they completed treatment and not entered the Follow-up Period provided they answered the corresponding question in the eCRF ("Did the subject complete the study?") with "Yes".

Reasons for study and study treatment discontinuation will be presented in the order they are displayed in the eCRF.

The following by-subject listings will be provided:

- Disposition including date of informed consent, date of eligibility, date of first and last IP administration, EoT Visit date, Follow-up Visit date, reason for treatment discontinuation and/or study discontinuation.
- Assignment to analysis sets (included in Analysis Set: Screened Analysis Set [yes, no], Enrolled Analysis Set [yes, no], PP Analysis Set [yes, no], Safety Analysis Set [yes, no], PK Analysis Set [yes, no], PD Analysis Set [yes, no], reason(s) for exclusion from any analysis set).

8.2 Protocol Deviations

A protocol deviation occurs when an investigator site, or study subject, does not adhere to protocol-stipulated requirements. Deviations will be assessed by CSL as they are reported and evaluated periodically during study conduct. All identified protocol deviations throughout the study will be listed prior to DBL and will be classified as minor or major by CSL. Major protocol deviations are defined as deviations that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data. All protocol deviations will be listed.

The protocol deviations' classification into minor and major will be reassessed under statistical considerations. Under statistical considerations, protocol deviations leading to exclusion from an analysis set will be considered major. Protocol deviations not leading to exclusion from an analysis set will be considered minor. The classification of protocol deviations under statistical considerations, the subject's assignment to analysis sets, and the occurrence of intercurrent events (ICEs) will be discussed in detail during the PARM based on by-subject listings provided for the PARM. The decisions made during the PARM will be documented in the pre-DBL Planned Analysis Review Report prior to DBL for final analysis. After DBL, the PARM listings will be re-run on database locked data, and it will be checked/confirmed that no changes which may have an impact on the assignment of subjects to analysis sets or ICEs occurred. The final assignment of subjects to analysis sets will be documented in the post-DBL Planned Analysis Review Report.

Table 4 Potential Protocol Deviations and/or Reasons for Exclusion From Analysis Sets

Potential Protocol Deviations/Reasons for Exclusion	Potential Exclusion From Analysis Set
Subject did not provide informed consent and/or informed consent date missing	Screened, Enrolled, Safety, PP, PK, PD
Subject enrolled but not treated with IP	Safety, PP, PK, PD
Subject treated but with wrong dosing regimen	PP
Subject treated but does not have at least one measurable PK concentration after IP administration	PK
Subject treated but does not have at least one PD measurement	PD
Subject violated inclusion and/or exclusion criteria	Enrolled, PP, (Safety, PK, PD)
Subject treated but compliance outside 80-120%	PP, (PK, PD)
Subject treated but received prohibited concomitant medication	PP, (PK, PD)

Prior to the PARM, a list of concomitant medications used in the study will be provided to CSL as an Excel file in the same format as the corresponding listing of concomitant medications in the TLF shells. This Excel file will be reviewed by CSL and concomitant medication potentially interfering with the PK/PD analysis or with the efficacy analysis will be flagged. It will be discussed if subjects with such a concomitant medication flagged will be entirely excluded from the respective analysis set, if data after a specific time point will be excluded, or if the subject and data will not be excluded at all.

The following by-subject listings will be provided using the Screened Analysis Set (see Section 5.1):

- protocol deviations related to inclusion and exclusion criteria,
- protocol deviations leading to exclusion from any analysis set,
- other protocol deviations,

For the PARM, the following by-subject listings will be provided in addition based on the Enrolled Analysis Set:

- concomitant medications,
- study drug exposure,
- compliance,
- adverse events.

8.3 Demographic and Baseline Characteristics

The following summaries will be provided for the Safety Analysis Set and for the PK Analysis Set if the PK Analysis Set differs (see Sections 5.3 and 5.5):

- Demographic characteristics: sex, race, ethnicity, age, height at Screening, body weight and body mass index (BMI) at Baseline.
- HAE history: history of laryngeal attack (yes, no), family history of HAE (yes, no), age at diagnosis of HAE, HAE type (C1-INH type 1, C1-INH type 2), number of HAE attacks during 6 months before Screening or before the start of prophylactic therapy, prophylactic HAE therapy within 6 months before Screening (yes, no), primary locations of HAE attacks in the last 6 months prior to Screening (up to 3 may be selected).
- Medical history by system organ class (SOC) and preferred term (PT) – include medical history with an end date prior to informed consent date.
- Concomitant diseases by SOC and PT – include medical history with an end date after informed consent or flagged as ongoing.

Medical history and concomitant diseases will be coded by Medical Dictionary for Regulatory Activities (MedDRA). There will be periodic updates of the MedDRA version. The latest licensed version will be used and indicated in the final analysis, and version updates will be implemented upon availability.

By-subject listings for all available data using the Enrolled Analysis Set (see Section 5.2) will be provided for each category mentioned above and further for:

- Reproductive system findings (childbearing potential, method of birth control, date and time of pregnancy test, specimen type, and pregnancy test result) – applicable to children above 5 years of age.

Those listings will contain a Safety and PK flag.

8.4 Prior/Concomitant Medications

Reported medications will be coded using World Health Organization (WHO) Drug Global Dictionary. There will be periodic updates of the WHO Drug Global Dictionary version. The latest licensed version will be used and indicated in the final analysis, and version updates will be implemented upon availability. The summary of medications will show the number and percentage of subjects taking medication displayed for Anatomical Therapeutic Chemical

(ATC) class level 4 and PT. If the level 4 ATC name is not available, then the available next lower level will be used.

The reported medication will be classified as "Prior only", "Prior and concomitant" or "Concomitant only". These 3 categories are mutually exclusive:

- "Prior only": if the subject has not taken any IP; or if the medication end date [/time] is before IP start date [/time]. If the medication end date is partially missing, the medication will only be assigned to 'Prior only' if the partial date gives clear evidence that the medication stopped before IP start date.
- "Concomitant only": if the medication start date [/time] is on or after IP start date [/time]. If the medication start date is partially missing, the medication will only be assigned to 'Concomitant only' if the partial date gives clear evidence that the medication started on or after IP start date.
- "Prior and concomitant": if the medication start date [/time] is before IP start date [/time] and the medication end date [/time] is on or after IP start date [/time]. If the medication start date or end date are partially or completely missing, the medication will be assigned to 'Prior and concomitant' unless there is clear evidence that the medication stopped before IP start date (that is, the medication should be assigned to "Prior only") or that the medication started after IP start date [/time] (that is, the medication should be assigned to "Concomitant only").

Summary tables will be provided for "Prior and concomitant" and "Concomitant only" medications. In the summary of prior and concomitant medications, each subject will be counted once within each unique term.

On-demand HAE medication will be summarized besides the WHO Drug ATC classes as a separate block (as a "virtual" ATC class "On-demand HAE Medication") within the summaries of prior and concomitant medication including:

- On-demand HAE medications prior to the Treatment Period collected in the eCRF 'Concomitant and Prior Medications' with Primary Indication as "Study Indication (Acute HAE Treatment)".

- On-demand HAE medications on/after start of the Treatment Period collected in a separate eCRF 'On-demand Treatment'.

The on-demand HAE medication will also be reported in their original ATC class.

Summaries and by-subject listings will be provided based on the Safety Analysis Set (see Section 5.3). Listings will include medication/therapy start and end date/time or ongoing status, dose, route, frequency, primary indication for the medication, AE term if applicable, medical history term if applicable and concomitant medication flag (Prior, Prior / Concomitant, Concomitant).

8.5 Study Population - Derived Variables

Derivation of BMI at Baseline

BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

using the height measured at Screening and the weight measured at Baseline (see Section 7.2.3). If weight at Baseline is not available, the BMI will be missing.

BMI at later visits will be derived based on the most recent assessment of height and weight at the respective visit.

9 Efficacy Analyses

The primary objective of the study is to evaluate the safety and PK of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE. Thus, the primary endpoints of the study are a safety and PK endpoint and not an efficacy endpoint. Please see Section 10.2.1 and Section 11 for a description of the primary safety and PK endpoints, respectively, and corresponding analysis.

Subjects who turn 6 years of age during the study will remain on their dosing regimen from study start and will be analyzed in the age group according to the subject's age at the time of consent.

The efficacy endpoints will not be included in any efficacy summary if the subject's duration for the Treatment Period is less than 30 days, i.e., the subject discontinued within 30 days after the Day 1 Visit date or the date of first IP, if available. The reason why an endpoint is not included will be provided in the by-subject listing.

The efficacy endpoints will also be assessed over time for 6-months' time windows, with the first window starting at the Day 1 Visit date or the date of first IP, if available. Only subjects who completed the entire time window (i.e., completed Visit Month 6 and Visit Month 12,

respectively) – allowing for visit windows as per Schedule of Assessment in the protocol – will be included in the analysis of this time window.

9.1 Analysis of Primary Endpoint

The primary endpoint of the study is not an efficacy variable.

9.2 Analysis of Secondary Endpoints

The secondary efficacy endpoints are:

- Time-normalized number of HAE attacks.
- Time-normalized number of HAE attacks treated with on-demand treatment.
- Time-normalized number of moderate and / or severe HAE attacks.
- Time-normalized number of HAE attacks by severity (mild, moderate, severe).
- Percentage reduction in the time-normalized number of HAE attacks.

9.2.1 Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed using the Enrolled Analysis Set (see Section 5.2). The endpoint "time-normalized number of HAE attacks" will also be analyzed using the PP Analysis Set (see Section 5.4). This will also be applied to the supplementary analysis of secondary endpoints.

Subjects / caregivers will enter HAE symptoms into their electronic Diary and the start and end date and time, the interference of HAE symptom(s) with daily activities, and location(s) of the HAE symptom(s). Investigator-reported HAE attacks will be based upon review of subject diaries, relevant interval medical history, and physician judgment. The investigator may ask clarifying questions to assist in his / her assessment of whether an HAE attack occurred. If an attack occurred, the investigator would record the attack in the eCRF, the start / end date, the attack location(s), and the severity of the attack based on the most severe symptoms.

For all analyses considering HAE attacks, only the HAE attacks confirmed and reported by the investigator on the eCRF 'HAE Attacks' will be used.

HAE attacks with a start date and time after the first IP administration through the EoT Visit date (or last available visit or event date [whichever is later] if no EoT Visit date is available) will be counted for the Treatment Period and will be included in the analyses of efficacy. If the EoT Visit of a subject is delayed by more than the treatment time window relative to the

last IP administration, HAE attacks with a start date and time after first IP administration through the date and time of the last IP administration + 30 or 60 days for Q1M or Q2M regimen, respectively, will be counted for the Treatment Period. For subjects not treated, start date for counting the HAE attacks will be the Day 1 Visit date. HAE attacks without start time will be counted only if they start after Day 1 or the day after the date of first IP.

HAE attacks will be listed, including start date / time, end date / time, time between start of the attack and end of the most recent preceding attack or Day 1 Visit /first IP administration (if no preceding attack), anatomical locations, severity, most recent actual CSL312 dose and dosing date and time, potential trigger, duration in hours and days, period in which the HAE attack occurred and how many and which on-demand medications were taken per HAE attack.

The following derived endpoints based on HAE attacks will be presented together in a listing (overall, by 6-months' time window, and until Day 31 of the Treatment Period):

- Time-normalized number of HAE attacks (per month and per year).
- Time-normalized number of HAE attacks treated with on-demand treatment (per month and per year).
- Time-normalized number of moderate and / or severe HAE attacks (per month and per year).
- Time-normalized number of HAE attacks by severity - mild, moderate, severe (per month and per year).
- Length of the Treatment Period.
- Total number of HAE attacks.
- Time-normalized number of HAE attacks based on historical data.
- Reduction in attack rate (treatment period versus historical data).

9.2.1.1 Time-normalized Number of HAE Attacks

The time-normalized number of HAE attacks per subject will be calculated as defined in Section 9.3.

The time-normalized number of HAE attacks per month and per year will be summarized descriptively including median (of primary interest) and mean (of secondary interest) with corresponding two-sided 95% confidence intervals (CIs). The CIs for the mean will be based on the t-distribution while distribution-free CIs will be calculated for the median.

The time-normalized number of HAE attacks will also be calculated for the historical data collected at Screening (number of HAE attacks 6 months prior to Screening or the start of prophylactic treatment). The length of the period (denominator) will be set to 6 months.

Besides the time-normalized number of HAE attacks, the total number of HAE attacks (i.e., not time-normalized) will also be summarized.

9.2.1.2 Time-normalized Number of HAE Attacks Treated with On-demand Treatment

An HAE attack treated with on-demand treatment is identified by the question "On demand treatment taken?" being answered with "Yes" on the eCRF 'HAE Attacks'. The time-normalized number of HAE attacks treated with on-demand treatment will be calculated as defined in Section 9.3.

The monthly and yearly rates will be summarized descriptively.

This summary table will also include the number and percentage of subjects who took a specific medication at least once and the total number of times a specific on-demand medication was used across all subjects. For each on-demand medication, the number of uses of the on-demand medication per HAE attack will be summarized descriptively. ATC classification and PT will be included in the by-subject listing.

The analysis described above will be repeated including only moderate / severe HAE attacks as well as by attack severity (mild, moderate, severe).

9.2.1.3 Time-normalized Number of HAE Attacks by Attack Severity and for Moderate and/or Severe HAE Attacks

The analysis and derivation as described in Section 9.2.1.1 will be repeated including only moderate and/or severe HAE attacks as well as by attack severity (mild, moderate, severe).

9.2.1.4 Percentage Reduction in the Time-normalized Number of HAE Attacks

The percentage reduction in the time-normalized number of HAE attacks will be calculated for each subject as defined in Section 9.3.

The percentage reduction in the time-normalized number of HAE attacks will be summarized descriptively.

The number and percentage of responders and non-responders will be presented with 95% CIs. A subject is classified as a responder if the percentage reduction in the time-normalized number of HAE attacks under treatment compared to the historical data in the medical records is ≥ 50%. In addition, the number and percentage of subjects with percentage reductions of ≥ 70% and ≥ 90% will be presented with 95% CIs.

Furthermore, the number and percentage of subjects with a percentage reduction of 100%, i.e., who did not experience an HAE attack (attack-free) will be presented and summarized with 95% CIs.

The 95% CIs for percentages will be calculated based on Wilson's asymptotic confidence limits.

9.2.1.5 Supplementary Analysis of Secondary Endpoints

The endpoints listed in Section 9.2 will be calculated for the entire Treatment Period and by 6-months' time window.

Time-normalized number of HAE attacks, the time-normalized number of HAE attacks treated with on-demand treatment, time-normalized number of HAE attacks by severity (mild, moderate, severe), and time-normalized number of moderate/severe HAE attacks will also be assessed for a time window starting from date of first IP (or Day 1 Visit date if the subject did not receive IP, see Table 3) until Day 31 of the Treatment Period. This summary will be provided by dosing regimen and overall. The number and percentage of subjects not experiencing any attacks in the first month (i.e., 31 days) will also be displayed.

Subjects who completed the first month (Day 31 of the Treatment Period) will be included in the analysis for this window.

Subjects' profiles will be generated for each subject. The x-axis will show the HAE historical data and the Treatment Period. The different subject IDs will be plotted on the y-axis. For each subject, a horizontal bar will show the duration of his / her study participation; dots at the respective position of the x-axis will symbolize a mild (white dot), moderate (gray dot), and severe (black dot) HAE attack; an arrow above the bar at a certain position of the x-axis will show the time point when the subject took on-demand medication during the Treatment Period (for historical data prior to Screening information about on-demand medication will be used if available), and an asterisk will show the time of CSL312 administration. In addition, the subject's reason for study discontinuation (if applicable) will be given. Subjects'

profiles will be sorted by dosing regimen, showing subjects receiving 100 mg Q2M, followed by the profiles of subjects receiving 100 mg Q1M.

Time to Event Analysis

The following events will be analyzed:

- Time to first HAE attack after Day 1 Visit date (if no start time for the attack available or for subjects not treated) or after the date and time of first IP. Subjects without attacks will be censored at the EoT Visit date (or last available visit or event date if no EoT Visit date is available).
- Time from end of first HAE attack to start of second HAE attack (only for subjects experiencing at least one attack which ends within the Treatment Period). Subjects without a second attack will be censored at the EoT Visit date (or last available visit or event date if no EoT Visit date is available).
- Time from end of second to start of third HAE attack (only for subjects experiencing a second attack which ends within the Treatment Period). Subjects without a third attack will be censored at the EoT Visit date (or last available visit or event date if no EoT Visit date is available).

The following will be derived and analyzed for all subjects in the Enrolled Analysis Set:

- Maximum attack-free time.

The maximum attack-free time is defined as the maximum time a subject was attack-free between all subsequent HAE attacks the subject experienced. The maximum attack-free time for subjects without attacks is equal to the length of the subject's efficacy evaluation period. For the derivation see Section 9.3.

For derivation of the times-to-event see Section 7.2.2. Time-to-events will be derived within the Treatment/Efficacy Evaluation Period (see Table 2).

For each of the events above the following will be presented:

- The number and percentage of subjects who do not experience the event (not applicable for the maximum attack-free time).
- The median time, the 75% and 25% percentile times of subjects being event-free / having no second / having no third HAE attack, respectively. The median, 25%, and 75% percentile times are defined as the times for which the Kaplan-Meier estimates for the time-to-event functions equal 0.5, 0.75, and 0.25, respectively.
  If the time-to-event function is horizontal at 75%, 50% or 25%, the median or

percentiles will be calculated as the average of the two values between which the time-to-event function is horizontal.
- The minimum and maximum times to the event.

Kaplan-Meier curves with two-sided 95% CI will be plotted showing the percentage of subjects being event-free at certain times.

For time between first and second/time between second and third attack the percentages will be calculated using the number of subjects not having the second/third attack at that time as the numerator and the number of subjects having at least one/two event(s) as the denominator.

The corresponding life tables will also be presented.

A by-subject listing will be provided for
- Time to first attack (in days),
- Time between first and second attack and time between second and third attack, if applicable,
    - or Time until the EoT Visit (or last available visit or event date if no EoT Visit date is available) if no subsequent attack occurred.
- Maximum attack-free time (in days).

It will be indicated whether the observation is censored.

9.3 Efficacy – Derived Variables

This section defines how the secondary efficacy variables will be derived.

The length of the subject's Treatment Period will be calculated as (see Table 3):

EoT Visit date - Day 1 Visit or first IP date (if available) + 1

For subjects without EoT visit date, the last available visit or event date will be used (whichever is later).

To transform the daily rate to monthly or yearly rates, the daily rate will be multiplied by 30.4375 or 365.25, respectively.

To calculate the time-normalized number of HAE attacks for historical data use the entry on the eCRF 'HAE History' "Number of HAE attacks during the 6 months before Screening" or in the case of prophylactic HAE therapy within the 6 months before the Screening Visit "If

yes, Number of HAE attacks within 6 months before initiation of prophylactic therapy". The length of the period in the denominator will be 6 and 0.5 for the monthly and yearly rate, respectively.

The derivation of the different secondary efficacy variables are provided below.

Time-normalized number of HAE attacks per day:

$$\frac{\text{Number of HAE attacks}}{\text{Length of subject's Treatment Period (days)}}$$

Time-normalized number of HAE attacks treated with on-demand treatment per day:

$$\frac{\text{Number of HAE attacks treated with on-demand treatment during Treatment Period}}{\text{Length of subject's Treatment Period (days)}}$$

Percentage reduction in time-normalized number of HAE attack:

$$100 * \left(1 - \frac{\text{time-normalized number of HAE attacks per month during the Treatment Period}}{\text{time-normalized number of HAE attacks per month from historical data}}\right)$$

Maximum attack-free time:

First, the following will be calculated:

(1) For subjects with at least 1 HAE attack calculate the time to the first attack following Section 7.2.2.

(2) After the last HAE attack a subject experienced, the remaining time will be censored at the EoT Visit and calculated as EoT Visit date - end date of the last attack. For subjects without EoT visit date, the last available visit or event date will be used (whichever is later).

(3) The time between subsequent HAE attacks will be calculated as start date/time of the following HAE attack - end date/time of the preceding HAE attack.

Maximum attack-free time will be derived as follows:

Subjects without attacks: censored at the EoT Visit date and equal to the length of the Treatment Period.

Subjects with only 1 attack: the maximum of the time to the first attack (1) and the remaining time until EoT Visit (2). If the maximum is the remaining time until EoT maximum attack-free time will be considered censored.

Subjects with multiple attacks: the maximum attack-free time will be the maximum of the time to the first attack (1), the time(s) between subsequent attacks (3), and the remaining time (2). If the maximum is the remaining time until EoT maximum attack-free time will be considered censored.

9.4 Multiple Comparisons and Multiplicity

The study is single-arm open-label. Comparisons are not planned, and multiplicity is not applicable.

9.5 Missing Data and Imputation

Efficacy endpoints will be only missing for analysis if the subject discontinued the study within 30 days after the Day 1 Visit date. Missing data will not be imputed.

9.6 Treatment Compliance

The calculation of overall compliance will be based on the planned SC administrations of CSL312 with complete volume and the planned dose:

Treatment compliance (%) =
100 * (Number of injections with complete volume administered / Total planned number of injections).

The planned number of injections will be derived from the length of the subject's Treatment Period and the assigned dosing regimen. It will be calculated as:

For ongoing or discontinued subjects:
Q1M: Planned number of injections = floor[Duration of Treatment Period (days) / 30] + 1.
Q2M: Planned number of injections = floor[Duration of Treatment Period (days) / 30]/2 + 1.

For completed subjects:
Q1M: Planned number of injections = floor[Duration of Treatment Period (days) / 30].
Q2M: Planned number of injections = floor[Duration of Treatment Period (days) / 30]/2.

The number of planned injections will be rounded down to the next integer.

The following summaries will be provided for the Enrolled Analysis Set (see Section 5.2):

- Percentage overall compliance (descriptive statistics).
- Percentage overall compliance categorized by < 80%, 80%-120%, and > 120% (number and percentage of subjects in the categories).
- Number of injections not administered with reasons as per categories in the eCRF.
- Number of injections administered which deviate from the complete volume.
    - Reasons for not administering the planned volume with the categories in the eCRF.

A by-subject listing with the following information will be provided:

- Number of injections deviating from the planned volume.
- Planned and actual dosing regimen.
- Overall compliance.

10 Safety Analyses

Safety analyses will be based on the Safety Analysis Set (see Section 5.3).

10.1 Extent of Exposure

Exposure to the IP will be descriptively summarized by dosing regimen and overall:

- Duration of exposure (months and years) per subject.
- Number of SC administrations per subject.
- Total dose received (mg) per subject.

In addition, the following will be provided by dosing regimen and overall:

- Overall duration of exposure (total subject years).
- Overall number of SC administrations.

By-subject listings of individual subject data will include all variables presented in the summary tables and in addition details collected in the eCRF:

- Start and end date/time of the administration,
- Duration of the administration,
- Reason why an administration was not done
- Reason why the planned volume was not administered,
- Actual and planned volume and dose,
- Kit number,
- By whom the injection was administered,
- To which anatomical location the injection was administered.

10.2 Adverse Events

AEs will be coded using the MedDRA dictionary. There will be periodic updates of the MedDRA version. The latest licensed version will be used, and version updates will be implemented upon availability. AEs will be primarily classified by MedDRA PT. Analyses will be performed by SOC and PT. Aggregated incidences at SOC level and any TEAE will also be provided.

TEAEs are AEs that start on or after the date (and time if available) of the first administration of IP until the Follow-up Visit. TEAEs until the Follow-up Visit will be summarized. Subjects who continue with CSL312 or another prophylactic treatment after this study will not enter into the Follow-up Period and thus only TEAEs until the EoT are reported.

For the primary estimand, the TEAEs will be summarized until the EoT Visit (see Section 10.2.1).

All AEs regardless of whether they were treatment-emergent or not will be listed.

COVID-19-associated AEs will be included in TEAE tables identified by standard MedDRA coding.

Subjects with multiple occurrences of the same TEAE will be counted once in the total of those experiencing this PT. Similarly, a subject with 1 or more PT in a SOC will be counted once in the total of those experiencing PTs in that SOC. Percentages for subject incidence rates will be based on the Safety Analysis Set.

Injection site reactions (ISRs) will be summarized by an additional (artificial) "SOC" called "Injection Site Reactions". To identify PTs belonging to this (artificial) "SOC" of ISRs, CSL will be provided a list in Excel format of all PTs found in the database with verbatim. CSL will review this list and mark the corresponding PTs in a column of this Excel sheet. These identified PTs will be reported in the (artificial) "SOC" of ISR as well as in their original MedDRA SOC. For the overall "Any TEAE" entry at the beginning of the table, these ISRs will be reported once. ISRs will be presented as first "SOC" following the overall "Any TEAE" entry. The MedDRA SOCs and PTs will be presented in descending frequency of the overall category. Within the same frequency, SOCs and PTs will be ordered alphabetically.

Where AE start dates and/or times are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates and/or times or the AE end date and/or time indicate that the AE started before the first administration of IP (see Table 5).

Table 5 TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	Rule	
Regardless of any missing information for AE start: AE end date / time < IP start date / time		non-TEAE
Otherwise (i.e., if AE end date / time ≥ IP start date / time)		
- All		TEAE
- Day and Month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
- Day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non-TEAE
- Time	AE start date ≥ IP start date	TEAE
	AE start date < IP start date	non-TEAE

If AE start dates or end dates are missing or partially missing for an AE, no duration will be calculated. If for a TEAE the relationship to study treatment is missing the worst case will be assumed for summarizing analysis (i.e., the relationship to study treatment will be assumed to be "Related"). In case of missing study treatment relationship for non-treatment-emergent AEs, the relationship will be set to "Not related".

Temporally associated TEAEs are defined as AEs with an onset between the start of the injection and up to 24 hours after the end of the injection. In the case the time of the onset of the AE is missing, the AE is considered temporally associated, if the onset of the AE is between the day of the start of injection and the day of the end of injection + 1 day (inclusive). If the start date of the AE is (partially) missing the temporally association cannot be assessed.

Severe hypersensitivity including anaphylaxis is defined as AESI per study protocol . In addition to AESIs reported by Investigators per study protocol, events suggestive of any hypersensitivity including anaphylaxis will be identified for further review by:

- Standardised MedDRA Query "Hypersensitivity (SMQ)" (broad).
- Anaphylactic reaction (SMQ) (broad).
- Anaphylactic/anaphylactoid shock conditions (SMQ) (broad).

The broad scope includes narrow and broad search. The SMQ search does not account for severity (also non-severe cases will be included) while the AESI assessment by the investigator will do.

TEAE rates per subject year of exposure will be calculated as:

$$\text{TEAE rate per subject year} = \frac{\text{Number of TEAEs}}{\text{Subject Years of Exposure}}$$

where subject years of exposure will be the sum of the exposure duration in years for all subjects under this dosing regimen or overall. For the time exposed to a dosing regimen, each study day will be counted under the corresponding dosing regimen.

TEAE rates per injection will be calculated as:

$$\text{TEAE rates per injection} = \frac{\text{Number of TEAEs}}{\text{Number of Injections}}$$

where number of injections will be the sum of injections subjects received during the Safety Evaluation Period (see Table 3) under the dosing regimen the TEAE is assigned to.

10.2.1 Primary Safety Estimand

The primary safety interest is to assess whether TEAEs occurred at least once during SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE during treatment from the first IP administration at Day 1 Visit through the EoT Visit or the latest available visit or event (whichever is later) for subjects without EoT Visit while subjects are allowed to treat HAE attacks with on-demand medications.

The primary safety estimand, in line with the primary safety interest of the study, follows the treatment policy strategy and is described as follows:

- Treatment condition: Q1M or Q2M treatment with 100 mg CSL312.
- Population: The target patient population, defined by eligibility criteria and who received at least 1 dose of IP (Safety Analysis Set).
- Variable: TEAEs
- ICE: The occurrence of an ICE is ignorable. All observed values will be used, regardless of occurrence of any of the following ICEs (treatment-policy strategy) :
    - Administration of on-demand medication in addition to prophylactic treatment with CSL312.
    - Prohibited concomitant medications due or not due to COVID-19 or COVID-19 vaccination.
    - Treatment adherence or early treatment discontinuation due or not due to COVID-19.
- Population-level summary: TEAE rate per subject year.

10.2.2 Analysis of Primary Safety Endpoint

Following the estimand described in Section 10.2.1, the TEAEs for pediatric subjects with C1-INH HAE will be summarized by event rate per subject year using the Safety Analysis Set. All summary tables described will be presented by 100 mg Q2M, 100 mg Q1M, and overall.

In addition, TEAEs will be summarized by the number of subjects and percentage of subjects experiencing at least 1 TEAE, the number of events, as well as the event rate per injection.

For the presentation by 3-months' time windows, the TEAE will be allocated to the time window based on the TEAE start date.

An overview summary of TEAEs as well as a table by SOC and PT will be provided.

The overview summary of TEAEs will include the following:

- Any TEAE.
- TEAEs related to IP.
- TEAEs related to device issues.
- Treatment-emergent ISRs.
- Treatment-emergent ISRs related to IP.
- Treatment-emergent ISRs related to device issues.
- Temporally related TEAEs occurring within 24 hours after end of administration.
- TEAEs leading to study discontinuation.
- TEAEs leading to discontinuation of study treatment.
- TEAEs by severity and relationship to IP and to device issues.
- TEAEs by outcome.
- Treatment-emergent ISRs by severity and relationship to IP and to device issues.
- Treatment-emergent AESIs as reported by the investigator (severe hypersensitivity including anaphylaxis).
- TEAEs by SMQ search (hypersensitivity including anaphylaxis).
- Treatment-emergent AESIs and TEAEs by SMQ search (hypersensitivity including anaphylaxis) related to IP and to device issues.
- Any serious TEAEs.

To evaluate the COVID-19 impact on the primary endpoint, the overview summary of TEAEs and the summary table by SOC and PT will be repeated as a sensitivity analysis excluding all COVID-19 related TEAEs (selected by "COVID-19 (SMQ)" scope "narrow").

All AEs will be presented in a by-subject listing.

10.2.3 Analysis of Secondary Safety Endpoints

TEAEs

The following descriptive tables will be generated for TEAEs until the Follow-up Visit, including number and percentages of subjects, the number of events, and the TEAE rates per subject year of exposure and per injection:

- Overview table of TEAEs (same as described above, but until the Follow-up Visit).
- Overview table of serious TEAEs (same as described above, , but until the Follow-up Visit and restricted to serious TEAEs).
- TEAEs by SOC and PT (same as described above, but until the Follow-up Visit).
- TEAEs by SOC and PT by 3-months' time windows.
- TEAEs by SOC, PT, and severity.
- Related TEAEs by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT
- Treatment-emergent TEAEs related to clinically significant laboratory abnormalities by SOC and PT.
- Non-serious TEAEs by SOC and PT.
- Treatment-emergent AESIs and TEAEs by SMQ search (hypersensitivity including anaphylaxis) by SOC and PT.
- Related treatment-emergent AESIs and TEAEs by SMQ search (hypersensitivity including anaphylaxis) by SOC and PT.
- Serious TEAEs by SOC and PT.
- Related serious TEAEs by SOC and PT.

The following listings will be provided:

- TEAEs.
- Non-treatment-emergent AEs.
- SAEs.
- SAEs resulting in death.
- Related TEAEs.
- AEs leading to study withdrawal.
- AEs leading to permanent discontinuation of study treatment.
- AESIs and TEAEs by SMQ search (hypersensitivity including anaphylaxis).

Anti-CSL312 Antibodies

Number and percentages of subjects with total and neutralizing anti-CSL312 antibodies will be provided by study visit.

10.3 Clinical Laboratory Evaluations

Laboratory tests will be summarized descriptively in standard units by scheduled visit for each dosing regimen and overall. For continuous laboratory tests, descriptive statistics for the measured values and for change from Baseline will be presented. For definition of the Baseline assessment see Section 7.2.3. Categorical laboratory tests will be summarized by number and percentage of subjects in the respective categories (based on the Safety Analysis Set with non-missing values at each visit). Summary tables will be provided for hematology, biochemistry, and coagulation.

All laboratory test results (scheduled and unscheduled) will be listed. By-subject listings for hematology, biochemistry, coagulation, and immunogenicity will be provided. Comments to the laboratory test may be provided in a separate listing, if applicable and if the comment is too long to fit into the column width of the general listing.

A by-subject listing for laboratory abnormalities will be provided in the same format as the laboratory listings described above only including abnormal laboratory results.

The number and percentage of subjects with clinically significant laboratory findings related to a TEAE will be summarized by laboratory test. Those will be identified through the eCRF 'Clinical Significant Safety Lab Data.' Percentages will be based on the Safety Analysis Set with non-missing values at each visit.

10.4 Other Safety Measures

10.4.1 Vital Signs

Systolic and diastolic blood pressure, respiratory rate, pulse rate, and temperature including body weight and height will be collected as vital signs. BMI will be derived at the visits when height or weight are assessed. No change from Baseline will be calculated for weight.

Vital signs will be presented in standard units and in alphabetical order. Descriptive statistics for vital signs at each scheduled visits and change from Baseline (see Section 7.2.4) will be provided.

A by-subject listing for vital signs results and change from Baseline for each visit (scheduled and unscheduled) with visit date and time will be provided.

10.4.2 Physical Examination

Date and time of performed physical examinations will be listed only.

11 Pharmacokinetic Analyses

The PK analysis will be performed using the PK Analysis Set. PK parameters after SC administration of CSL312 at steady-state (C_{max}, C_{trough}, and T_{max}) are one of the two primary endpoints in this study.

All non-compartmental analyses are to be performed according to CSL guideline for conducting non-compartmental pharmacokinetic analysis and will be performed by CSL Behring Clinical Pharmacology and Pharmacometrics (CPP) or their designate.

The External Service Provider (ESP) for Statistical Programming and Biostatistics will receive SDTM data including PC and PP domain from CSL. The PC and PP process will be according to CSL guidelines.

11.1 Drug Concentration Measures

Handling of PK concentration data and imputation of below limit of quantification (BLQ) values for noncompartmental analyses will be performed according to the CSL guideline for conducting non-compartmental pharmacokinetic analysis. Plasma concentrations of CSL312 will be summarized by nominal time points and dosing regimen (100 mg Q2M and 100 mg Q1M). Plasma concentrations will be summarized with descriptive statistics: number of observations, i.e., values > lower limit of quantification (LLOQ) plus values below limit of quantification (BLQ), number and percentage of BLQ values, with percentage BLQ values being calculated as 100 * number of values BLQ / number of observations, mean, SD, CV%, median, minimum, maximum, Q1 and Q3, geometric mean and its respective 90% CI, and geometric CV%.

The geometric statistics will be using (natural) log-transformation of the plasma concentration data. The CV% will be expressed as a percentage. It will be calculated as 100 * sqrt (exp (SD_{log}^2) - 1) with SD_{log} being the SD of the log-transformed data. The geometric mean and its two-sided 90% CI will be calculated as the arithmetic mean and the lower and upper limits of the two-sided 90% Wald CI of the log-transformed data, and subsequently back-transforming the mean and the lower and upper confidence limits.

For summary statistics, calculation of mean concentrations at any individual time points are performed if at least 50% of the individual values are available with measurement values > LLOQ (i.e., are quantifiable); else reports as NC.

The imputation rules below will be used for summary statistics of CSL312 plasma concentrations.

- The sampling time of pre-dose samples relative to start of the dose will be treated as 0.
- Concentration values below LLOQ in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as 0.
- Post-dose BLQ concentrations flanked by quantifiable concentrations will be set to missing.
- If 2 or more BLQ concentrations occur in succession, the profile will be considered to have terminated the quantifiable concentration prior to the 2 consecutive BLQs. All subsequent values will be treated as missing.
- Post-dose BLQ concentrations after the last quantifiable point will be set to missing for summary statistics of plasma concentrations.
- Mean or median values of 0 will be included in summary tables.

The LLOQ for CSL312 will be documented in the PK assay validation report to be provided prior to DBL.

Mean (± SD) CSL312 concentrations versus nominal sampling time point will be plotted on linear and semi-logarithmic scales by dosing regimen.

Individual concentration-time plots will be presented by actual sampling time point on linear and semi-logarithmic scale.

CSL312 plasma concentrations will be listed by subject, including actual sampling date and time, nominal time point and actual time from end of previous injection. Concentrations that are BLQ will be reported as "<LLOQ" in the by-subject listings.

Any plasma concentration data excluded from the derivation of PK parameters will be flagged. These data will be included in the relevant data listings, with a footnote to indicate that these values have been excluded in the PK analysis.

Time deviations from scheduled sampling time points and its impact on the PK parameter derivation will be discussed during the PARM. PK parameter derivation will be based on actual sampling time.

11.2 Deriving and Summarizing Pharmacokinetic Parameters

PK parameters will be derived using non-compartmental PK analyses and will be summarized descriptively by dosing regimen (i.e., 100 mg Q2M, 100 mg Q1M).

The following descriptive statistics will be presented for all PK parameters, except for T_{max}: number of observations (for definition see Section 11.1), mean, SD, CV%, median, minimum, and maximum, geometric mean, geometric CV% (for definition see Section 11.1). For T_{max}, number of observations, median, minimum, and maximum will be provided.

By-subject listings will be provided for the PK parameters.

12 Pharmacodynamic and Biomarkers Analyses

All analyses in this section will be based on the PD Analysis Set.

12.1 Pharmacodynamic Analyses

FXIIa-mediated kallikrein activity and FXII concentrations will be summarized by nominal time point and dosing regimen (i.e., 100 mg Q2M, 100 mg Q1M). The following descriptive statistics will be provided: number of observations (values ≥ LLOQ plus BLQ values), number and percentage of BLQ values, mean, SD, CV%, median, minimum, maximum, and Q1 and Q3, geometric mean and its respective 90% CI, and geometric CV% (for definition see Section 11.1).

Mean (± SD) concentration/activity-time profiles will be plotted using nominal (planned) time. Individual concentration/activity-time plots will be presented by actual sampling time point.

By-subject listings will be provided for FXIIa-mediated kallikrein activity and FXII concentration including actual sampling date and time, nominal time point and actual time from end of previous injection.

For FXIIa-mediated kallikrein activity, % of Baseline values will be provided in the listings and summaries. For calculation of % of Baseline values see Section 7.2.4.

BLQ results will not be considered for summaries and will only be listed.