STATISTICAL ANALYSIS PLAN (SAP)

An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema

Study Number:	CSL312_3002
Study Product:	CSL312 (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:	2.0 – FINAL
Version Date:	02 October 2025
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) ethical principles that have their origin in the Declaration of Helsinki, and all applicable national and local regulations.

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1 Modification History

Version	Effective Date	Author of Modification	Summary of Change
1.0	25 Jun 2021		N/A – First Version
2.0	02 Oct 2025	Erik Peter	• Updates due to Protocol Amendment 1 to consider transition to autoinjector device and dose modifications no longer being permitted. • Inclusion of additional subgroups and analysis windows. • Correction of the description of the Treatment Satisfaction for Medication Questionnaire version II derivations. • Consolidation of all information regarding adverse events in Section 11. • Formatting and abbreviation edits. • New analysis for number and proportion of attack-free days. • Removal of most Corona Virus Disease 2019 related analysis. • Removal of Mixed Model and Sidak correction of confidence intervals for analysis of quality of life endpoints.

2 List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	AE of Special Interest
AI	Autoinjector
ATC	Anatomical Therapeutic Chemical
ATS	All Treated Subjects
AUC	Area under the Curve
$AUC_{0\text{-}30days}$	Area under the Concentration-time curve from 0-30 days
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
C_{max}	Maximum Concentration
COVID-19	Corona Virus Disease 2019
CSR	Clinical Study Report
DBL	Database Lock
eCOA	electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FXII(a)	(Activated) Factor XII
HAE	Hereditary Angioedema
ICH	International Conference on Harmonisation
ID	Identifier
IDMC	Independent Data Monitoring Committee
IGART	Investigator's Global Assessment of Response to Therapy
ISR	Injection site reaction
IRT	Interactive Response Technology
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
nC1-INH	Normal C1-esterase inhibitor
NSD	Needle safety device
PARM	Planned Analysis Review Meeting
PD	Pharmacodynamics

Abbreviation	Definition
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard deviation
SDTM	Study Data Tabulation Model
SGART	Subject's Global Assessment of Response to Therapy
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Tables, figures, listings
Tmax	Time to Maximum Concentration
TSQM II	Treatment Satisfaction for Medication Questionnaire version II
WHODrug Global	World Health Organization Drug Global
WPAI:GH	Work Productivity and Activity Impairment: General Health

Glossary of Terms

Include important definitions which are referred to multiple times in the SAP and providing definitions in the glossary facilitate understanding.

Term	Definition
CSL312-naïve subjects	Subjects who did not previously participate in CSL312_2001 or CSL312_3001.
C1-INH HAE	Hereditary angioedema type 1 (quantitative decrease in C1-esterase inhibitor plasma concentrations) and hereditary angioedema type 2 (dysfunctional C1-esterase inhibitor present in normal or high plasma concentrations).
nC1-INH	Hereditary angioedema with normal C1-INH, formerly known as type 3.
Treatment-naïve subjects	Subjects who did not receive any dose of CSL312 before this study. This includes CSL312-naïve subjects and subjects who received placebo in previous studies.

3 Purpose

This Statistical Analysis Plan (SAP) provides a detailed and complete description of the planned statistical analyses of the study CSL312_3002 [An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema] 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 1, dated 27 Oct 2022.
- electronic Case Report Form (eCRF), V6.0, dated 18 Feb 2025.

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 analyses in this SAP will be detailed in the CSR.

4 Study Design

This is a multicenter, open-label, phase 3b study designed to investigate long-term safety and efficacy of CSL312 when administered once monthly for at least 12 months. Subjects eligible to participate in this study may be:

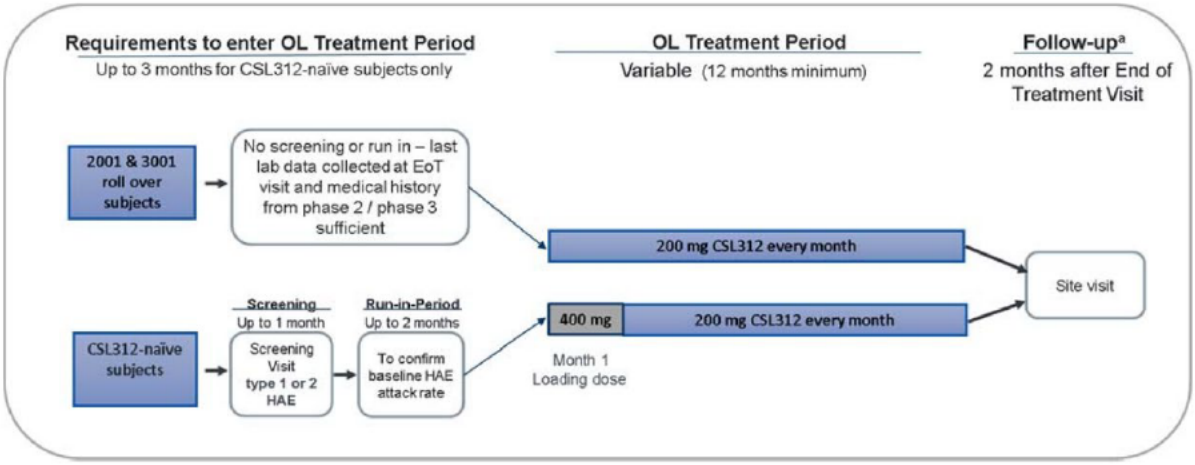
- Subjects who participated in the phase 3 double-blind study CSL312_3001,
- Subjects who participated in study CSL312_2001,
- CSL312-naïve subjects with C1-INH HAE Type 1 / 2.

The study consists of 4 periods: Screening, Run-in (only for CSL312-naïve subjects), Open label Treatment Period, and a Follow-up Period.

For subjects naïve to CSL312, there will be a Screening Period of up to 1 month followed by a Run-In Period, which may last at least 1 month and up to 2 months. CSL312-naïve subjects who meet all eligibility criteria during the Run-In Period will then enter the Treatment Period. Subjects who complete Studies CSL312_3001 and CSL312_2001 according to their respective protocols will be offered the opportunity to continue treatment by entering the CSL312_3002 Open-label Treatment Period. Subjects who reach the end of treatment or terminate the study early will have a follow-up phone call 2 months after the End of Treatment (EOT) Visit. Subjects may switch to a HAE prophylaxis medication during the Follow-up Period.

The study schematic is shown in Figure 1.

Figure 1 CSL312_3002 Study Schematic



EoT = end of treatment; HAE = hereditary angioedema; OL = open-label

[a] Follow-up Visit may be conducted via telephone instead of at the study site. This visit is only applicable for subjects ending study participation following the original protocol (for subjects who consent into the Protocol Amendment 1, refer to Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1).

4.1 Objectives and Endpoints

The primary objective of the study is to evaluate the long-term safety of subcutaneous (SC) administration of CSL312 in the prophylactic treatment of subjects with C1-INH HAE.

Table 1 Primary Objective and Endpoint

Objectives	Endpoints	Summary Measure(s)
Primary	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.

The secondary objectives of this study are to evaluate:

1. Long-term efficacy, including patient-reported assessment of response to therapy,
2. Long-term safety.

Table 2 Secondary Objectives and Endpoints

Objectives	Endpoints	Summary Measure(s)
1.	Time-normalized number of HAE attacks	The time-normalized number (per month and year) of HAE attacks for the run-in and Treatment period.
1.	The reduction in the attack rate during the Treatment Period compared to the Run-in Period	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 Run-in Period.
1.	The time-normalized number of HAE attacks requiring on-demand treatment	The time-normalized number (per month and year) of HAE attacks requiring on-demand treatment in subjects on treatment.
1.	The time-normalized number of moderate and / or severe HAE attacks	The time-normalized number (per month and year) of moderate and / or severe HAE attacks in subjects on treatment.
1.	Subject's Global Assessment of Response to Therapy (SGART)	Number and percentage of subjects rating their response to therapy as good or excellent.

Objectives	Endpoints	Summary Measure(s)
2.	• Serious Adverse Events (SAEs) • Deaths • Related TEAEs • TEAEs leading to study discontinuation • TEAEs by severity • Anti-CSL312 antibodies • Laboratory findings reported as an adverse event (AE) • Adverse Events of Special Interest (AESIs), ie, thromboembolic events, abnormal bleeding events, severe hypersensitivity, including anaphylaxis events • TEAE (for nC1-INH subjects only)	The number and percentage of subjects experiencing the specified safety events on treatment with CSL312.

The exploratory objectives of the study are to evaluate the efficacy and quality of life (QoL) associated with the use of CSL312 in subjects with HAE. Pharmacokinetics (PK) and pharmacodynamics (PD) will also be evaluated.

The exploratory efficacy endpoints are the time to first attack after Day 1 administration and after Day 14 for CSL312-naïve subjects, and the maximum attack-free time for all subjects.

Exploratory QoL endpoints include the following:

- Subject reported outcome measures: Angioedema Quality of Life Questionnaire (AE-QoL), Work Productivity and Activity Impairment: General Health (WPAI:GH) and Treatment Satisfaction for Medication Questionnaire version II (TSQM II),
- Investigator's Global Assessment of Response to Therapy (IGART).

The exploratory PK and PD endpoints are:

- CSL312 concentrations at scheduled time points,
- Activated Factor XII (FXIIa)-mediated kallikrein activity at scheduled time points,

- CSL312 PK parameters (maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the concentration-time curve from 0-30 days [$AUC_{0\text{-}30days}$]).

4.1.1 Primary Study Hypotheses

There are no formal hypotheses for this study. Instead, this study is designed for the assessment of long-term safety and efficacy of CSL312 (200 mg) in HAE subjects.

4.2 Study Treatments

There will only be a single treatment arm in this study with the study treatment being CSL312.

All subjects who meet the criteria to enter the study will be assigned to 1 dose of CSL312, 200 mg, to be given SC once monthly for a minimum of 12 doses. For CSL312-naïve subjects, a loading dose of 400 mg (two 200 mg doses) will be administered SC on the first month, then 200 mg once per month in subsequent months. Per original protocol, the dose could have been increased in 200 mg increments for safety reasons and the maximum allowed dose for C1-INH subject was 400 mg per month. The maximum allowed dose for nC1-INH subjects was 600 mg per month. Per Amendment 1, no dosing modifications will be permitted.
No dosing modifications occurred prior to Amendment 1.

All subjects will be trained in CSL312 self-administration at Baseline (Day 1 of the Treatment Period). Subjects who participated in Study CSL312_3001 and subjects naïve to CSL312 will also be trained in CSL312 self-administration at the Month 1, 2, and 3 visits. Starting at Month 4, these subjects will self-administer monthly at home. Subjects who participated in Study CSL312_2001 will have the first dose administered at the site and will self-administer CSL312 at home thereafter. Subjects will complete a medication dosing electronic diary (eDiary) for all doses administered, including doses administered at the site.

Per Amendment 1, subjects or caregivers will SC administer CSL312 200 mg autoinjector (AI) instead of CSL312 200 mg needle safety device (NSD). The first administration with CSL312 200 mg AI will be on site, and training will be provided for subjects and caregivers. Additional CSL312 200 mg AI administration training at subsequent scheduled onsite visits may be provided if it is requested. Subsequent administrations with CSL312 200 mg AI will occur at home (either self-administered or with the help of a caregiver).

The dose and dosing regimen will continue to be 200 mg once monthly. Subjects who decline switching to CSL312 200 mg AI and who have participated in the study for at least

12 months will receive 1 more dose of CSL312 200 mg NSD at the time of the scheduled site visit and subsequently proceed with the EOT Visit 1 month later, as well as a Follow-up Visit 2 months after the EOT Visit, as per the original protocol.

4.3 Randomization Procedures and Blinding

Not applicable, this is an open-label study with a single treatment arm.

4.4 Determination of the Sample Size

Approximately 150 subjects (including 8 Japanese subjects) are planned to be enrolled into the study and a minimum of 100 subjects are planned to receive treatment for a minimum of 12 months.

This is a single arm study without a control arm. The sample size for this single arm, open-label study is not based on a formal statistical sample size calculation but on the guideline E1A issued by the International Conference on Harmonisation, March 1995. The sample size of 100 subjects allows observation of ≥ 1 AE with a probability of 3% at 95% confidence.

4.5 Planned Interim Analyses

Two interim analyses are planned for this study.

4.5.1 Interim Analyses Other Than Sample Size Re-estimation

Interim analyses will be conducted in order to support regulatory activities. The results of the interim analyses are not intended to be used to stop, adapt the study, or adjust the sample size.

As this study is an open-label, single arm study no blinding needs to be protected. The same CSL and Parexel staff who will be involved in the final analysis, will also execute the interim analyses.

The sample size is not based on a formal statistical sample size calculation but on the guideline E1A and therefore no overall Type I or II error rates need to be controlled.

An interim analysis is planned to be conducted when approximately 100 subjects have 12 months exposure of CSL312 in Study CSL312_3002 alone or across all studies, ie, CSL312_2001, CSL312_3001 and CSL312_3002, dependent on subjects' enrollment in Study CSL312_3002.

The analyses performed and the table, listing, figure outputs generated for the interim analyses will follow the final SAP and consider all data up to the defined data cut-off.

In addition, further interim analyses will be conducted on an as-needed basis in order to support regulatory activities.

4.5.2 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 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. CSL 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.

5 Changes from the Protocol Planned Analyses

This version of the SAP includes several changes that reflect Amendment 1 of the Clinical Study Protocol. This section only describes changes to the analyses that were not already described in the protocol amendment.

The scope of analysis related to the Corona Virus Disease 2019 (COVID-19) pandemic has been reduced to items directly related to the primary endpoint.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened Analysis Set comprises all subjects who provide written informed consent.

6.2 All Treated Subjects Analysis Set

The All Treated Subjects (ATS) Analysis Set comprises all subjects in the Screened Analysis Set who were assigned to treatment. The ATS Analysis Set will be analyzed using the treatment to which the subject was assigned, regardless of the treatment actually received.

Technical Note: inclusion in the ATS will be determined based on whether the subject is marked as eligible on the Subject Eligibility form.

6.3 Safety Analysis Set

The Safety Analysis Set comprises all subjects in the ATS Analysis Set who receive at least 1 dose of investigational product (IP) and will be analyzed using the actual treatment received. The actual treatment is planned to be CSL312 for all subjects.

Technical Note: The handling of unplanned dosing deviations for individual subjects will be discussed and decided at the Planned Analyses Review Meeting (PARM). Unless stated otherwise below, the treatment will be considered the same whether administered with NSD or AI.

The loading dose for CSL312-naïve subjects will be shown as part of the 200 mg dose.

6.4 Per Protocol Analysis Set

The Per-protocol (PP) Analysis Set comprises all subjects in the ATS Analysis Set who receive at least 1 dose of IP and who comply with the protocol. Decisions regarding exclusion from the PP Analysis Set will be made and documented before DBL.

Technical Note: unless stated otherwise below, the treatment will be considered the same whether administered with NSD or AI.

6.5 Pharmacokinetic Analysis Set

The PK Analysis Set comprises all subjects in the Safety Analysis Set who receive an injection of CSL312 with at least 1 measurable concentration of CSL312.

6.6 Pharmacodynamic Analysis Set

The PD Analysis Set comprises all subjects in the Safety Analysis Set for whom at least 1 PD measurement was obtained.

7 General Considerations

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, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), 95% confidence interval (CI), minimum, and maximum. Other descriptive statistics (eg, standard error, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

All listings will contain the subject identifier (ID). Listings will generally be sorted first by site and within site by subject ID.

The main listing of TEAEs (see Section 11.4) and the listing of individual HAE attacks (see Section 10.2.1) will include the most recent CSL312 dose (level, device [NSD or AI] and date).

7.1 Treatment Descriptors

For efficacy, PK and PD analyses (see Section 10) all subjects regardless of used administration device (NSD or AI) will be displayed under the 200mg CSL312 dose. Per the original protocol it was planned that for safety, PK and PD analyses (see Sections 11, 12 and 13 respectively) subjects would be displayed under their actual dose, which could have been 200 mg, 400 mg or 600 mg CSL312.

Per Amendment 1 subjects will still be shown under their actual dose, but dosing modifications will not be permitted, and all subjects receive 200 mg CSL312. As no dosing modifications occurred before Protocol Amendment 1, all subjects will be shown under the actual dose level of 200 mg CSL312. Columns for 400 mg and 600 mg CSL312 will not be required. If there should be unplanned dosing different from the planned 200 mg CSL312, it will be discussed and documented during the PARM how this will be handled in the analysis.

For AE tables, treatment may be further differentiated by administration device in use when the AE started:

- 200mg CSL312 AI,
- 200mg CSL312 NSD,
- 200mg CSL312 Overall.

8 Data Handling Conventions

8.1 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 by the use of 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 the TEAEs for C1-INH HAE subjects, and a result of zero TEAEs is considered a valid outcome, not missing data. The monitoring of reported AEs is performed throughout the study. If inconsistencies are detected, queries will be generated. Even if date or time of an AE will be completely or partially missing, it will be considered

treatment-emergent following the worst-case principle, unless the partial date clearly indicates that the AE started before the first administration of study treatment.

The details of handling missing data are presented in the corresponding sections of this SAP for respective analyses (eg, primary, and secondary safety analyses).

8.2 General Derived Variables

8.2.1 Reference Dates and Study Days

Reference dates are used to assign study periods relative to treatment (Section 8.4). The main reference date for safety and efficacy is the treatment start date, which will be used to calculate study day for those 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, then the study day will be calculated as (date of interest – reference date). There will be no study day zero.

For PK, the reference date is the treatment start date.

For the additional PK assessments performed for adolescents and the subset of CSL312-naïve subjects, the reference date/time is the start of administration of the Day 1 Visit dose for the subset of CSL312 naïve subjects and the Month 3 dose for adolescents. The respective study day relative to the reference date will be calculated for figures as (date of interest - reference date) if the date of interest occurs on or after the reference date.

The reference date/time for treatment while on AI will be derived based on the dosing data and the Autoinjector confirmation page of the eCRF, as the first recorded dose date/time with date on or after the date on the Autoinjector confirmation page.

8.2.2 Durations and Time to Event Data

Durations (eg, the duration of an AE) are calculated in days as:

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

Thus, there will be no duration of 0. If an AE has missing or partially missing start or end date, no duration will be calculated.

For elapsed time (eg, the time to event), use:

- (event date – reference date) or
- 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, divide the number of days by 7; to report in months, divide the number of days by 30.4375; to report in years, divide the number of days by 365.25. These algorithms return decimal numbers and ignore the actual numbers 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.

8.2.3 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to first study drug administration in this study. Determination of the baseline value considers unscheduled visits during the Run-in and Screening Periods.

If the measurement of a variable is not made on a given subject prior to first study drug administration, the baseline value for that subject will be set to missing for that variable.

8.2.4 Change from Baseline

Change from baseline is calculated as:

- visit value at respective visit – baseline value.

Percentage change from baseline is calculated as:

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

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline will be missing.

8.2.5 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 summaries but may

contribute to the End of Study (EOS) value, or best/worst case value (eg, shift tables) and will appear in listings.

If multiple laboratory samples for the same visit occur, it will be distinguished why this is the case. If an assessment was repeated due to technical problems the results from the valid measurement for this visit will be used in the analysis. If the measurement was repeated for safety reasons (ie, follow-up of abnormal lab values) or the reason for the repeated measurement cannot be ascertained, the initial measurement will be used.

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

8.2.6 Actual and Planned Treatment

Both planned vial numbers integrated from the Interactive Response Technology (IRT) and the actual administered vial numbers will be collected via eCRF. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment.

The planned treatment for all subjects is 200 mg. Efficacy outputs will be displayed by planned treatment of 200 mg. For details on the derivation of efficacy variables see Section 10.2.1.

The 400 mg loading dose for CSL312 naïve subjects is considered a single injection and a regular part of the planned 200 mg treatment regimen. AEs where the most recent dose was the loading dose will be flagged in listings of AEs.

In case of unexpected deviations from planned treatment including undefined dose modifications, overdoses and other deviations, an evaluation of that case and a final decision under what actual dose the subject should be presented for analysis will be done before DBL in the PARM.

8.3 Pre-defined Subgroups

The following subgroups are defined for the efficacy, safety, and/or PK/PD analyses. An overview table of which analyses are planned for specific subgroups is provided in Table 5 (see Section 17).

8.3.1 CSL312-naïve and Non-CSL312-naïve Subpopulations

The following two subpopulations will be defined:

- CSL312-naïve subjects: subjects who were newly screened and enrolled for CSL312, without having taken part in a previous CSL312 study.
- Non-CSL312-naïve subjects: roll-over subjects from CSL312_2001 or CSL312_3001 who were part of a previous CSL 312 study. Subjects are included in this subpopulation regardless of which treatment they received in the previous study.

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

8.3.2 Treatment-naïve and Non-treatment-naïve Subpopulations

The following two subpopulations will be defined:

- Treatment-naïve: Subjects who did not receive CSL312 before the start of this study, including CSL312-naïve subjects and rollover subjects who received only placebo in the CSL312_3001 study. There are no placebo subjects from CSL312_2001, so no subject rolling over from that study will be included in this subpopulation.
- Non-treatment-naïve: Rollover subjects who received CSL312 previously (ie, non-placebo subjects from CSL312_3001 and subjects from CSL312_2001).

In specific tables, the treatment-naïve subjects may be further differentiated into subjects with loading dose (newly enrolled for CSL312_3002) or without loading dose (rollover subjects previously receiving placebo).

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

The main tables for QoL questionnaires WPAI:GH, TSQM II and AE-QoL will be presented stratified by treatment-naïve and non-treatment-naïve subjects (see Sections 10.3.2.1 and 12 for further details). The time-to-event analysis (see Section 10.3.1) will be performed only for treatment-naïve subjects, with a further break-down of whether they received a loading dose. For these endpoints, this is considered the main analysis, not an additional subgroup analysis.

8.3.3 Previous Study and Treatment

The following three subpopulations will be defined:

- Roll-over subjects from CSL312_3001 who previously received Placebo.
- Roll-over subjects from CSL312_3001 who previously received CSL312.
- Roll-over subjects from CSL312_2001 who previously received CSL312.

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

8.3.4 Japanese Subjects

Subjects will be counted as Japanese subjects if the respective site is in Japan and the race is entered as Asian in the eCRF. For the corresponding subgroup analyses, the following columns/groups will be presented:

- Japanese subjects.
- Non-Japanese subjects.
- Global study population (all subjects).

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

8.3.5 Chinese and Asian Subjects

Asian subjects are all subjects with race "Asian" in the eCRF regardless where the site is located. Non-Asian subjects are all subject with race other than "Asian" in the eCRF. Asian subjects will be counted as Chinese subjects if the respective site is in Hong Kong or Taiwan. Chinese subjects will therefore be a subset of Asian subjects.

For the corresponding subgroup analyses, the following columns/groups will be presented:

- Asian subjects.
- Non-Asian subjects.
- Chinese Subjects.

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

8.3.6 Adolescents

Adolescents are defined in this study as subjects with an age at date of informed consent (as entered into the eCRF on the Demographics page, information coming to the eCRF from IRT) ≤17 years.

For the corresponding subgroup analyses, the following columns/groups will be presented:

- Adults (> 17 years of age).
- Adolescents.

The subgroup analyses that will be conducted for those subpopulations are presented in Table 5 (see Section 17).

Adolescents have additional PK/PD assessments at 3 days, 7 days, 14 days, 21 days, and 30 days after Visit Month 3. For details of the corresponding analyses, please see Section 12 and Section 13.

8.3.7 Pharmacokinetic Subgroup of Adult CSL312-naïve Subjects

There is a PK subgroup in a sub-set of adult CSL312-naïve subjects with additional PK/PD assessments to further characterize the PK of CSL312 following the SC loading dose. A target number of 12 CSL312-naïve adult subjects will be recruited from a subset of sites to be included in the subgroup. Additional analysis to be performed for this subgroup is described in Section 12 and Section 13.

8.4 Study Periods Relative to Treatment

AEs, HAE attacks, laboratory data, vital signs and other measurements will be assigned to the study time periods defined below.

Table 3 Definitions of Study Periods Relative to Treatment

Period	Start Date	End Date
Screening Period	Date of Informed Consent	Run-in Period Start Date
Run-in Period	Run-in Period Start Date	Day 1 Visit date of the Treatment Period or Date of Run-in Non-completion [whichever is first]
Treatment/Efficacy evaluation period	Date of Day 1 Visit of Treatment Period	Date of EOT Visit or EOS date [whichever is first]
Treatment/Efficacy before transition to AI evaluation period	Date of Day 1 Visit of Treatment Period	Date of first dose with AI – 1 Day (see Section 8.2.1)
Treatment/Efficacy after transition to AI evaluation period	Date of first dose with AI (see Section 8.2.1)	Date of EOT Visit or EOS date [whichever is first]
Follow-up	Date of EOT Visit	Date of Final/ Follow-up Visit
Safety evaluation period	Date and start time of First CSL312 Administration as entered in the eDiary	Date of Final/ Follow-up Visit
Safety Evaluation before transition to AI evaluation period	Date and start time of First CSL312 Administration as entered in the eDiary	Date of first dose with AI – 1 Day (see Section 8.2.1)
Safety Evaluation after transition to AI evaluation period	Date of first dose with AI (see Section 8.2.1)	Date of Final/ Follow-up Visit

The EOS date is the date entered in the Conclusion of Subject Participation eCRF page and should generally be identical to the date of the Follow-up Visit.

The handling of any unplanned dose changes or device changes will be discussed in the PARM. The safety evaluation period consists of the Treatment/Efficacy evaluation period plus the Follow-up Period.

Screening and Run-in periods will not be performed for roll-over subjects, instead relevant endpoint data (such as HAE attacks during the Run-in period) will be used from the CSL312_2001 and CSL312_3001 studies.

The duration of the Efficacy evaluation and the Safety evaluation period in days will be calculated as:
End Date – Start Date + 1 Day.

Screening, Run-in and Follow-up periods in days will be calculated as:

End Date – Start Date.

For CSL312-naïve subjects to assign events starting on Study Day 1 to the Run-in or Treatment/Efficacy evaluation period the start time of the event will be compared to the time of the first dose to determine if the event took place prior to the first dose (leading to assigning the event to Run-in) or after the first dose (leading to assigning the event to the Treatment/Efficacy or Safety evaluation period).

In the case that a non-CSL312-naïve (rollover) subject has an event recorded in this study that takes place prior to first treatment in this study, it will not be assigned to a period but still displayed in listings.

9 Study Population

Unless otherwise stated, all tables and listings in this section will be based on the Screened Analysis Set.

9.1 Subject Disposition

A summary of subject disposition will be provided by CSL312 200 mg AI, CSL312 200 mg NSD, and overall, for the Screened Analysis Set. This summary table will include the number and percentage for the following:

- Subjects who provided informed consent,
- Subjects rolling over from studies CSL312_2001 and CSL312_3001,
- CSL312-naïve subjects screened,
- Screen failed subjects with reason for screening failure,
- Subjects who entered Run-in Period,

- Subjects discontinued during Run-in Period with reason for discontinuation (percentage based on number of discontinued subjects),
- Subjects not assigned to study treatment,
- Subjects assigned to study treatment,
- Subjects entered the Treatment Period,
- Subjects treated using the respective device (NSD or AI)
- Subjects who discontinued the study while using the respective device (NSD or AI) with reason for discontinuation (percentages based on number of discontinued subjects),
- Subjects who prematurely discontinued the study treatment while using the respective device (NSD or AI) with reason for discontinuation (percentages based on number of discontinued subjects),
- Subjects who completed the respective treatment while using the respective device (NSD or AI),
- Subjects who completed the study,
- Subjects in each of the analysis sets defined in Section 6,
- Subjects in each of the subgroups defined in Section 8.3.

Discontinuations due to COVID-19 will be included as a specific reason for discontinuation. Reasons for study withdrawal and study treatment discontinuation will be presented in the order they are displayed in the eCRF.

The following listings will be provided:

- Subjects included in analysis sets and reasons for exclusion from analysis sets.
- Subject discontinuations.
- Disposition (date of informed consent, date of eligibility for Run-in, date of entering treatment period, date of first and last study drug administration, whether the subject participated for at least one month in the treatment period. EoT date, EOS date, whether subject transitioned to AI and date of transition, reason for treatment discontinuation and/or study discontinuation).

9.2 Protocol Deviations

All identified protocol deviations throughout the study will be listed prior to DBL and will be classified into minor/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.

The protocol deviations' classification into minor and major will be reassessed under statistical considerations. During the PARM, the classification and the subject's assignment to

the analysis sets will be discussed in detail. The Planned Analysis Review report will include these decisions and classifications and will be approved before each data-cut for interim analyses and prior to DBL for final analysis.

Possible major protocol deviations especially include the following but are not limited to:

Potential Major Protocol Deviations	**Potential Exclusion From Analysis Set**
Subject did not provide informed consent (informed consent date missing)	Screening, Safety, ATS, PP, PK, PD
Subject assigned to treatment but not treated with study treatment	Safety, PP, PK, PD
Subject assigned to treatment and treated but does not have at least one measurable PK concentration	PK
Subject assigned to treatment and treated but does not have at least one PD measurement	PD
Subject assigned to treatment and treated but violated inclusion or exclusion criteria	PP, potentially others to be discussed during the PARM
Subject assigned to treatment and treated but treatment compliance outside 80-120%	PP, potentially also PK, PD
Subject assigned to treatment and treated but received prohibited concomitant medication	PP, potentially also PK, PD

Presumably other protocol deviations will be classified as major and lead to the exclusion of subjects or data from analysis sets.

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 table, figure, and listing (TFL) 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. Subjects with such a concomitant medication flagged may be excluded from the respective analysis set.

The following listings will be provided using the Screened Analysis Set:

- Planned and actual treatment.
- Protocol deviations with an indication whether it is major and any action for analysis, including exclusion from specific analysis sets.

9.3 Demographic and Baseline Characteristics

The following summaries will be provided using the ATS and PP Analysis Set.

The Body Mass Index (BMI) will be defined as body weight [kg]/height [m^2].

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

- Demographic characteristics (age, race, ethnicity, sex, height, body weight and BMI at Baseline). In addition to summarization as a continuous variable, age will also be categorized and summarized by ≤ 17 years, >17 years, and ≤ 65 years, >65 years.
- HAE History: history of laryngeal attack (yes, no), family history of HAE (yes, no), HAE type (C1-INH type 1, C1-INH type 2), prophylactic HAE therapy within 3 months before Screening (yes, no), number of HAE attacks within 3 months before the start of prophylactic therapy, number of HAE attacks within 3 months before Screening, number of HAE within 3 months before screening for subjects without prophylactic therapy or 3 months before start of prophylactic therapy for subjects with prophylactic therapy.
- Medical history by SOC and PT. This includes medical history terms with end date prior to informed consent date.
- Concomitant diseases by SOC and PT, this includes all medical history flagged as ongoing or with end date after date of informed consent or missing end date.

All demographic and baseline characteristics tables will also be provided for the subset of subjects who used AI.

The following listings will be provided for the ATS:

- Demographic characteristics.
- HAE History.
- Medical history and concomitant diseases.
- Reproductive Findings/Assessment at Screening/Day 1 and additional pregnancy testing throughout the study.

Those listings will further contain a PK and PP Analysis Set inclusion flag.

9.4 Prior/Concomitant Medications and Procedures

Prior/concomitant medications will be coded using World Health Organization Drug Global dictionary (WHODrug Global) B3.

The reported medication will be classified as 'Prior only', 'Prior and concomitant' or 'Concomitant only' in relation to the treatment period.

These 3 categories are mutually exclusive:

- 'Prior only': if the subject has not taken any IP; or if the medication end date is before treatment start date.
- 'Concomitant only': if the medication start date is on or after treatment start date.
- 'Prior and concomitant': if the medication start date/ is before treatment start date and the medication end date is on or after treatment start date.

If medication start and/or stop dates are partially or completely missing, medications will be assumed to be 'Concomitant Only', unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the date of the first administration of study treatment. If there is clear evidence to suggest that the medication started prior to the date of first administration of study treatment (the available parts of the date are prior to the corresponding parts of the date of first administration of study), the medication will be assumed to be 'Prior and Concomitant', unless there is clear evidence to suggest that the medication stopped prior to the date of the first administration of study (the available parts of the medication end date are prior to the corresponding parts of the date of first administration of study treatment). If this is the case, the medication will be considered 'Prior Only'.

In addition, 'Prior only' medications will be flagged if the end date lies within the run-in period.

Concomitant medications (ie, medication classified as 'Concomitant only' or 'Prior and concomitant') will be summarized showing the number and percentage of subjects taking

concomitant medications by Anatomical Therapeutic Chemical (ATC) classification level 4 and generic name. If the ATC level 4 coding is not available for a generic name, the next available lower level ATC code will be used.

In the summary of prior and concomitant medications, each subject will be counted once within each unique term. For example, if a subject takes Amoxycillin on 2 separate occasions, the subject is counted only once under the corresponding ATC class.

On-demand HAE medication will be summarized as separate block within the summaries of prior and concomitant medication (as a "virtual" ATC class "On-demand HAE Medication"). The on-demand HAE medication will also be reported in their original ATC class.

Technical Note: On-demand HAE medications prior to Run-in Period are collected in the eCRF form 'Concomitant and Prior Medications' with Primary Indication as 'Study Indication Acute HAE Treatment'. On-demand HAE medications on/after start of the Run-in Period are collected in a separate eCRF form 'On-demand Treatment'. On-demand medication during the treatment period given for pre-procedure prophylaxis instead of an HAE attack is also documented on the CM and Prior Medication form with the indication "Study Indication (Pre-Procedure/Short Term HAE Prophylaxis".

For rollover subjects, on-demand HAE medications for attacks that occurred during the Run-in Period of the lead-in study will be imported from the final analysis datasets of the respective lead-in study. Study day will be recalculated to be relative to the reference date for CSL312_3002.

Tables and listings will be provided for ATS.

A listing of prior/concomitant medication will be provided, including the flag for prior medication taken during the run-in period. Non-pharmacological procedures will be listed.

10 Efficacy Analyses

10.1 Analysis of Primary Endpoint

The primary objective of the study is to evaluate the long-term safety of SC administration of CSL312 in the prophylactic treatment of subjects with C1-INH HAE and thus the primary endpoint of the study is a safety endpoint and not an efficacy endpoint. Please see Section 11.3 for a detailed description of the primary safety endpoint and its analysis.

10.1.1 Primary Efficacy Analysis

There is no primary efficacy analysis.

10.2 Analysis of Secondary Endpoints

The secondary efficacy endpoints are:

- Time-normalized number of HAE attacks,
- The reduction in the attack rate during the Treatment Period compared to the Run-in Period,
- The time-normalized number of HAE attacks requiring on-demand treatment,
- The time-normalized number of moderate and / or severe HAE attacks,
- SGART.

10.2.1 Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed using the ATS Analysis Set. The endpoint "Time-normalized number of HAE attacks" will also be analyzed using the PP Analysis Set. All efficacy analysis will not differentiate between treatment administration with NSD or AI and will be based on the overall Treatment/Efficacy evaluation period.

Subjects will enter HAE symptoms into their eDiary 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 will record an 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 using the eCRF 'HAE Attacks' form will be used.

For CSL312-naïve subjects, HAE attacks with a start date on or after the first day of the Run-in Period but prior to the date and time of the first study drug administration will be counted for the Run-in Period. For subjects from CSL312_2001 and CSL312_3001 the number of HAE attacks in the Run-in Period of the previous study will be used. The HAE attacks that occurred during the Run-in Period of the lead-in study will be imported from the final analysis datasets of the respective lead-in study.

HAE attacks with a start date and time after the first study drug administration through the EOT Visit will be counted for the Treatment Period and will be included in the analyses of efficacy.

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, anatomical locations, severity, most recent actual CSL312 dose (loading dose of 400 mg or the monthly 200 mg dose), injection device (NSD or AI), potential trigger, duration in days, period in which the HAE attack occurred and how many on-demand medications were taken per HAE attack.

The following derived endpoints based on HAE attacks will be presented together in a listing:

- Time-normalized number of HAE attacks (per month and per year),
- Time-normalized number of HAE attacks requiring on-demand treatment (per month and per year),
- Time-normalized number of HAE attacks with moderate or severe severity (per month and per year),
- Duration of the treatment period,
- Total number of HAE attacks,
- Reduction in Attack Rate (Treatment period versus Run-in),
- Time to first attack (in days),
- Maximum Time between attacks.

Subjects excluded from the efficacy analysis will be presented in a listing, including the reason for exclusion.

Possible reasons for exclusion from efficacy analysis include exclusion from the ATS Analysis Set and insufficient time spent in the study which is defined as a Treatment/Efficacy evaluation period duration of less than 30 days.

10.2.1.1 Time-normalized number of HAE attacks

The time-normalized number (per month) of HAE attacks is calculated per subject as:

$$\frac{\text{the number of HAE attacks}}{\text{length of subject treatment in days}} * 30.4375$$

where the length of subject treatment is calculated as the duration of the Treatment/Efficacy evaluation period described in Section 8.4.

To transform the length of subject treatment which is calculated in days in years the number of days is divided by 365.25. Thus, time-normalized number of HAE attacks per year is calculated per subject as:

$$\frac{\text{the number of HAE attacks}}{\text{length of subject treatment in days}} * 365.25$$

The time-normalized number of HAE attacks will also be calculated for the Run-in Period. For non-CSL312-naïve subjects, the Run-in Period of their previous CSL312 study will be used.

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

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

10.2.1.2 The Reduction in the Attack Rate during the Treatment Period compared to the Run-in Period

The secondary efficacy endpoint of the percentage reduction in the time-normalized number of HAE attacks is calculated within a subject as:

$$100 * \left(1 - \frac{\text{time normalized number of HAE attacks per month during treatment}}{\text{time-normalized number of HAE attacks per month during Run-in}}\right)$$

and will be summarized descriptively. For non-CSL312-naïve subjects, the Run-in Period of their previous CSL312 study will be used.

The number and percentage of responders and non-responders will be presented combined with corresponding 95% CI. A subject is classified as a responder if the percentage reduction in HAE attacks under treatment compared to the Run-in Period is ≥ 50%. In addition, the number and percentage of subjects with percentage reductions of ≥ 70% and ≥ 90% will be presented with corresponding 95% CIs.

Furthermore, the number and percentage of subjects with a percentage reduction of 100%, ie, who are attack-free, will be presented and summarized with corresponding 95% CI.

Wilson confidence intervals will be used to calculate the CIs for percentages.

10.2.1.3 The Time-normalized number of HAE Attacks requiring on-demand treatment

An HAE attack requiring on-demand treatment is identified using the HAE Attack page of the eCRF, where whether on-demand treatment was required is a field to be filled out.

The time-normalized number of HAE attacks per month requiring on-demand treatment is calculated as:

$$\frac{\text{number of HAE attacks requiring on demand treatment during treatment period}}{\text{length of subject treatment in days}} * 30.4375$$

and will be summarized descriptively. To report in years, the number of days will be multiplied by 365.25 instead of 30.4375.

This summary table will also include a categorical breakdown of the used on-demand medication by ATC and PT, including 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 by ATC and PT, the number of uses of the on-demand medication per HAE attack will be summarized descriptively.

Both the categorical overview and the time-normalized number of HAE attacks will also be provided for moderate/severe HAE attacks.

The time-normalized number of HAE attacks will also be calculated for the Run-in period. For non-naïve subjects, the Run-in period from the previous study will be used.

10.2.1.4 The Time-normalized number of moderate and / or severe HAE attacks

For the analysis of the time-normalized number of moderate and / or severe HAE attacks, an analogue calculation and analyses will be performed as described in Section 10.2.1.1 using all HAE attacks classified as moderate or severe.

10.2.1.5 Subject's Global Assessment of Response to Therapy

SGART is a patient-reported outcome that represents the subject's overall response to treatment (Question: Considering all of the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this Treatment Period.) using the following ratings:

- none – worse or no response at all, not acceptable,
- poor – very little response, not acceptable,
- fair – some response, acceptable but could be better,
- good – good response, acceptable,
- excellent – excellent response, as good as can be imagined.

The SGART response will be provided via electronic Clinical Outcome Assessment (eCOA) data. Missing answers will not be imputed and will be shown as missing.

The SGART results will be presented descriptively by study visit. The number and percentage of subjects with each rating will be presented. In addition, cumulative responses "Poor or better", "Fair or better", "Good or Excellent" will be given. For the percentage for cumulative responses a two-sided 95% CI will be presented. The Friedman test will be used to compare the percentage of subjects with good or excellent responses between study Visit Month 12 and study visits Visit Month 24 and Month 36, respectively, including subjects with assessments for both visits being compared. The tests will be exploratory with an alpha of 5%.

A shift table for SGART will also be provided showing the shift between study visits. For each post-baseline visit, the summary table will show the number and percentages for the following:

- Shift from specific response at previous visit to response at current visit (for example, a shift from poor to fair),
- Any improvement,
- Any worsening of the reported outcome.

The responses to SGART will be listed.

10.2.2 Supplementary Analyses of Secondary Endpoints

All secondary efficacy endpoints described above except the SGART will also be assessed over time for 3-month (ie, 91 days) time windows, with the first window starting on the

Day 1 Visit. Subjects will be included in a 3-month window, only if the respective window is completely contained within their Treatment/Efficacy evaluation period.

The time-normalized number of HAE attacks and the time-normalized number of HAE attacks requiring on-demand treatment will also be assessed for the first 31 days of the Treatment Period. This summary will be provided by whether subjects received a loading dose or not. The analyses will also be repeated for attacks, that are moderate or severe. The number and percentage of subjects not experiencing any attacks in the first month will also be displayed.

In addition, 6-month windows will also be provided for the time-normalized number of HAE attacks, where each 6-month window consists of 182 days.

Summaries for cumulative 3-month windows for the time-normalized number of HAE attacks will also be provided (ie, Day 1 to 91, Day 1 to 182, ...). As with other analysis windows, the subject will only be considered if the subject's Treatment/Efficacy evaluation period contains the entire window.

Subject profiles will be generated for each subject. The x-axis will show the Run-in Period 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 and an asterisk will show the time of CSL312 administration. In addition, the subject's reason for study discontinuation (if applicable) and a subgroup indicator will be given.

10.2.2.1 Duration of HAE Attacks

The duration of each HAE attack in days will be derived by:

HAE attack's end date – HAE attack's start date + 1.

The following will be summarized descriptively:

- The duration of all HAE attacks.
- The per-subject average duration of HAE attacks.

10.2.2.2 Number and Proportion of Attack-free Days

The number of attack-free days will be calculated per subject. For each date included in the Treatment/Efficacy evaluation period it will be checked whether the subject has an HAE attack with:

$$\text{HAE Attack Start Date} \leq \text{Date} \leq \text{HAE Attack End Date}$$

If no such attack exists, that day will be considered attack-free.

The proportion of attack-free days will be calculated as a percentage:

$$100\frac{\text{Number of attack-free days}}{\text{Duration of Efficacy evaluation period (days)}}$$

The number of attack-free days per month will then be calculated as 30.4375 days times the proportion of attack-free days.

The number and proportion of attack-free days as well as the duration of the Efficacy evaluation period and the number of attack-free days per month will be summarized descriptively.

10.3 Analysis of Exploratory Endpoints

The analyses of PK and PD exploratory endpoints are described in Sections 12 and 13 respectively.

For efficacy the following exploratory endpoint analyses will be performed, including changes from baseline as applicable. For all measures, the ATS Analysis Set will be used. No imputation will be performed for missing values.

10.3.1 Time to Event Analysis

The following events will be analyzed only for treatment-naïve subjects:

- Time from Visit Day 1 to start of first HAE attack.
- Time to first HAE attack after Day 14.
- Time from end of first HAE attack to start of second HAE attack. (only for subjects experiencing at least one attack).
- Time from end of second to start of third HAE attack (only for subjects experiencing a second attack).

The following will be analyzed for all subjects in the ATS Analysis Set instead of only for treatment-naïve subjects:

- Maximum attack-free time.

The time to event will be derived as described in Section 8.2.2 within the Treatment/Efficacy evaluation period.

Attack-free time between subsequent HAE attacks is calculated as start date/time of the following HAE attack – end date/time of the preceding HAE attack. Subjects with no HAE attack or no second or third HAE attack will be censored at EOT Visit.

For each of the HAE events (1st, 2nd, 3rd attack and 1st attack after Day 14) the following will be displayed:

- The number and percentage of subjects who do not experience the event.
- The median time, the 25% and 75% 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 are equal 0.5, 0.25, and 0.75, respectively.

  If the time to event function is horizontal at 25%, 50% or 75%, 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 95% CI will be plotted showing the percentage of subjects being event-free at certain times.

The corresponding life tables will also be presented.

The maximum attack-free time will be summarized by the median time, the 25% and 75% percentile times and the minimum and maximum times to the event.

The number and percentage of subjects who have a maximum attack-free time of at least 6 months and of at least 12 months will also be displayed in the summary for maximum attack-free time.

By-subject listings will be provided with time until the first, the second and the third HAE attack as applicable, or until EOT Visit with indication whether the observation is censored. The maximum attack-free time will be flagged.

10.3.2 Quality of Life Endpoints

Investigator's Global Assessment of Response to Therapy

The IGART will require the investigator to rate subjects using the following direction (or an appropriate translation, as applicable): "Considering all of the ways HAE affects your patient, please rate your patient's response to the study medication provided to prevent HAE attacks during this Treatment Period". Whenever possible, the same investigator will perform the IGART for each subject throughout the study.

The following ratings can be chosen by the investigator:

- none – worse or no response at all, not acceptable;
- poor – very little response, not acceptable;
- fair – some response, acceptable but could be better;
- good – good response, acceptable;
- excellent – excellent response, as good as can be imagined.

TSQM II

The TSQM II consists of 11 items of which 8 items are made up of 3 specific scales (EFFECT, SIDEFFECTS and CONVENIENCE) and 2 global satisfaction scale (GLOBAL); one item (Item 3) questions if as a result of taking this medication, the subject experiences any side effects at all, which can be answered by yes and no. Scale scores are calculated for each scale and are transformed into scores ranging from 0 to 100.

The scale scores are calculated as:

EFFECT

([(Item 1 + Item 2) − 3] divided by 12) × 100.

If one item is missing: ([(Sum of Available Items) − 2] divided by 6) × 100.

SIDE EFFECTS

([(Sum of Item 4 to Item 6) − 3] divided by 12) × 100.

If one item is missing: ([(Sum of Available Items) − 2] divided by 8) × 100.

CONVENIENCE

([(Sum of Item 7 to Item 9) − 3] divided by 18) × 100.

If one item is missing: ([(Sum of Available Items) − 2] divided by 12) × 100.

GLOBAL

([(Sum of Item 10 to Item 11) − 2] divided by 12) × 100.

If one item is missing: ([(Sum of Available Items) − 1] divided by 6) × 100.

If more than one item is missing from any subscale then the subscale will not be calculated.

WPAI:GH

The WPAI:GH yields four types of scores: 1. Absenteeism, 2. Presenteeism, 3. Work productivity loss, and 4. Activity impairment.

WPAI :GH outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes). The scoring is as follows:

1. Absenteeism: Percent work time missed due to problem: 100*[Q2/(Q2+Q4)].
2. Presenteeism: Percent impairment while working due to problem: 100*[Q5/10].
1. Work productivity loss: Percent overall work impairment due to problem: 100*{Q2/(Q2+Q4)+(1-Q2/(Q2+Q4))*(Q5/10)}.
3. Activity impairment: Percent activity impairment due to problem: 100*(Q6/10).

Where,

Q2 = hours missed due to health problems,

Q4 = hours actually worked,

Q5 = degree health affected productivity while working,

Q6 = degree health affected regular activities.

Each score is interpreted separately.

AE-QoL

The AE-QoL consists of 17 items and subjects are asked to judge how often they have been restricted in different areas of their daily life because of angioedema and to give more details about their difficulties during the last 4 weeks. The rating for each of the 17 items consists of "Never", "Rarely", "Occasionally", "Often" and "Very Often". Responses are scored on a scale from 1 to 5, where 1 is "Never" and 5 is "Very Often".

The items are assigned to four dimensions - Functioning, Fatigue/Mood, Fears/Shame and Nutrition - as follows:

Dimensions	**Item**
Functioning	1. Impairment of work
	2. Impairment of physical activity
	3. Impairment of spare time activities
	4. Impairment of social relations
Fatigue/Mood	6.Difficulties of falling asleep
	7. Waking up during the night
	8. Feeling tired during the day
	9. Difficulties in concentrating
	10. Feeling downhearted
Fears/Shame	12. Feeling burdened at having swellings
	13. Fear of new suddenly appearing swellings
	14. Fear of increased frequency of swellings
	15. Ashamed to visit public places
	16. Embarrassed by the appearance of swellings

	17. Fear of long term negative drug effects
Nutrition	5. General limitations in foods and eating
	11. Limitations in the selection of food and beverages

It is possible to calculate four individual AE-QoL scores for the four different dimensions or to calculate one AE-QoL total score (Item 1 to Item 17).

The four AE-QoL scores for the four different dimensions as well as the AE-QoL total score are calculated by using the following formula:

$$[(\Sigma \text{ items} - \min \Sigma \text{ items}) / (\max \Sigma \text{ items} - \min \Sigma \text{ items})] \times 100$$

where

Σ items is the sum of all non-missing item scores within a dimension or all items, respectively,

min Σ items is the sum of the minimum score 1 which is added up as many times as there are non-missing item scores within a dimension or all items, respectively,

max Σ items is the sum of the maximum score 5 which is added up as many times as there are non-missing item scores within a dimension or all items, respectively.

For the following example for the dimension “Functioning”:

Item 1: Occasionally (3)

Item 2: Rarely (2)

Item 3: Often (4)

Item 4: Very Often (5)

the AE-QoL score would be calculated by

Σ items: (3+2+4+5) = 14

min Σ items: (1+1+1+1) = 4

max Σ items: (5+5+5+5) = 20

resulting in [(14 - 4) / (20 – 4)] x 100 = 62.5%.

The four AE-QoL scores for the four different dimensions should not be calculated if more than one item is missing in that dimension. The AE-QoL total score should not be calculated if more than 4 items are missing.

The scores are range between 0 and 100 %. The higher the percentage the stronger the impairment the subject has.

10.3.2.1 Analysis of Quality of Life Endpoints

IGART

The number and percentage of subjects with each response for the IGART (none, poor, fair, good or excellent) as well as for the cumulative categories poor or better, fair or better, good or better will be presented by visit.

For the percentage of cumulative responses, a two-sided 95% CI will be presented. The Friedman test will be used to compare the percentage of subjects with good or excellent responses between study Visit Month 12, study Visit Month 24 and study Visit Month 36. The test will be exploratory with an alpha of 5%. The shift tables for SGART (described in Section 10.2.1.5) will be repeated for IGART.

WPAI:GH, TQSM and AE-QoL

Unlike for the other analyses in this SAP, the analyses described in this section will be only performed separately for treatment-naïve subjects and non-treatment-naïve subjects (see Section 8.3.2), without pooling them together.

For the WPAI:GH, TSQM, and AE-QoL, total and domain scores will be presented descriptively by study visit as well as the individual changes in scores between the baseline visit and subsequent visits.

Two-sided 95% CIs for the differences will be presented.

The proportion of subjects achieving a minimal clinically important difference (MCID) will be calculated for Baseline and Visit Month 24 and Visit Month 30 for the total and domain scores.

The MCID for the AE-QoL is defined as -6. For the WPAI:GH and the TSQM, the MCID will be estimated using the half SD approach which has been shown to approximate the threshold of discrimination for a clinically meaningful change. The SD at Baseline will be used to derive the MCID.

10.4 Multiple Comparisons and Multiplicity

Type I error rate adjustment is not applicable as there is no confirmatory test planned in this study. The efficacy analysis is exploratory, and no statistical tests are planned.

10.5 Missing Data and Imputation

Missing efficacy data will not be imputed, as there is no formal statistical analysis planned. All subjects who drop out without completing the first 30 days of the treatment period will be regarded as missing for all efficacy analysis.

There will be no imputation of partial or complete missing dates.

10.6 Treatment Compliance

Information about administered doses is taken from the subject diary. Details about any issues with the dosing device (incomplete dose, device malfunction, use error) are recorded on the Device Event page of the eCRF.

The calculation of compliance will be based on the number of injections taken as planned and the number of planned injections:

$$\text{Compliance}[\%] = 100 \times \frac{\text{Actual Number of Injections Taken as Planned}}{\text{Planned Number of Injections}}$$

The number of planned doses is calculated and rounded down to the next integer as:

$$\text{Planned Number of Injections} = \text{floor}\left(\frac{\text{Duration of the treatment period [days]}}{30}\right)$$

As this calculation considers that the last dose should be taken 30 days prior to the EOT Visit, for interim analysis the following rule will be used instead for subjects still ongoing at the time of the data-cut:

$$\text{Planned Number of Injections} = 1 + \text{floor}\left(\frac{\text{Duration of the treatment period [days]}}{30}\right)$$

An injection counts as "taken as planned" if a dose is recorded in the eDiary and the "Incomplete Dose" field is not checked on the corresponding Device Event page. If necessary, dose diary data will be matched to data from the Device Event page by date and subject number.

For calculating treatment compliance, the loading dose is counted as a single injection.

The following summary will be provided using the ATS Analysis Set:

- Number of SC injections received,
- Overall compliance (%),
- Number and percentage of subjects with overall compliance categorized by < 80%, 80%-100% and >100%,
- Number of injections with not the full volume administered,
- Number of use errors,
- Number of device malfunctions by category of malfunction,
- Number of other issues.

Compliance data will be listed together with exposure date, see Section 11.1.

11 Safety Analyses

All safety analyses will be based on the Safety Analysis Set as defined in Section 6.3.

In general, all tables stated to be provided for subgroups are conditional on there being at least 5 subjects in that subgroup who are included in the Safety Analysis Set.

11.1 Extent of Exposure

Exposure to the IP will be summarized descriptively, including the following:

- Duration of exposure [months], calculated as exposure in days/30.4375, using NSD, AI, and overall,
- Duration of exposure [years], calculated as exposure in days/365.25, using NSD, AI, and overall,
- Number of injections,

- Total cumulative number of injections,
- Number of subjects transitioned to AI,
- Number of subjects with more than 12, 15, 18, 21, … (3-month increments) months of exposure during NSD use, during AI use, and overall,
- Number of subjects with more than 12, 15, 18, 21, … (3-injection increments) injections using NSD, using AI, and overall,
- Total cumulative dose received [mg],
- Total subject years of exposure.

The listing of individual subject data will include all variables presented in the summary tables. The same listing will include overall compliance and the planned number of injections (see Section 10.6 for derivation).

An additional listing by subject and by injection will show all injection details from the subject diary: date, start time, end time, number of syringes and whether the injection was in the abdomen (yes/no). Any issue with the injections recorded on the Device Event page of the eCRF will be included in this listing as well. Bar charts will be produced for the duration of exposure in months and the number of injections, by injection device and overall.

11.2 Adverse Events – Coding and Definitions

TEAEs are AEs which start on or after the date and time of the first administration of study treatment. TEAEs occurring until the Follow-up Visit will be summarized.

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.

Table 4 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 < first IP start date / time		non-TEAE
Otherwise (ie, if AE end date / time ≥ first IP start date / time or AE end date is missing, or AE is ongoing)		
- 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

Similarly, for subjects who transitioned to AI, where start dates and/or times of a TEAE are missing will be assumed to be on AI, except if the partial start dates and/or times or the AE end date and/or time indicate that the AE started before first dose with AI. The AI reference date/time will be used instead of the IP start date/time (see Section 8.2.1).

All reported AEs regardless of when they occurred will be listed.

COVID-19 associated AEs will be identified using the COVID-19 SMQ and will generally be included in TEAE tables identified by their standard MedDRA coding.

If for a TEAE the relationship to study treatment is missing the worst case will be assumed for summarizing analysis (ie, the relationship to study treatment will be assumed to be "Yes"). If the AE or SAE with missing relationship started before the first injection of study treatment it will be considered as "not related" (realistic case). No other imputations for missing AE information will be done.

AEs will be coded using MedDRA. 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.

Subjects with multiple occurrences of the same TEAE will be counted once in the total of those experiencing this PT. Similarly, a subject with one 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 identified by CSL expert review. Prior to the PARM, a list of reported terms and PTs of AEs observed in the study will be provided to CSL as an Excel file. This Excel file will be reviewed by CSL and terms identified as ISRs will be flagged, and the flag will be imported in the ADaM for AEs. ISRs will be considered as a virtual SOC, and ISRs will be reported both under the virtual SOC "Injection Site Reactions" and under their MedDRA SOC. ISRs will be counted towards the "Any" row only once.

TEAEs will be considered clearly identified to be related to an HAE therapy other than CSL312 during the Follow-up Period, if they fulfill all the following criteria:

1. The start date of the TEAE is in the Follow-up Period and is at least 30 days after the last dose of CSL312,

2. The TEAE is an ISR with start time within 72 hours after the start of the administration of another HAE medication, defined as a medication which started in the Follow-up Period, and has the primary indication 'Study Indication (Acute HAE Treatment or HAE Prophylaxis)' according to the eCRF form 'Concomitant and Prior Medications'.

3. The TEAE is considered not related to study treatment or to a device issue and did not occur with overdose of study treatment according to the eCRF form 'Adverse Events/SAEs',

TEAEs with partially missing date will never be considered to be clearly identified to be related to an HAE therapy other than CSL312.

The AESIs defined for this study are:

- Thromboembolic events.
- Bleeding events.
- Severe Hypersensitivity / Anaphylaxis.

Note that non-systemic thrombosis (eg, localized thrombosis associated with vascular access) is not considered an AESI.

In addition to AESIs reported by the investigators according to their judgment, the following suggestive events will be independently identified for further review with a SMQ search:

- Thromboembolic events (TEE) – SMQ "Embolic and thrombotic events (SMQ)" (narrow), consisting of:
  - Embolic and thrombotic events, arterial (SMQ),
  - Embolic and thrombotic events, venous (SMQ),
  - Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).
- Bleeding events – SMQ "Haemorrhages (SMQ)" (narrow),
- Hypersensitivity including anaphylaxis – SMQ "Hypersensitivity (SMQ)" (broad), Anaphylactic reaction (SMQ) (broad), Anaphylactic/anaphylactoid shock conditions (SMQ) (broad). Here, broad scope includes narrow and broad search.

In the following, these will also be referred to as "AESI as identified via SMQ".

11.3 Analysis of Primary Safety Endpoint

All analyses described in this section are applicable for C1-INH HAE subjects only. TEAEs will be presented for the following:

- All subjects in the Safety Analysis Set (all subjects on 200 mg CSL312 once monthly, independent of the use of CSL312 200 mg AI or CSL312 200 mg NSD).
- Subjects on 200 mg CSL312 using AI.
- Subjects on 200 mg CSL312 using NSD.

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 rates per injection and per subject year.

TEAE rates per injection will be calculated as follows:

$$\text{TEAE Rate per Injection} = \frac{\text{Number of TEAEs}}{\text{Number of injections}}$$

where the number of injections will be the sum of the injections that subjects received during the respective safety evaluation period with the respective device (NSD, AI, or overall) the TEAE is assigned to.

TEAE rates per subject years will be calculated as follows:

$$\text{TEAE Rate per Subject Year} = \frac{\text{Number of TEAEs}}{\text{Subject years}}$$

where subject years will be the sum of the time in years that subjects were exposed to study treatment using that device (NSD, AI, or overall) during the respective safety evaluation period.

An overview summary of TEAEs will be provided including:

- TEAE,
- SAEs,
- Deaths,
- ISRs,
- TEAEs occurring within 24 hours of start of IP administration,
- SAEs occurring within 24 hours of start of IP administration,
- Related TEAEs,
- Related SAEs,
- TEAEs leading to study discontinuation,
- TEAEs in each severity category,
- ISRs, in each severity category,
- TEAEs in each outcome category,
- SAEs in each severity category,
- SAEs in each outcome category,
- AESIs, both as reported by the investigators and as identified via SMQ (see Section 11.4 for definitions).

A summary table by SOC and PT will be provided.

These two summaries will exclude all TEAEs clearly identified to be related to an HAE therapy other than CSL312 during the Follow-up Period. Both summaries will be repeated for TEAEs that can clearly be identified to be related to an HAE therapy medication other than CSL312.

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 (per the corresponding SMQ).

The TEAEs will be presented in a by-subject listing. TEAEs clearly identified to be related to an HAE therapy other than CSL312 will be included and flagged.

11.4 Analysis of Secondary Endpoints based on Adverse Events

The analysis for the primary endpoints described in Section 11.3 will be repeated for the nC1-INH subjects, without the exclusion of TEAEs clearly identified to be related to an HAE therapy other than CSL312 and excluding the tables and listings associated with COVID-19.

The following summary tables will be provided for all subjects (C1-INH and nC1-INH) in the Safety Analysis Set, without excluding TEAEs clearly identified to be related to a HAE therapy other than CSL312:

- Overview table of TEAEs (same items as described in Section 11.3).
- Overview table of SAEs (same as above, restricted to SAEs).
- SAEs by SOC and PT.
- TEAEs by severity, SOC and PT.
- Related TEAEs by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT.
- TEAEs by 3-month windows. Rates will still be based on the cumulative safety period. Assignment of TEAEs to 3-month windows will be based on the start date of the AE, similarly as for HAE attacks (see Section 10.2.1). Unclear assignments due to incomplete AE start dates will be discussed during the PARM.
- AESI by SOC and PT as identified via SMQ (definition of AESI as in Section 11.2).
- Non-serious TEAEs by SOC and PT.
- Laboratory Findings reported as AEs.
- Anti-CSL312 antibodies.

Summary tables will be presented for the following:

- All subjects in the Safety Analysis Set (all subjects on 200 mg CSL312 once monthly, independent of the use of CSL312 200 mg AI or CSL312 200 mg NSD).
- Subjects on 200 mg CSL312 using AI.
- Subjects on 200 mg CSL312 using NSD.

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 rates per injection and per subject year calculated in the same manner as for the primary endpoint described in Section 11.3.

The following listings will be provided:

- Non TEAEs.
- TEAEs.
- TEAEs for Japanese subjects.
- TEAEs for adolescents.
- SAEs.
- SAEs with fatal outcome.
- AEs leading to study withdrawal.
- AEs leading to permanent discontinuation of study treatment.
- AESIs.
- Related AEs.
- TEAEs related to laboratory findings.
- AEs related to COVID-19.

TEAEs clearly identified to be related to an HAE therapy other than CSL312 will be flagged in listings.

Listings of AEs will at least include site, subject ID, HAE type, start and end date/times, reported term, SOC, PT, relationship to study drug, severity, whether it is serious, action taken. As stated in Section 8.2.6 the listings will also include the most recent dose of CSL312 (dose level, device [NSD or AI] and date).

11.5 Clinical Laboratory Evaluations

The laboratory tests in Section 8.1.1 of the protocol will be summarized as described in this section. Unscheduled visits will be handled as described in Section 8.2.5. Definition of the baseline assessment is in Section 8.2.3.

The test names and units from the central laboratory transfer will be used. The sequence and groupings in which parameters are provided will match Table 2 of the protocol.

Separate summary tables for hematology, biochemistry, coagulation, urinalysis, and immunogenicity tests will be produced.

Summaries to be produced are:

- Laboratory values and changes from baseline by scheduled study visit for continuous tests and number and percentages per category for categorical tests.
- The number and percentage of subjects with clinically significant laboratory findings reported as AEs by test and visit. Those will be identified through the eCRF form 'Clinical Significant Safety Lab Data.'.

The percentages for categorical tests will be based on the number of subjects with non-missing values at each visit.

The presence of anti-CSL312 antibodies will be summarized descriptively by visit. This summary will include the number and percentage of subjects who experience anti-drug antibodies.

A laboratory value that is outside the reference range is either high abnormal (value above the upper limit of the normal [ULN] reference range) or low abnormal (value below the lower limit of the normal [LLN] reference range). An abnormal laboratory value is not necessarily of potential clinical interest.

Listings of laboratory data will include test name and unit along with normal range, the sampling date and time, the test result, an assessment whether the result is high (above normal range) or low (below normal range). Any comments to the laboratory test will be provided in a separate listing, if applicable.

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

Listings to be produced are:

- All laboratory values including flags for values outside the normal range.
- Laboratory data for subjects with values outside the normal range.

11.6 Other Safety Measures

The denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

11.6.1 Vital Signs

Vital signs include blood pressure (systolic and diastolic), respiratory rate, pulse rate, temperature, and height and weight.

The following summaries will be provided by actual dose:

- Values of vital signs and changes from baseline by study visit.

A by-subject listing will be provided, including the parameters, nominal visit, visit date and time, result and change from baseline, position, and location of body temperature measurement.

12 Pharmacokinetic Analyses

All non-compartmental analyses are to be performed according to PK-GDL-01.

PK parameters will be derived only for the PK subgroup of CSL312-naïve adult subjects, who have additional PK/PD samples taken to further characterize the PK of CSL312 following a SC loading dose. The following parameters will be determined: C_{max}, T_{max}, and $AUC_{0\text{-}30days}$. Further information can be found in Section 12.2.

Additional samples (but no parameter derivations) will also be performed for all adolescents at steady-state.

After DBL and for interim analyses, Parexel will upload the SDTM domains DM, EX, PC, and VS to CSLs Data Warehouse. CSL Behring Clinical Pharmacology & Pharmacometrics (CPP) or their designate will have access to all relevant datasets in the Data Warehouse. CSL Behring CPP or their designate will derive the PK parameters and provide Parexel with the derived PK parameters as Excel file in a format which will be agreed upon upfront between Parexel and CSL Behring CPP or their designate. Parexel will produce the SDTM PP domain and the analysis datasets from the Excel file received from CSL Behring CPP or their designate. In an additional Excel file, CSL Behring CPP or their designate will flag any CSL312 plasma concentrations which will have been excluded from the derivation of the PK parameters.

Parexel will produce the TFLs for the CSL312 plasma concentrations and the PK parameters as specified below.

Unless otherwise stated, all analyses in this section will be based on the PK Analysis Set.

12.1 Drug Concentration Measures

Handling of PK concentration data for noncompartmental analyses will be performed according to PK-GDL-01.

Plasma concentrations of CSL312 will be listed, including flags for concentrations excluded for PK derivations (where applicable).

Below limit of quantification (BLQ) concentrations before the first administration of the IP will be substituted with zero. Any other post-dose BLQ concentrations will be treated as missing for summaries and figures. The number and percentage of subjects with BLQ concentrations will be included in the summary tables. This percentage will be calculated relative to the number of observations at the visit. If 50% of values are BLQ then the SD and

other measures of variance will not be calculated. Further details on the handling of imputation of BLQ values are detailed in PK-GDL-01.

The summaries will be given by nominal (planned) time point. Summary statistics for CSL312 concentration-time data will be presented as follows: n, % BLQ, mean, SD, percent coefficient of variation (CV%), geometric coefficient of variation (geoCV%), median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean and its respective 90% CI, will be calculated. The 90% CI will be obtained by calculating and then back transforming the 90% CI on log scale, based on the assumption of lognormality. The geometric coefficient of variation will be calculated as $100*\text{sqrt}(\exp(SD_{log}^2)-1)$, where the SD is calculated on the log scale.

The summaries and figures for CSL312 concentrations will also be presented for the following subgroups:

- PK subgroup of CSL312-naïve adult subjects with additional PK assessments,
- Age (adolescent [12 to ≤ 17 years] and adult [>17 years] subjects),
- Race (Japanese and non-Japanese subjects; Chinese, Asian and non-Asian subjects),
- Treatment-naïve subjects (see Section 8.3.2).

The following figures will be generated, with the CSL312 concentration on the y-axis and time on the x-axis in both linear and log-linear scales. Nominal time will be used for mean (± SD) plots while actual time will be used for individual plots.

- Mean (± SD) CSL312 concentrations vs. time with a scheduled measurement not specific to adolescents or the PK subgroup.
- Mean (± SD) CSL312 concentrations vs. time in adolescents only.
- Mean (± SD) CSL312 concentrations vs time for the PK subgroup up to the pre-dose measurement before the 2nd injection.
- Individual CSL312 concentration-time profiles for adolescents only, with all profiles at the Month 3 visit overlaid on the same page. The samples from the Month 3 visit up to and including the pre-dose sample before the next dose will be included.
- Individual CSL312 concentration-time profiles for the PK subgroup, with all profiles overlaid on the same page. All samples taken before the second dose will be included.

12.2 Deriving and Summarizing Pharmacokinetic Parameters

All PK parameters for the PK subgroup of CSL312-naïve adult subjects with additional PK assessments to further characterize the PK of CSL312 following the SC loading dose will be listed by subject and summarized. The PK parameters will be calculated by standard non-compartmental analysis according to PK-GDL-01 and using WinNonlin® Version 8.0 or later.

All calculations of non-compartmental parameters will be based on actual sampling times and doses.

The following descriptive statistics will be presented for the PK parameters, except for T_{max}: n, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum, and maximum. For T_{max}, n, median, minimum, and maximum will be presented.

All PK parameters will be reported to at least 3 significant digits unless the precision of the original data has less than 3 significant digits.

13 Pharmacodynamic and Biomarkers Analyses

13.1 Pharmacodynamic Analyses

PD data will be summarized using the PD Analysis Set.

FXIIa-mediated kallikrein activity will be assessed for the PD of CSL312 as described in Section 8.1.2 of the protocol.

FXIIa-mediated kallikrein activity will be listed by individual subjects and will be summarized by nominal time points, study subpopulation and actual treatment.

FXIIa-mediated kallikrein activity % of Baseline values will also be provided in the listings, summaries, and figures. The % of Baseline values will be derived as 100*visit value/baseline value.

The same summaries and figures, including subgroup analyses, as described for the PK analysis (see Section 12.1) will be generated for FXIIa-mediated kallikrein activity and FXIIa-mediated kallikrein activity % of Baseline values.

13.2 Biomarker Analyses

Biomarker analyses will be described within a Biomarker Analysis Plan and reported separately.

14 Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

15 Pharmacogenetic Data Analyses

Not applicable.

16 References

Not applicable.

17 Appendices

The following table gives an overview of analyses being repeated for specific subgroups. It doesn't include analyses which are exclusively performed for a subset of patients such as the time-to-event analysis described in Section 10.3.1 or analyses which are only done exclusively for specific subgroups such as the ones for WPAI:GH, TQSM and AE-QoL described in Section 10.3.2.

Table 5 Overview of Subgroup Analyses

	Subgroup Definition					
Analysis	CSL312-naive and Non-CSL312-naive (Section 8.3.1)	Treatment-naïve and Non-treatment-naive (Section 8.3.2)	Previous Study and Treatment (Section 8.3.3)	Japanese Subjects (Section 8.3.4)	Chinese and Asian Subjects (Section 8.3.5)	Adolescent Subjects (Section 8.3.6)
Time-normalized number of HAE attacks(Section 10.2.1.1)			Y	Y	Y	Y
Reduction in attack rate during the Treatment Period compared to the Run-in period (Section 10.2.1.2)			Y	Y	Y	Y
Responder rates and attack-free subjects (Section 10.2.1.2)			Y	Y	Y	Y
Number and proportion of attack-free days (Section 10.2.2.2)	Y	Y		Y		
Time-normalized number of HAE attacks requiring on-demand treatment (Section 10.2.1.3)			Y	Y	Y	Y

Analysis	Subgroup Definition					
	CSL312-naive and Non-CSL312-naive (Section 8.3.1)	Treatment-naïve and Non-treatment-naive (Section 8.3.2)	Previous Study and Treatment (Section 8.3.3)	Japanese Subjects (Section 8.3.4)	Chinese and Asian Subjects (Section 8.3.5)	Adolescent Subjects (Section 8.3.6)
SGART (Section 10.2.1.5)	Y			Y	Y	Y
Time-normalized number of HAE attacks per month by 3-month windows (Section 10.2.2)		Y		Y		
Reduction in attack rate during the Treatment Period compared to the Run-in period by 3-month windows (Section 10.2.2)		Y		Y		
Responder rates and attack-free subjects by 3-month windows (Section 10.2.2)		Y		Y		
Maximum Attack-free Time (Section 10.3.1)		Y				
Exposure (Section 11.1)		Y	Y	Y	Y	Y
Overall Summary of TEAE for C1-INH subjects (Section 11.3)				Y	Y	Y
TEAEs by SOC and PT (Section 11.4)				Y	Y	Y

Analysis	Subgroup Definition					
	CSL312-naive and Non-CSL312-naive (Section 8.3.1)	Treatment-naïve and Non-treatment-naive (Section 8.3.2)	Previous Study and Treatment (Section 8.3.3)	Japanese Subjects (Section 8.3.4)	Chinese and Asian Subjects (Section 8.3.5)	Adolescent Subjects (Section 8.3.6)
TEAEs by 3-month time windows (Section 11.4)		Y		Y		
PK Concentrations (Section 12.1).		Y		Y	Y	Y
PD Concentrations (Section 13.1).		Y		Y	Y	Y

C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema; PD = pharmacodynamic; PK = pharmacokinetic; PT = Preferred Term; SGART = Subject's Global Assessment of Response to Therapy; SOC = System Organ Class; TEAE = treatment-emergent adverse event; Y = subgroup is applicable for this analysis.