STATISTICAL ANALYSIS PLAN (SAP)

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema

Study Number:	CSL312_3001
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:	1.0 - FINAL
Version Date:	21 Apr 2021
NCT Number:	NCT04656418
EudraCT Number:	2020-000570-25
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

COMMERCIAL IN CONFIDENCE

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1 Modification History

Version	Effective Date	Author of Modification	Summary of Change
1.0	21 April 2021		N/A – First Version

2 List of Abbreviations

Abbreviation	Term
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
CCI [redacted]	[redacted]
aPTT	Activated partial thromboplastin time
ATC	Anatomical therapeutic chemical
ATS	All treated subjects analysis set
BLQ	Below Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSL	CSL Behring
CSP	Clinical Study Protocol
CSR	Clinical study report
CTMS	Clinical Trial Management System
DBL	Database lock
BDRM	Blind Data review meeting
BMI	Body Mass Index
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
eDiary	Electronic diary
EOS	End of study
CCI [redacted]	[redacted]
FAS	Full analysis set
HAE	Hereditary angioedema
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
cci [redacted]	[redacted]
IP	Investigational product
IRT	Interactive response technology
ISR	Injection site reaction
ITT	Intention-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MSAP	Modeling and simulation analysis plan

Abbreviation	Term
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PT	Preferred term
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
SC	Subcutaneous
CCI	[redacted]
SOC	System organ class
TEAE	Treatment-emergent adverse events
TFLs	Tables, Listings, Figures
CCI	[redacted]

3 Purpose

This SAP provides a detailed and complete description of the planned statistical analyses of the study CSL312_3001 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 (CSP) Original (dated 04 Aug 2020),
- electronic Case Report Form (eCRF), Version 1.0 (dated 16 Dec 2020).

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

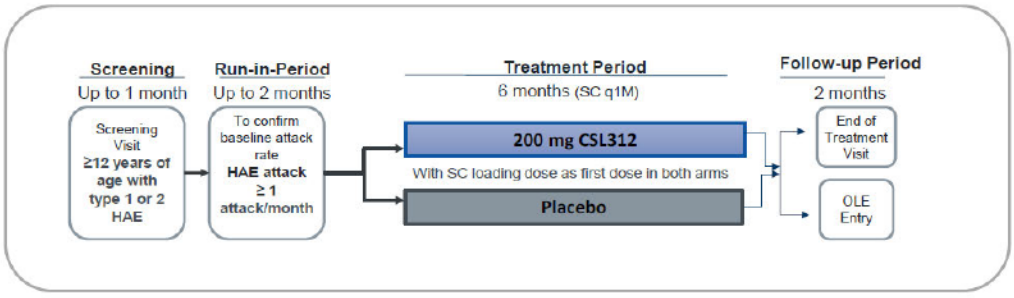
Mock tables, listings, and figures shells are provided in a separate supporting document.

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

4 Study Design

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of a single dose of 200 mg CSL312 administered by subcutaneous (SC) injection once monthly as prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent (12 to 17 years, inclusive) and adult subjects with HAE. This study will be conducted globally. As shown in Figure 1, the study consists of a Screening Period (up to 1 month), a Run-in Period (up to 2 months), a Treatment Period (6 months), and either a 2-month Follow-up Period (ie, 3 months after last investigational product administration) or entry into the open-label Phase 3b Study CSL312_3002.

Figure 1 Study Overview



Abbreviations: HAE = hereditary angioedema; OLE = open-label phase 3b Study CSL312_3002; q1M = once a month; SC = subcutaneous.

Screened subjects who meet all the inclusion criteria and none of the exclusion criteria will enter the Run-in Period. Subjects who do not meet the screening criteria for entering the Run-in Period within 30 days may be rescreened with confirmation from the sponsor. Rescreening is allowed once. Subjects who do not meet the minimum HAE attack rate during the Run-in Period and / or all other criteria for entering the Treatment Period will be considered Run-in failures and cannot be rescreened.

Subjects meeting the eligibility criteria will enter the Treatment Period after the Run-in Period. If a subject is unable to enter the Treatment Period by Day 60, CSL Behring (CSL) approval is required for the subject to enter the Treatment Period.

Eligible subjects will be randomized 3:2 to either the CSL312 Active Arm (CSL312 SC once a month) or the Placebo Arm (Placebo SC once a month). All subjects will be randomized based on age ($\leq$ 17 years, $>$ 17 years) and baseline attack rate observed during the Run-in Period (1 to $<$ 3 attacks / month, and $\geq$ 3 attacks / month) for adults only.

Subjects who terminate early from the study (ie, before Day 182) will undergo the assessments specified for the End of Treatment Visit (Day 182), if possible.

Subjects who discontinue treatment with CSL312 will be encouraged to remain in the study until Day 182 in order to collect study assessments. Subjects may withdraw from the study at any time at their own request, or at the discretion of the investigator or CSL for safety, behavioral, or administrative reasons. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data and samples collected before withdrawal of consent.

Subjects who successfully complete the current study (CSL312_3001) may have the option to roll over into an open-label phase 3b Study CSL312_3002. The Day 182 End of Treatment Period Visit corresponds to the first day of the open-label phase 3b study for subjects rolling-over into Study CSL312_3002. Subjects will enter Study CSL312_3002 after completing the Day 182 assessments and signing the ICF for Study CSL312_3002. Subjects who choose not to participate in Study CSL312_3002 are required to complete the Follow-up Visit (Day 242, which is approximately 3 months after the last dose of investigational product).

4.1 Objectives and Endpoints

The primary objective of this study is to evaluate the efficacy of SC administration of CSL312 as prophylaxis to prevent HAE attacks in subjects with HAE.

Table 1 Primary Study Objective and Endpoint

Objective	Endpoint	Summary Measure(s)
Primary	Time-normalized number of hereditary angioedema (HAE) attacks during treatment from Day 1 through Day 182[a]	The time-normalized number of HAE attacks (per month and annualized) in subjects treated once a month with either CSL312 (Active Arm) or placebo (Placebo Arm) during the period from Day 1 through Day 182 (6 months).

[a]Only investigator-confirmed HAE attacks based on the investigator's assessment of subject-reported symptoms will be included in the analysis of primary efficacy endpoint. Descriptions of confirmed HAE attack are provided in CSP Section 8.1.3 and CSP Appendix 2.

The secondary objectives of the study are:

1. To characterize the clinical efficacy of SC CSL312 in the prophylactic treatment of HAE.
2. To evaluate the safety of SC CSL312 in the prophylactic treatment of HAE.

Table 2 Secondary Study Objectives and Endpoints

Objective	Endpoint	Summary Measure(s)
Efficacy Endpoints		
1.	The reduction in the attack rate during the Treatment Period compared to the Run-in Period	The percentage reduction (at least ≥ 50%, ≥ 70%, ≥ 90 or equal to 100% [attack free]) in the time-normalized number of HAE attacks in subjects treated once a month with either CSL312 (Active Arm) or placebo (Placebo Arm) during the period from Day 1 through Day 182 (6 months) compared to the Run-in Period, as well as for the first 3-month time period and for the second 3-month time period of the Active and Placebo Arms compared to the Run-in Period.
1.	The time-normalized number of HAE attacks requiring on-demand treatment	The time-normalized number (per month and annualized) of HAE attacks requiring on-demand treatment in subjects treated once a month with either CSL312 (Active Arm) or placebo (Placebo Arm) during the period from Day 1 through Day 182 (6 months), as well as for the first 3-month time period and for the second 3-month time period of the Active and Placebo Arms.

Objective	Endpoint	Summary Measure(s)
Efficacy Endpoints		
1.	The time-normalized number of moderate and / or severe HAE attacks	The time-normalized number (per month and annualized) of moderate and / or severe HAE attacks in subjects treated once a month with either CSL312 (Active Arm) or placebo (Placebo Arm) during the period from Day 1 through Day 182 (6 months), as well as for the first 3-month time period and for the second 3-month time period of the Active and Placebo arm.
1.	Time-normalized number of HAE attacks at various time points during the treatment period	The time-normalized number of HAE attacks (per month and annualized) in subjects treated once monthly with either CSL312 (Active Arm) or placebo (Placebo Arm) during the first 3-month time period and the second 3-month time period of CSL312 (Active Arm) and placebo (Placebo Arm). The percentage reduction will be calculated for the time-normalized number of HAE attacks between the Active Arm and the Placebo Arm for the 6-month treatment period, as well as for the first 3 months and the second 3 months of the treatment period.
1.	CCI [redacted]	Comparison of the distribution of responses to therapy between CSL312 and placebo at the end of the Treatment Period at Day 182 based on the proportions of subjects with a "excellent, good, fair, poor or none" response to therapy.
Safety Endpoints		
2.	• AEs • AESIs • SAEs • CSL312 induced anti-CSL312 antibodies • Clinically significant abnormalities in laboratory assessments (ie, laboratory abnormalities reported as AEs).	The number and percentage of subjects experiencing the specified safety events on treatment with CSL312 or placebo during the entire Treatment Period until Follow-up or Final Visit.

4.2 Study Hypotheses

Four tests, one for the primary endpoint (H01) and 3 for the secondary endpoints (H02, H03, H04), will be performed in a hierarchical order with an 2-sided alpha of 5% each.

Four null hypotheses are defined:

- H01: the time-normalized number of HAE attacks in the first 6-month time period of the Active Arm and in the Placebo Arm period are equal.
- H02: the percentage reduction in the means of the time-normalized number of HAE attacks for the 6-months of the Active Arm compared to the 6-month Placebo Arm period are equal to zero.
- H03: the number of subjects who do not experience a HAE attack in the first 3 months of the Active Arm and the first 3-month Placebo Period are equal.
- H04: the percent of subjects with good or excellent responses to the CCI at the end of Treatment Period (Day 182) are equal for subjects treated with CSL312 and placebo.

Methods to control for multiplicity are described in Section 10.5.

4.3 Study Treatments

The investigational products in this study are 200 mg CSL312 and placebo.

Subjects randomized to the Active Arm will receive CSL312 SC once a month for 6 months. The first dose of CSL312 will be a 400 mg loading dose administered subcutaneously on the same day as 2 separate injections at the study site (ie, Month 1). Subsequent doses of CSL312 will be 200 mg administered SC once monthly for 5 consecutive months (ie, Months 2 through 6).

Subjects randomized to the Placebo Arm will receive volume-matched placebo once monthly for 6 months. The first dose of placebo in the Placebo Arm will be volume-matched (400mg loading dose) placebo administered SC as 2 separate injections (ie, Month 1). Subjects will then receive volume-matched placebo SC once a month for 5 consecutive months (ie, Months 2 through 6).

4.4 Randomization Procedures and Blinding

Subjects will be randomized using a block randomization by means of centralized Interactive Response Technology (IRT) to 1 of 2 treatment arms in a 3:2 ratio to either the Active Arm or to the Placebo Arm. Stratifying variables will be age ($\leq$ 17 years, $>$ 17 years) and, for adults, the subject's baseline attack rate (1 to $<$ 3 attacks/month, and $\geq$ 3 attacks/month).

Randomization will be done centrally. The randomization list will be generated according to the approved randomization specifications, which includes further randomization details. The IRT service provider will keep the randomization code on file. Investigational site staff, including the investigators, will be blinded to treatment allocation. Subjects and CSL staff / designates participating in the conduct of the study will also be blinded to treatment allocation (double-blind).

The IRT will assign the investigational product (IP) to each subject. The IP will be packaged and labelled to ensure blinding is maintained and CSL312 Prefilled Syringe is not distinguishable from the placebo.

Study unblinding will take place following locking of the study database except in the situations as breaking the blind for an emergency or an ad-hoc safety unblinding. Outputs including unblinded information might also be generated for meetings with the independent data monitoring committee (IDMC, see Section 4.6.3). Adequate procedures are in place to ensure the integrity of the blinded data within CSL.

All blood samples collected for PK / PD analyzed by the central laboratory will remain

blinded until database lock. In addition, results from assessment of aPTT will not be available to subjects, study site personnel, or CSL and their delegates who are blinded to treatment assignment.

The bioanalyst and pharmacokineticist responsible for the sample analysis and PK / PD, immunogenicity, and coagulation evaluations will be unblinded. However, they will agree not to disclose the randomization schedule or any data prior final data base lock and unblinding.

For further details please see the CSP.

4.5 Determination of the Sample Size

In total, 60 subjects are planned to be randomized.

Forty subjects with C1-INH HAE type 1 and type 2 completing the 6-month Treatment Period are needed to achieve a power of approximately 90% for a two-sided Wilcoxon Test (alpha of 5%). Subjects will be randomized to the Active Arm or the Placebo Arm with a ratio of 3:2. An attack rate per month of 0.3125 for CSL312-treated subjects and of 1.3 for subjects receiving placebo are assumed. The monthly attack rates of placebo and of CSL312 are assumed to be Poisson distributed.

The sample size calculation is performed with SAS 9.4 using proc power procedure with twosamplewilcoxon test=WMW which performs power analyses for the Wilcoxon-Test for two independent groups, i.e. the CSL312 and the Placebo treatment in Study CSL312_3001. The Wilcoxon Rank Sum test is testing from departure from the null hypothesis and is assessing if there is a location shift between the distributions of the HAE attack rates of the CSL312 and the Placebo treatment. SAS Proc Power procedure uses the O'Brien-Castelloe approach to compute approximate power. Alpha is set to 5% [O'Brien & Castelloe, 2006]. The assumed monthly attack rates of placebo and of CSL312 (i.e. 1.3 and 0.3125 attacks/month, respectively) are used as the two means of the two Poisson distributions. The randomization ratio of 3:2 was implemented by GROUPNS = (24 16) resulting in a total sample size of 40 which is the lowest one reaching 90% power.

It is targeted to randomize approximately 5 adolescents into the treatment period with a randomization ratio of 3:2 (active:placebo).

To allow for sufficient safety data, to increase the likelihood of adolescents entering the study and, to have at least 40 subjects reaching the end of the study, an additional 20 subjects are planned to be randomized.

In case it is not feasible to randomize the targeted number of adolescents, the targeted total sample size will be achieved by randomizing the needed number with adult subjects.

In addition, it is targeted to include 5 Japanese subjects into the total 60 subjects randomized.

Based on Method 1 and Method 2 in the [Basic principles on Global Clinical Trials] the sample size of the Japanese subjects are planned as below. The point estimate of the endpoint in each arm for Japanese population and other regions (for Method 2) are assumed as the same as that for the global population.

Method 1

With setting the notations of treatment differences between CSL312 and placebo arm as D, the treatment difference in the global population as D_{all}, and the treatment difference in the Japanese subpopulation as D_{Japan}, the probabilities of $D_{Japan}/ D_{all} >0.5$ were calculated for the settings that the global sample size is 60 patients (CSL312 arm = 36 patients, and placebo arm = 24 patients) including the Japanese sample size of 5 – 8. The Japanese sample sizes of each arm were rounded based on the 3:2 randomization ratio.

Table 4 Sample Size Justification for Japanese Subjects - Method 1

Japanese sample size			**Probability (%) of $D_{Japan}/ D_{all} >0.5$**	
Total	CSL312	Placebo	With median	With mean
5	3	2	64	70
6	4	2	63	71
7	4	3	65	76
8	5	3	73	76

Method 2

With setting the notations of treatment differences between CSL312 and placebo arm as D, the treatment difference in the global population as D_{all}, the treatment difference in the Japanese subpopulation as D_{Japan} and the treatment difference in other regions x as $D_{other-x}$, the probabilities of that all of the global, Japan and other regions of D>0 were calculated for the settings that the global sample size is 60 patients (CSL312 arm = 36 patients, and placebo arm = 24 patients) , the Japanese sample size is 5 – 8, the sample size of North America and Europe are assumed to be the same. The sample sizes of each arm for Japan and other regions were rounded up based on 3:2 randomization ratio.

Table 5 Sample Size Justification for Japanese Subjects - Method 2

Sample size for each region			Probability (%) of all of D >0	
Japan	North America*	Europe*	With median	With mean
5	27	28	75	86
6	27	27	73	85
7	26	27	70	91
8	26	26	67	92

* Expected that the sample sizes for North America and Europe would be the same. If not divisible, the sample size of Europe includes one more patients than that of North America.

As the results, if the Japanese sample size is 8, the probabilities to achieve consistency between the Japanese subset and the global population are 67%－92% using mean and median with 3:2 randomization ratio based on Method 1 and 2. Eighty percent probability would be achieved with 5 Japanese patients already when using the mean and Method 2.

4.6 Planned Interim Analyses and Reviews

4.6.1 Interim Analyses Other Than Sample Size Re-estimation

No formal interim analyses are planned for this study.

4.6.2 Interim Sample Size Re-estimation

Interim sample size re-estimation is not applicable for this study.

4.6.3 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to monitor the safety and efficacy data generated during the study. The IDMC will consist of an independent statistician and clinical specialists in the fields of HAE management, who also have experience in clinical trials. The IDMC will review accumulating data from the ongoing study. Based on these reviews, the IDMC will advise on the further conduct of the study. No success or futility thresholds will be set for the IDMC reviews; CSL will not stop the study unless a major safety issue has been identified. The composition, activities, and responsibilities of the IDMC will be described separately in the IDMC charter. A separate IDMC SAP and IDMC TFL Shells will be created.

5 Changes from the Protocol Planned Analyses

Estimand definition has been updated to reflect the potential impact of the ongoing coronavirus disease 2019 (COVID-19) pandemic, see Section 7.1 and Section 10.1.1.

Comparison of the distribution of responses to therapy between CSL312 and placebo at the end of the Treatment Period will use the CCI at Visit Day 182 only. If subject's Study Visit Day 182 CCI value is missing the subject will not be included in the CCI, see Section 10.4.

Also, hypothesis H02 and hypothesis H04 have been defined more clearly by modifying the wording, see Section 4.2.

There are no further changes to the analyses planned compared to the CSP. Any changes conducted after finalization of the SAP will be noted in the Clinical Study Report.

6 Study Analysis Sets

6.1 Screened Analysis Set

The screened analysis set comprises all subjects who provide written informed consent and who undergo study screening procedures.

Technical Note: Consider all subjects with an informed consent date collected.

6.2 Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises all subjects in the screened analysis set who were randomized. The ITT analysis set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received.

Any subject who receives a treatment randomization number will be considered to have been randomized.

6.3 Safety Analysis Set

The safety (SAF) analysis set comprises all subjects in the ITT analysis set who received at least 1 dose of investigational product and will be analyzed using the actual treatment received.

6.4 Per Protocol Analysis Set

The per-protocol (PP) analysis set comprises all subjects in the ITT analysis set who receive at least 1 dose of investigational product and who comply with the protocol. Decisions regarding exclusion from the PP analysis will be made and documented before the study data

are unblinded.

6.5 Pharmacokinetic Analysis Set

The PK analysis set comprises all subjects in the safety analysis set with at least 1 measurable concentration of CSL312. PK analysis set will be analyzed using the actual treatment received.

6.6 Pharmacodynamic Analysis Set

The PD analysis set comprise subjects in the safety analysis set for whom at least 1 PD measurement was obtained. PD analysis set will be analyzed using the actual treatment received.

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 and to generate Tables, Figures and Listings (TFLs).

All ICH required data in the database will be presented in data listings.

Depending on the analysis sets, all data from a subject or a subset of data may be excluded from certain analyses as defined in Section 9.2 (e.g., analyses based on the PP Analysis set).

Summaries of continuous variables will be in terms of the number of missing and non-missing observations, mean (with respective 95% confidence interval (CI), if applicable), standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum.

Categorical variables will be summarized using counts and percentages.

Analyses that use other descriptive statistics will be defined and described in the applicable SAP section.

Summary statistics of location parameters (e.g., mean, median, quartiles) will be reported to one more decimal place than the collected data. Summary statistics of variability (e.g., SD) will be reported to one more decimal place than the commensurate location parameter. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The SD of age will then be reported to 2 decimal places. Descriptive percentages and proportions will be displayed to one decimal place. Percentages and proportions to be tested will be calculated to 4 decimal places. Durations will be display to 1 decimal place.

The by-subject listings will be sorted by the treatment arm, subject number, and then by visit / date and time, or item number (if applicable).

Formatting for dates and times will be:

- Dates only – ddmmmyyyy;
- Times only – hh:mm or hh:mm:ss (as appropriate);
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate).

Generally, only data of pre-specified planned visits will be used in statistical summary analyses, and calculations of any derived parameters; data of unscheduled visits will be included in the listings only.

Actual, rather than planned, sampling time points will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of PK concentration data. Planned sampling time points will be used in the descriptive summaries and in mean and median plots. Concentration-time data will be listed according to actual sampling time points relative to dosing time.

Assessment windows will not be defined for classifying measurements obtained outside scheduled assessment times.

7.1 Coronavirus Disease 2019 (COVID-19) Impact

As it is expected that the COVID-19 pandemic will be ongoing during the conduct of the study, the impact of COVID-19 will be assessed and reported.

Primary Estimand

The primary estimand is defined in Section 10.1.1 and is taking into account intercurrent events such as:

- missed doses which might be caused by issues in the drug delivery to the patient due to COVID-19, the COVID-19 disease itself or COVID-19 vaccination scheduling/side effects (intercurrent event of non-compliance to treatment);
- early treatment or study discontinuation which might be caused by COVID-19 (intercurrent events of early treatment or study discontinuation).

Further events introduced by COVID-19 (for example concomitant medications used to treat COVID-19 or vaccinations) will be assessed in the Blind Data Review Meeting (BDRM) and might lead to an exclusion of a subject or subject's data from the PP Analysis Set which is the study analysis set defined for the supplementary analysis of the primary estimand. HAE attacks

will be also assessed during BDRM if those could be triggered by COVID-19 and decision will be made to exclude those subjects or subject's data from the PP Analysis Set.

Subject Disposition: Study Treatment Discontinuation or Study Discontinuation

Subjects who experience either study treatment discontinuation or study discontinuation due to COVID-19 will have the reason captured in the eCRF. On the appropriate eCRF form for study discontinuation ("Conclusion of Subject Participation" form) or eCRF form for treatment discontinuation ("End of Treatment" form) as reason 'Pandemic Related' can be selected. Cases of study treatment discontinuation or study discontinuation due to pandemic will be included in the summary of subject disposition.

Adverse Events

Adverse events associated with COVID-19, which can include a clinically significant laboratory finding like a positive test result for COVID-19, will be reported by investigators. COVID-19 associated adverse events are identified via MedDRA coding. Relevant adverse events will be identified for reporting by the following Standardised MedDRA Query (SMQ): COVID-19 (SMQ). All COVID-19 associated adverse events will be included in standard AE tables.

An overview summary table of COVID-19 associated treatment-emergent adverse events (TEAEs), including number and percentages of subjects as well as the number of events, will be provided for the Safety Analysis Set including for the following:

- Any TEAE (related/not related),
- Serious TEAE (related/not related),
- TEAE resulting in death (related/not related),
- TEAE leading to discontinuation of study treatment (related/not related),
- TEAE leading to study withdrawal (related/not related),
- TEAE by maximum severity (mild, moderate, severe, missing).

The following summary tables will be provided:

- TEAEs occurring within 7 days of COVID-19 vaccine administration by PT, Among Subjects Receiving COVID-19 Vaccination
- TEAEs excluding those occurring within 7 days of COVID-19 vaccine administration by PT.

The following listings of COVID-19 associated adverse events will be provided:

- Any AE,
- AEs within 7 days of COVID-19 vaccine administration.

Concomitant Medications

Concomitant medications used to treat COVID-19 associated adverse events will be flagged in the listing of prior and concomitant medications.

For concomitant medications which are linked to specific adverse events, the eCRF collects information to identify the specific adverse event (e.g., Adverse Event ID). As described in the Adverse Events section, relevant adverse events will be identified by the following Standardized MedDRA Query (SMQ): COVID-19 (SMQ).

For identification of COVID-19 vaccines the WHODrug Standardised Drug Grouping (SDG) '*Vaccines for COVID-19*' will be utilized, based on the WHODrug-Global dictionary version used for coding of prior and concomitant medications.

COVID-19 vaccinations will be listed by subject showing start and end date:time, dose, route, frequency, primary indication for the medication, and concomitant medication flag (Prior, Prior/Concomitant, Concomitant). If the vaccination manufacturer name is provided, it will be listed as well.

Further, a listing will be prepared including the date of COVID-19 vaccinations, along with date and time of previous and subsequent study treatment, date of first HAE attack after vaccination with corresponding HAE ID and date of first AE with AE ID after vaccination for all subjects in the Safety Analysis Set. If the vaccination manufacturer name is provided, it will be added.

Visit Modality and Missed Visits

Changes to subjects' visits caused by the COVID-19 pandemic will be captured for each subject in the eCRF on the "Visit" form. It can be determined if a visit was not done due to "Epidemic/Pandemic Related (Specify)" or if an visit contact mode/ modality changed due to Epidemic/Pandemic reason (Yes, No). The number of subjects with missed visits or alternate visit modality (e.g., remote visit) due to COVID-19 will be summarized by visit and overall and will be listed.

Protocol Deviations (PDs)

Protocol deviations due to the COVID-19 pandemic will be collected in the Clinical Trial Management System (CTMS) per the study specific Protocol Deviation plan.

Pandemic related protocol deviations are identified within CTMS by using the term "COVID-19" as the first term within the deviation description. In addition, the sub-category of 'other' will be chosen.

COVID-19-related protocol deviations will be summarized as sub-categories under existing categories of protocol deviations. All COVID-19 related protocol deviations will appear in the listing of protocol deviations and will be flagged. All PDs will be reviewed during Blinded Data Review Meeting (BDRM, see Section 9.2).

Overview of COVID-19 Impact

Number and percentages of subjects with at least one of the following due to COVID-19 will be summarized in an overview table:

- Subjects with Any COVID-19 Impact,
- Protocol Deviations,
- Missing Visit,
- Alternate Visit Modality,
- Study Treatment Discontinuation,
- Study Discontinuation,
- Any AEs/TEAEs,
- Any Serious AEs/TEAEs,
- Subjects received COVID-19 vaccine.

7.2 Multicenter Studies

Data from all participating sites will be pooled prior to analysis. Listings will include site information as part of the subject ID. The sites will not be considered in any analysis. There is no randomization stratification per site.

7.3 Treatment Descriptors

For table summaries displayed columns will be labelled and ordered:

- CSL312,
- Placebo,
- Total (not applicable for efficacy).

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 collected.

Only missing values for the primary efficacy endpoint (i.e., time-normalized number of HAE attacks) during Treatment Period will have an impact on the primary analyses of the comparison between CSL312 versus placebo. The time-normalized number of HAE attacks will be considered as missing for subjects who discontinued within 30 days after the first study drug administration.

The primary efficacy endpoint will be hardly missing due to the robust derivation rule (i.e., the normalization of the number of HAE attacks by time) and treatment policy strategy for the estimand. It is assumed that the outcomes for discontinued subjects are comparable to the outcomes for those who do not discontinue.

In the previous phase II study CSL312_2001 there was no pattern in the attacks under Placebo and CSL312 observed. It can be assumed from study CSL312_2001 that the attack rate for an observation period of > 30 days and < 6 months is comparable to the attack rate of ca. 6 months.

For secondary endpoints which are also based on the HAE attack rate the assumption above is subsequently also applicable.

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

8.1.1 Imputation of Non-Date Missing Data

Subjects with the assessment of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing and the event started on or after the first administration of study treatment it will be assumed to be "related". If the AE or SAE with missing relationship started before the first injection of study treatment (e.g., during Screening Period or Run-in Period), it will be considered as "not related" (realistic case). In listings these imputed relationships will be flagged.

For variables which determine the proportion of events e.g., Adverse Events, all subjects with a non-missing value in the respective analysis set will be included in the denominator when calculating the percentages, unless otherwise stated.

8.1.2 Imputation of Partial Dates

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

To determine if an AE is treatment-emergent, see rules in Section 11.2.

To determine the category for medications, see rules in Section 9.4.

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 8.3).

- The safety reference date is the treatment start date and will be used to calculate study day for safety 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.

- The efficacy reference date will be the same as the safety reference date and is the start date of the efficacy evaluation period.

8.2.2 Durations and Time to Event Data

Durations of an event (e.g., duration of an AE) will be calculated in days as:

- (event end date – event start date) + 1.

Thus, there will be no duration of 0. If start and end time are available, they will also be used to calculate the duration in hours or minutes. If start or end date are partially or completely missing duration will not be calculated.

For elapsed time (e.g., onset of AEs) use

- (event date – reference date) or
- event date:time – reference date:time if appropriate.

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. Determination of the baseline value also considers unscheduled visits during the Run-in Period or Screening Period.

All baseline measurements must have been collected prior to the first administration of study drug. Measurements that are obtained after the first study drug administration will be

considered post-baseline values. 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 will only be calculated for measures that have non-missing and valid baseline and post-baseline records.

Change from baseline is calculated as:

- visit value – baseline value.

Percentage change from baseline will be calculated as:

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

8.2.5 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during data set creation to re-assign assessments to other visits or time points based on such windows).

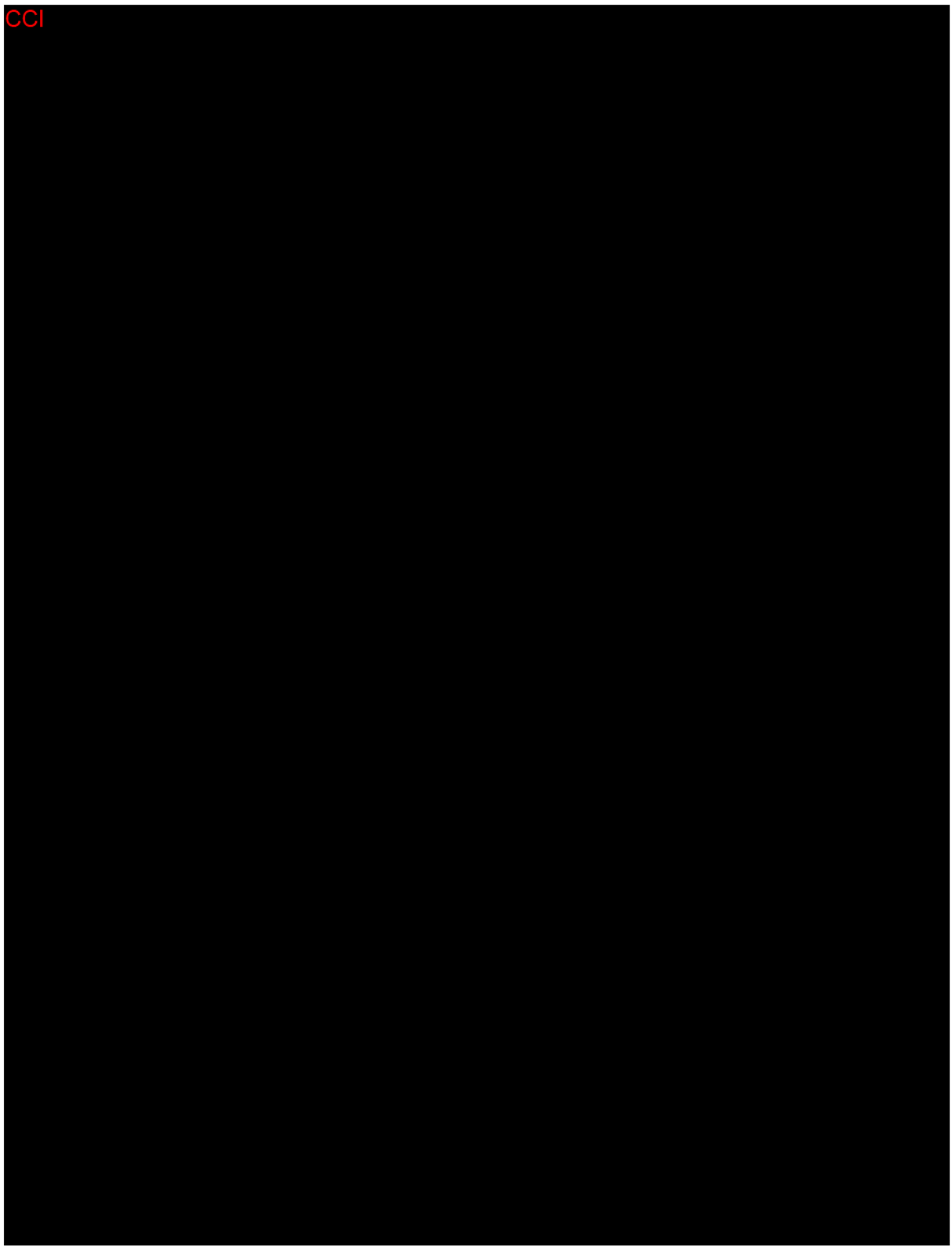
If a laboratory sample was repeated due to technical problems the results from the valid sample(s) for this visit will be used in the analysis. If a laboratory sample was repeated as safety follow-up to monitor abnormal values of the initial sample, the initial sample (revealing the abnormal values)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

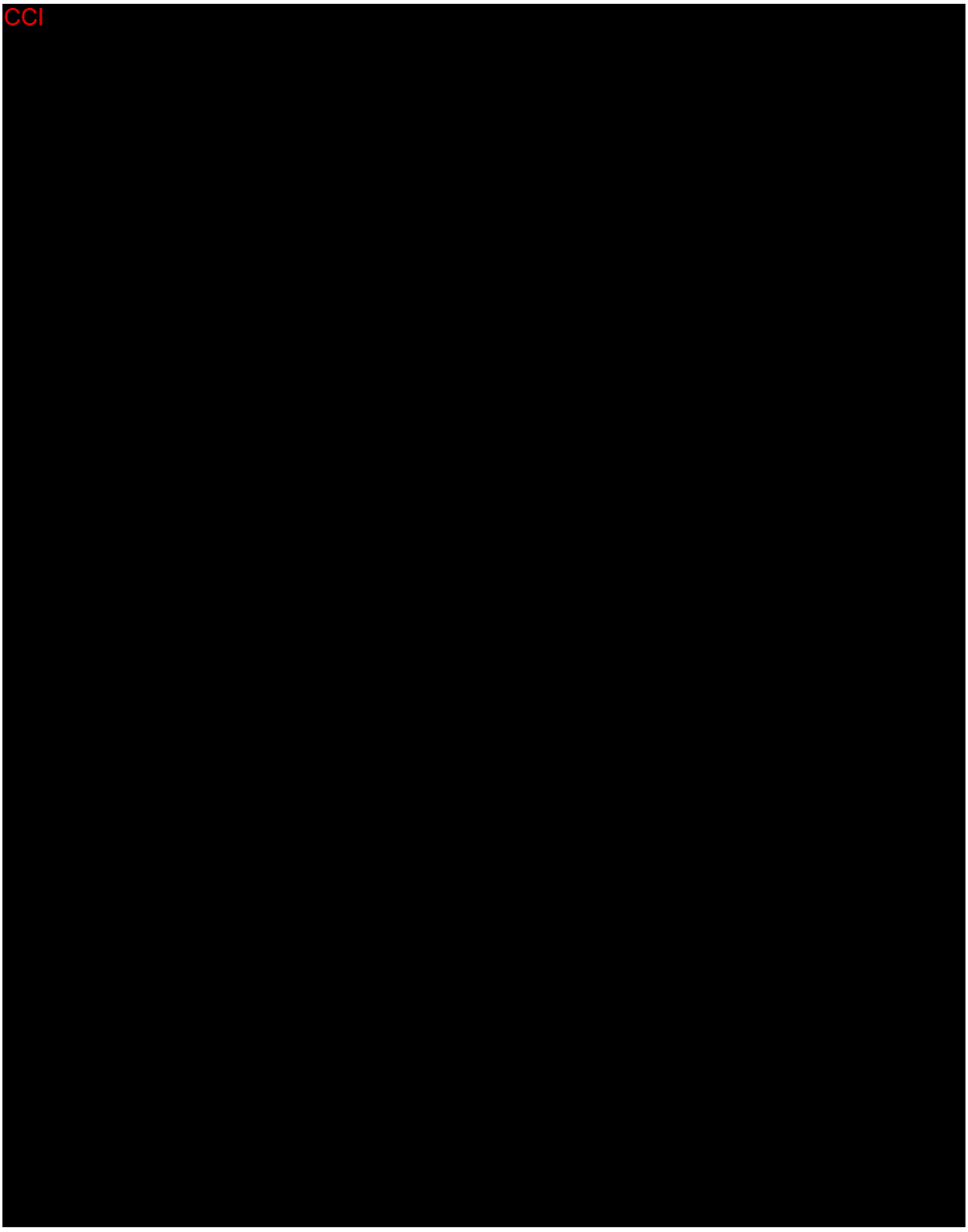
Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.6 Actual Treatment

Both, planned vial numbers integrated from IRT and the actual administered vial numbers will be collected via eCRF. After general unblinding the subjects' actual treatment will be derived from unblinded vial reports which include all vials with the vial number and actual treatment in those vials. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment.

If a subject receives a treatment different from the planned it will be decided during the Blinded Data Review Meeting on an individual base what will be considered the actual treatment.


CCI


CCI

CCI

[redacted]

8.2.12 BMI

Body Mass Index (BMI) will be provided via the eCRF and calculated using the following formula:

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

If only one or neither is available, then BMI is missing.

8.3 Study Periods relative to Treatment

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

Table 8 Overview Study Periods

Study Period	Start Date	End Date	Duration
Screening Period	date of Informed Consent	date/day on which eligibility for Run-in Period was confirmed	Day 1 Visit date of Run-in Period – date of Informed Consent
Run-in Period	date/day on which eligibility for Run-in Period was confirmed	date of the Day 1 Visit of Treatment Period	Day 1 Visit date of the Treatment Period or Date of Run-in Completion/Non-completion [whichever is first] – Day 1 Visit date of Run-in Period

Study Period	Start Date	End Date	Duration
Treatment Period/ Efficacy Evaluation Period	date of the Day 1 Visit of Treatment Period	date of the Day 182 Visit of the Treatment Period or the End of Study date for subjects who prematurely discontinued [whichever occurs earlier]	Day 182 Visit date of the Treatment Period or End of Study date [whichever is first] – Day 1 Visit date of the Treatment Period + 1
Follow-up Period	date of the Day 182 Visit of the Treatment Period	date of the Follow-up/ Final Visit (Day 242 Visit)	date of the Follow-up/Final Visit (Day 242 Visit) – date of the Day 182 Visit of Treatment Period
Safety Period	date and time of the first administration of investigational product	Date of End of Study	Date of End of Study - date of the first administration of investigational product

Technical Notes:

- Screening Period: The first day of the Run-in Period may occur on the same day as the Screening Visit for subjects meeting the eligibility criteria for the Run-in Period. Those subjects will then have no Screening Period.
- Run-in Period: The eCRF 'Study Completion' form will only be completed for subjects in the Treatment Period. Thus, if a subject is not eligible for treatment the Run-in Non-Completion is captured on the 'Treatment Period Inclusion Criteria' form.
- Follow-up Period: A Follow-up Period will be only available for subjects who did not roll over to CSL312_3002.

9 Study Population

9.1 Subject Disposition

The following summary will be provided by treatment arm and total using the Screened Analysis Set:

- The number and percentage of subjects who provided Informed Consent,
- The number and percentage of subjects screened,
- The number and percentage of subjects who entered the Run-in Period,
    - The number and percentage of subjects who discontinued from the study during the Run-in Period with reason for discontinuation (percentages based on the number who discontinued),
- The number and percentage of subjects who were not assigned to study treatment,
- The number and percentage of subjects who were randomized,

- The number and percentage of subjects who entered the Treatment Period (randomized and received loading dose),
    - The number and percentage of subjects who discontinued the study during the Treatment Period with reason for study discontinuation (percentages based on the number who discontinued),
    - The number and percentage of subjects who prematurely discontinue treatment during Treatment Period with reason for treatment discontinuation (percentages based on the number who discontinued),
    - The number and percentage of subjects who completed the treatment (6-month period with study drug administration once monthly),
- The number and percentage of subjects who completed the study,
- The number and percentage of subjects rolling over to the CSL312_3002 (open-label phase IIIb study),
- The number and percentage of subjects in Screened Analysis Set,
- The number and percentage of subjects in SAF Analysis Set,
- The number and percentage of subjects in ITT Analysis Set,
- The number and percentage of subjects in PP Analysis Set,
- The number and percentage of subjects in PK Analysis Set,
- The number and percentage of subjects in PD Analysis Set.

Technical Note: Subjects will be flagged as completed the study if "Did the subject complete the study?" answered with "Yes" on the EOS form.

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:

- Disposition (date of informed consent, date of eligibility for Run-in, date of randomization, date of first and last study drug administration, End of Treatment (EoT) date, End of Study (EOS) date, reason for treatment discontinuation and/or study discontinuation).
- Analysis Sets (included in Analysis Set: Screened Analysis Set (yes, no), ITT Analysis Set (yes, no), PP Analysis Set (yes, no), PK Analysis Set (yes, no), PD Analysis Set (yes, no), reason excluded from any analysis set).

9.2 Protocol Deviations

All identified protocol deviations throughout the study will be listed prior to database lock 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 blinded data review meeting (BDRM), the classification and the subject's assignment to any analysis set will be discussed in detail. The decisions made during the BDRM will be documented in the BDRM minutes and agreed upon prior to database lock for final analysis.

Table 9 Potential Protocol Deviations

Potential Protocol Deviations	Potential Exclusion From Analysis Set
Subject did not provide informed consent and/or informed consent date missing	Screening, SAF, ITT, PP, PK, PD
Subject randomized but not treated with study treatment	SAF, PP, PK, PD
Subjects treated with incorrect study treatment	PP, PK, PD
Subject randomized and treated but does not have at least one measurable PK concentration	PK
Subject randomized and treated but does not have at least one PD measurement	PD
Subject randomized and treated but without primary efficacy assessment	PP
Subject randomized and treated but violated inclusion and/or exclusion criteria	PP, (SAF, ITT, PK, PD)
Subject randomized and treated but compliance outside 80-120%	PP, (PK, PD)
Subject randomized and treated but received prohibited concomitant medication	PP, (PK, PD)
Subject with COVID-19 diagnosis	PP (SAF, PK, PD)

Protocol deviations caused by the COVID-19 pandemic will be documented throughout the entire study. They will be assigned as a separate protocol deviation category "other" with free-text "COVID-19" and discussed during the Blinded Data Review Meeting. COVID-19 related protocol deviations will be summarized and listed separately from all other protocol deviations and will also be discussed in the CSR.

Prior to the Blinded Data Review Meeting, 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 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 will be excluded from the respective analysis set.

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

- Randomized and actual treatment,
- all protocol deviations related to inclusion and exclusion criteria,
- all protocol deviations leading to exclusion from any analysis set,
- COVID-19 related protocol deviations,
- all other protocol deviations.

9.3 Demographic and Baseline Characteristics

The following summaries will be provided by treatment arm and total using ITT and PP Analysis Set:

- Demographic characteristics: sex, race, ethnicity, age, height and body weight at Screening, and body mass index at Screening.
- 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 before the start of prophylactic therapy, number of HAE attacks within 3 months before Screening, primary locations of HAE attacks in the last 3 months prior Screening.
- Medical history by system organ class (SOC) and preferred term (PT) – include medical history with an end date prior to informed consent date.
- Concomitant diseases by SOC and PT – include medical history with an end date after informed consent or flagged as ongoing.
- Stratification factors: age (≤17 year, >17), baseline HAE attack rate observed during the Run-in Period (1 to < 3 attacks /month, and ≥ 3 attacks/month).

Technical Note: The baseline HAE attack rate as used for randomization will not be captured in eCRF and can be only obtained from the unblinded randomization file at the end of the study and/or blinded randomization files, if available.

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

By-subject listings for all available data using the Screened Analysis Set will be provided for each category mentioned above and further for:

- Reproductive system findings (childbearing potential, method of birth control, date and time of pregnancy test, specimen type, and pregnancy test result).

Those listings will further contain an ITT and PP flag.

9.4 Prior/Concomitant Medications

Reported medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE, version used will be indicated in the corresponding TLF Shells). The summary of medications will show the number and percentage of subjects taking medication displayed for Anatomical Therapeutic Chemical (ATC) class level 4 and Preferred Term. If the level 4 ATC name is not available, then the level 3 ATC name will be used and if the level 3 ATC name is not available then the level 2 ATC name will be used.

The following classification of concomitant medication related to start date of study treatment period will be applied:

- Assign to 'Prior Only' if the concomitant medication start date and end date is prior to first study treatment start date; if the subject has not taken any study treatment; or the concomitant medication start date is missing and the concomitant medication end date is before the study treatment start date;
- Assign to 'Prior and Concomitant' if the concomitant medication start date is prior to first study treatment start date and the concomitant medication end date is on or after study treatment start date or ongoing treatment;
- Assign to 'Concomitant Only' if the concomitant medication start date is on or after the first study 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 study drug administration. If there is clear evidence to suggest that the medication started prior to the date of first study drug administration (the available parts of the date are prior to the corresponding parts of the date of first study drug administration), 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 study drug administration (the available parts of the medication end date are prior to the corresponding parts of the date of first study drug administration of study). If this is the case, the medication will be considered 'Prior Only'.

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 CRF 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 CRF form 'On-demand Treatment'.

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

Separate summaries and listings are planned for COVID-19 vaccines, see Section 7.1.

10 Efficacy Analyses

10.1 Analysis of Primary Endpoint

The primary endpoint is the time-normalized number of HAE attacks per month during the Treatment Period from Day 1 (first study drug administration) through Day 182 (inclusive).

Subjects will enter HAE symptoms into their eDiary, 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 or not an HAE attack occurred. If an attack occurred, then the investigator will record an attack in the eCRF form, the start/end date and time, the attack location(s), and the severity of the attack based on the most severe symptoms. For every visit, the investigator will report all HAE attacks that have occurred in the interim since the last visit the subject attended.
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.

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.

HAE attacks with a start date and time after the first study drug administration through Visit Day 182 (inclusive) or End of Study visit (whatever is first) will be counted for the Treatment Period and will be included in the analyses of efficacy.

The primary endpoint will be analyzed using the ITT and PP Analysis Set. The ITT Analysis Set will be used as the primary analysis and the PP Analysis Set will be used as the supplementary analysis (see Section 10.1.3).

The primary endpoint, time-normalized number of HAE attacks per month, is calculated per subject as:

[the number of HAE attacks / length of subject treatment in days] * 30.4375

where the length of subject treatment is calculated as:

[the date of Study Visit Day 182 or the End of Study date [whatever is first] – the date of Study Visit Day 1 of the Treatment Period +1].

To transform the length of subject treatment which are 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:

[the number of HAE attacks / length of subject treatment in days] * 365.25.

The time-normalized number of HAE attacks will not be calculated if the subject's observation time for the Treatment Period is less than 30 days, i.e. subject discontinued within 30 days after first study drug administration.

The randomization is stratified by the variables age (≤ 17 years, > 17 years) and, for adults, the subject's baseline attack rate (1 to < 3 attacks/month, and ≥ 3 attacks/month) during the Run-in period. Age and baseline attack rate are not regarded as confounder or effect modifier. The stratification by age is implemented to mitigate the risk that adolescent subjects could be randomized all to the same treatment, with worst case scenario that all adolescents are on placebo treatment. There is no significant physiological basis to suggest different efficacy or safety profiles in adults and adolescents and the distribution of attack locations in adolescent subjects typically mirrors that of adults [MacGinnitie, 2014].

It is expected that around 50% of subjects will have 1 to < 3 attacks/month and around 50% of subjects will have ≥ 3 attacks/month as baseline attack rate [Banerji, 2018]. Because of the stratified randomization these two subgroups of subjects will be equally distributed to the Active and to the Placebo arm. It is assumed that the treatment effect, i.e. the time-normalized number of HAE attacks observed under CSL312 treatment, is not impacted by the baseline attack rate. Nevertheless, the time-normalized number of HAE attacks will be compared for

the 6 months of the Active Arm and the 6 months of Placebo Arm using a Poisson Regression model including baseline attack rate as fixed effect in a sensitivity analysis, see Section 10.1.2.

10.1.1 Primary Estimand

The primary interest is to assess the treatment effect of CSL312 during treatment from Day 1 through Day 182 while subjects are allowed to treat HAE attacks with on-demand medications.

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

- Treatment Condition: monthly treatment of CSL312 or placebo
- Population: the target patient population defined by eligibility criteria and who were randomized (ITT).
- Variable: time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182.
  Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of any of the following intercurrent events:
  - administration of on-demand medication in addition to prophylactic treatment with CSL312,
  - Prohibited concomitant medications due or not due to COVID-19 or COVID-19 vaccination,
  - non-compliance to treatment due or not due to COVID-19 or COVID-19 vaccination,
  - early study discontinuation due or not due to COVID-19.
- Population-level summary: median time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182 by treatment.

If a subject discontinued the study early after being continuously the first 30 days in the treatment period, the observation is terminated by the Early Termination Visit. It is assumed that the attack rate for subjects, who discontinued the study after the 30th study day and before the end of the 6th month, is comparable to the attack rate from subjects who have the entire 6 months treatment period observed. This assumption is based on CSL312_2001 data which showed that the CSL312 treatment effect was maintained over time. Therefore, the primary endpoint will be considered measurable and not missing, ie, the time-normalized number of HAE attacks will be calculated based on the HAE attacks reported until the Early Termination Visit.

In case a subject discontinues study treatment due or not due to COVID-19 but continues participation in the study for more than 30 days beyond the last study drug administration,

the HAE attacks until the last study drug administration plus 30 days will be included in the HAE attack analysis and length of subject treatment in days will be derived as:

> [date of last study drug administration – the date of Study Visit Day 1 of the Treatment Period +31].

Missing data is only given if subjects discontinue the study within 30 days after the first study drug administration in the treatment period. An approach to handle these missing data by sensitivity analysis is described in Section 10.1.2.

During the BDRM, it will be assessed if subjects have missed subsequent study drug administrations and if this might lead to the exclusion of subject's data from the analyses. All decisions will be documented in the BDRM minutes.

A COVID-19 diagnosis and resulting intercurrent events are irrelevant for the primary estimand. All observed values will be used regardless of occurrence of any of the following COVID-19 related intercurrent events: medications given to treat COVID-19 or COVID-19 vaccinations. Non-compliance to treatment and early discontinuation will be handled the same independent if it is related to COVID-19 or not.

10.1.2 Primary Efficacy Analysis

Following the estimand described in Section 10.1.1, the primary efficacy endpoint between CSL312 and placebo is tested for a difference by comparing the time-normalized number of HAE attacks in the 6 months of the Active Arm and in the 6-month Placebo Arm period by using a two-sided Wilcoxon Test (Hierarchical Testing H01). The monthly CSL312 dose will be evaluated against monthly placebo at alpha = 5%:

$$H_{01}: a_1 = 0 \quad \text{versus} \quad H_{11}: a_1 \neq 0$$

In the above hypothesis, the term "a_1" is the shift between the 2 distributions of monthly CSL312 and monthly placebo.

The time-normalized number of HAE attacks per month and per year will be summarized descriptively for the 6 months of the Active Arm and the 6-month Placebo Arm period by median and mean with corresponding 95% CIs.

Sensitivity Analysis considering baseline attack rate

As a sensitivity analysis, the time-normalized number of HAE attacks will be compared for the 6 months of the Active Arm and the 6 months of the Placebo Arm using a generalized linear model (GLM) for count data assuming a Poisson distribution with the logarithm as link function and Pearson chi-square scaling of standard errors to account for potential over dispersion. The model includes treatment (categorical) and the time-normalized baseline attack rate during Run-in Period (continuous) as covariates. To account for the length of subject treatment, the logarithm of the length of subject treatment is used as an offset variable in the model:

$$\log \lambda_i = \log(t_i) + \beta' x_i$$

where λ_i is the expected number of HAE attacks of subject i (i = 1, …, n with n the number of subjects in ITT Analysis Set), $\log(t_i)$ is the offset with t_i as the length of the i-th subject treatment in days and x_i is the covariate of subject i which includes the time-normalized baseline attack rate of subject i and the treatment information of subject i.

From this model, the least squares mean time-normalized number of HAE attacks and the standard errors are estimated for CSL312 and placebo. The mean time-normalized number of HAE attacks ratio for CSL312 relative to the placebo and the corresponding 95% confidence interval are also estimated. To report as mean attack rate per month, the received estimates are transformed by the exponential function and scaled by time.

The mean time-normalized number of HAE attacks ratio for CSL312 relative to placebo and the corresponding 95% confidence interval estimated by the model described above will be used to calculate the percentage difference in the mean time-normalized number of HAE attacks for CSL312 from placebo as:

100% * (mean time-normalized number of HAE attacks ratio - 1).

The 95% CI for the percentage difference will be calculated with the estimated upper and lower confidence limits for the mean time-normalized number of HAE attacks ratio, transform by subtracting 1 and multiplying by 100%.

The sensitivity analysis considering baseline attack rate will be carried out using the ITT Analysis Set.

Technical Note: the time-normalized baseline attack rate during Run-in Period (continuous) will be derived as defined in Section 10.3.2.1.

Sensitivity Analysis for missing values

Missing values occur if the observation time for the treatment period is less than 30 days, i.e., a subject discontinued within 30 days after first study drug administration. Therefore, only a very low number of subjects with a missing primary endpoint are to be expected.

To assess the impact of missing data for the primary efficacy estimand a systematic approach will be applied. For each treatment arm, a range of values for the number of time-normalized HAE attacks per month from 0 to 6 subdivided into 9 increments between two consecutive integer values will be generated. All possible combinations from the subdivided ranges will be imputed to replace the missing values. For the comparison of active treatment versus placebo, observed and imputed data will be analyzed using the Wilcoxon Test and results will be classified into negative (i.e., placebo significantly better), neutral (i.e., no significant difference) and positive (i.e., active treatment significantly better).

A graph where the x-axis presents the subdivided range for placebo and the y-axis the subdivided range for the active treatment will visualize all scenarios and distinguished the different outcomes by different colors and symbols. The total number of subjects with missing outcome in placebo and active treatment arm will be added to the graph. This sensitivity analysis will only be applied to the ITT Analysis Set.

10.1.3 Supplementary Analyses of Primary Estimand

The primary estimand described above is complemented by an additional supplementary estimand and analysis.

Only subjects in the PP Analysis Set will be included. The interest is to assess the treatment effect of CSL312 during treatment from Day 1 through Day 182 while subjects are allowed to treat HAE attacks with on-demand medications but excluding subjects who do not comply with the protocol.

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

- Treatment Condition: monthly treatment of CSL312 or placebo.
- Population: the target subject population defined by eligibility criteria, who were randomized, received at least 1 dose of CSL312 and who comply with the protocol (PP).
- Variable: time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182.
- Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of any of the following intercurrent events:

  - administration of on-demand medication in addition to prophylactic treatment with CSL312,
  - early study discontinuation due or not due to COVID-19.
- Population-level summary: descriptive statistics of the time-normalized number of HAE attacks during treatment from Day 1 through Day 182 by treatment.

When a subject who was at least 30 days in the treatment period after the first study drug administration discontinues study treatment due or not due to COVID-19 but stays beyond the last study drug administration in the study for more than 30 days, the HAE attacks until the last study drug administration plus 30 days thereafter will be included in the supplementary analysis of the primary estimand.

If a subject has a COVID-19 infection while participating in the study, his/her attacks will be assessed during the BDRM to determine if they might be caused/triggered by other factors, e.g.COVID-19. If there is clear evidence that they are due to the COVID-19 infection or other, they might be excluded from the analyses. Missed study drug administrations not due or due to COVID-19 or COVID-19 vaccination might also lead to the exclusion of a subject or subject's data from the supplementary analysis as well as prohibited concomitant medications due or not due to COVID-19 or COVID-19 vaccination.

10.2 Subgroup Analyses

If ≥ 5 Japanese subjects are enrolled to the study, the following subgroup analysis will be carried out for Japanese and all subjects:

- Descriptive analysis of the primary endpoint: time-normalized number of HAE attacks per month during the Treatment Period, see Section 10.1;
- Descriptive analysis of the reduction in attack rate during the Treatment Period, see Section 10.3.2.1;
- Descriptive analysis of time-normalized number of HAE attacks requiring on-demand treatment, see Section 10.3.2.2;
- Overview summary of TEAEs, see Section 11.2;

If ≥ 5 Japanese subjects are enrolled to the study, the following subgroup analysis will be carried out for Japanese/non-Japanese subjects:

- Summary for CSL312 concentrations, see Section 12.1.

Summaries for CSL312 concentrations will further be stratified by Age group (adolescent [12 to $\leq$ 17 years] and adult [>17 years] subjects), see Section 12.1.

10.3 Analysis of Secondary Endpoints

Efficacy secondary endpoints are:

- 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,
- Time-normalized number of HAE attacks at various time points during the treatment period,
- CCI [redacted].

Safety secondary endpoints are:

- AEs,
- AESIs,
- SAEs,
- CSL312 induced anti-CSL312 antibodies,
- Clinically significant abnormalities in laboratory assessments (ie, laboratory abnormalities reported as AEs).

10.3.1 Secondary Estimand

No secondary estimand is defined.

10.3.2 Secondary Efficacy Analysis

Secondary efficacy endpoints will be analyzed for ITT Analysis Set.

10.3.2.1 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 * [1 – (time-normalized number of HAE attacks per month during Treatment Period/ time-normalized number of HAE attacks per month during Run-in Period)]

with time-normalized number of HAE attacks per month during Treatment Period as defined in Section 10.1 and with time-normalized number of HAE attacks per month during Run-in Period defined as:

> [the number of HAE attacks during Run-in Period / length Run-in Period in days] * 30.4375

where the length of subject's Run-in Period is calculated as:

[Day 1 Visit date of the Treatment Period or Date of Run-in Completion/Non-completion [whichever is first] – Day 1 Visit date of Run-in Period]

for the entire 6-months Treatment Period and will be summarized and tested via a two-sided Wilcoxon Test with alpha = 5%.

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

The number and percentage of subjects with a percentage reduction of 100%, ie, who do not experience a HAE attack and so are attack-free, will be presented and summarized with corresponding 95% CI for the 6-month Treatment Period, a Fisher-Test will be performed to assess for differences between treatment arms.

The number and percentage of subjects who do not experience a HAE attack in the first 3 months after first study drug administration and so are attack-free will be presented and summarized with corresponding 95% CIs. A Fisher-Test will be performed to assess for differences between treatment arms (Hierarchical Testing H03).

The same analysis will be repeated for the second 3 months after first study drug administration.

10.3.2.2 The time-normalized number of HAE attacks requiring on-demand treatment

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

100 * [1 – (number of HAE attacks requiring on-demand treatment during Treatment Period/ length of subject treatment in days)] * 30.4375

and annualized time-normalized number of HAE attacks requiring on-demand treatment is calculated as:

100 * [1 – (number of HAE attacks requiring on-demand treatment during Treatment Period / length of subject treatment in days)] * 365.25.

Both will be summarized descriptively for the 6-month Treatment Period. Differences between the treatment arms will be tested in an exploratory manner via a two-sided Wilcoxon Test with alpha = 5%.

An HAE attack requiring on-demand treatment is defined as an attack for which the date of administration of an on-demand treatment is between the start (including) and end date (including) of a HAE attack.

Technical Note: Use answer for "On demand treatment taken?" from CRF form "HAE attack" to flag HAEs requiring on-demand treatment.

10.3.2.3 The time-normalized number of moderate or severe HAE attacks

For the analysis of the time-normalized number of moderate or severe HAE attacks, an analogue calculation and analyses as described in Section 10.3.2.2 will be done considering all HAE attacks classified as moderate or severe.

10.3.2.4 Time-normalized number of HAE attacks at various time points during the Treatment Period

The time-normalized number of HAE attacks (per month and annualized) during, the first 3-months Treatment Period and the second 3-months Treatment Period will be summarized descriptively and compared between the treatment arms using a two-sided Wilcoxon Test with alpha = 5%.

The time-normalized number of HAE attacks (per month) for the different Treatment Periods is calculated for a subject as:

[number of HAE attacks within first 3-months or second 3-months Treatment Period/ length of subject treatment in days] * 30.4375

and the time-normalized number of HAE attacks (annualized) as:

[number of HAE attacks within first 3-months or second 3-months Treatment Period/ length of subject treatment in days] * 30.4375

with length of subjects treatment in days derived as:

- First 3-months Treatment Period: [the date of Study Visit Day 91 or the End of Study date [whatever is first] – the date of Study Visit Day 1 of the Treatment Period +1];

- Second 3-months Treatment Period: [the date of Study Visit Day 182 or the End of Study date [whatever is first] – the date of Study Visit Day 91 of the Treatment Period].

Technical Note: A subject who discontinued in the first three months of Treatment Period will have a time-normalized number of HAE attacks for the first 3-months but not for the second 3-months Treatment Period.

The percentage reduction in the time-normalized number of HAE attacks for the Active Arm compared to the time-normalized number of HAE attacks for the Placebo Arm (between subjects) will be calculated as:

100 * [(mean time-normalized number of HAE attacks for CSL312 - mean time-normalized number of HAE attacks for Placebo) / mean time-normalized number of HAE attacks for Placebo]

and

100 * [(median time-normalized number of HAE attacks for CSL312 - median time-normalized number of HAE attacks for Placebo) / median time-normalized number of HAE attacks for Placebo].

The 95% two-sided Confidence Intervals for the relative difference in means and medians will be calculated by using the estimated upper and lower confidence limits for the corresponding time-normalized number of HAE attacks ratio, transform by subtracting 1 and multiplying by 100% [Beyene & Moinedding, 2005, Price & Bonett, 2010].
The percentage reduction will be calculated for the time-normalized number of HAE attacks between the Active Arm and the Placebo Arm for the 6-month Treatment Period (Hierarchical Testing H02), as well as for the first 3 months and the second 3 months of the Treatment Period.

10.3.3 Supplementary Analyses of Secondary Endpoints

The secondary endpoints:

- percentage reduction in the time-normalized number of HAE attacks,
- number and percentage of subjects with percentage reductions of ≥ 50%, ≥ 70%, and ≥ 90%,
- time-normalized number of HAE attacks per month requiring on-demand treatment,
- the time-normalized number of moderate or severe HAE attacks,

(see Section 10.3.2.1, Section 10.3.2.2, Section 10.3.2.3) will be further summarized separately for the first 3 months Treatment Period (Study Day 1 to Day 91), as well as the second 3 months Treatment Period (Study Day 92 to Day 182).

Supplementary Analysis of Secondary Endpoints will be conducted for ITT Analysis Set.

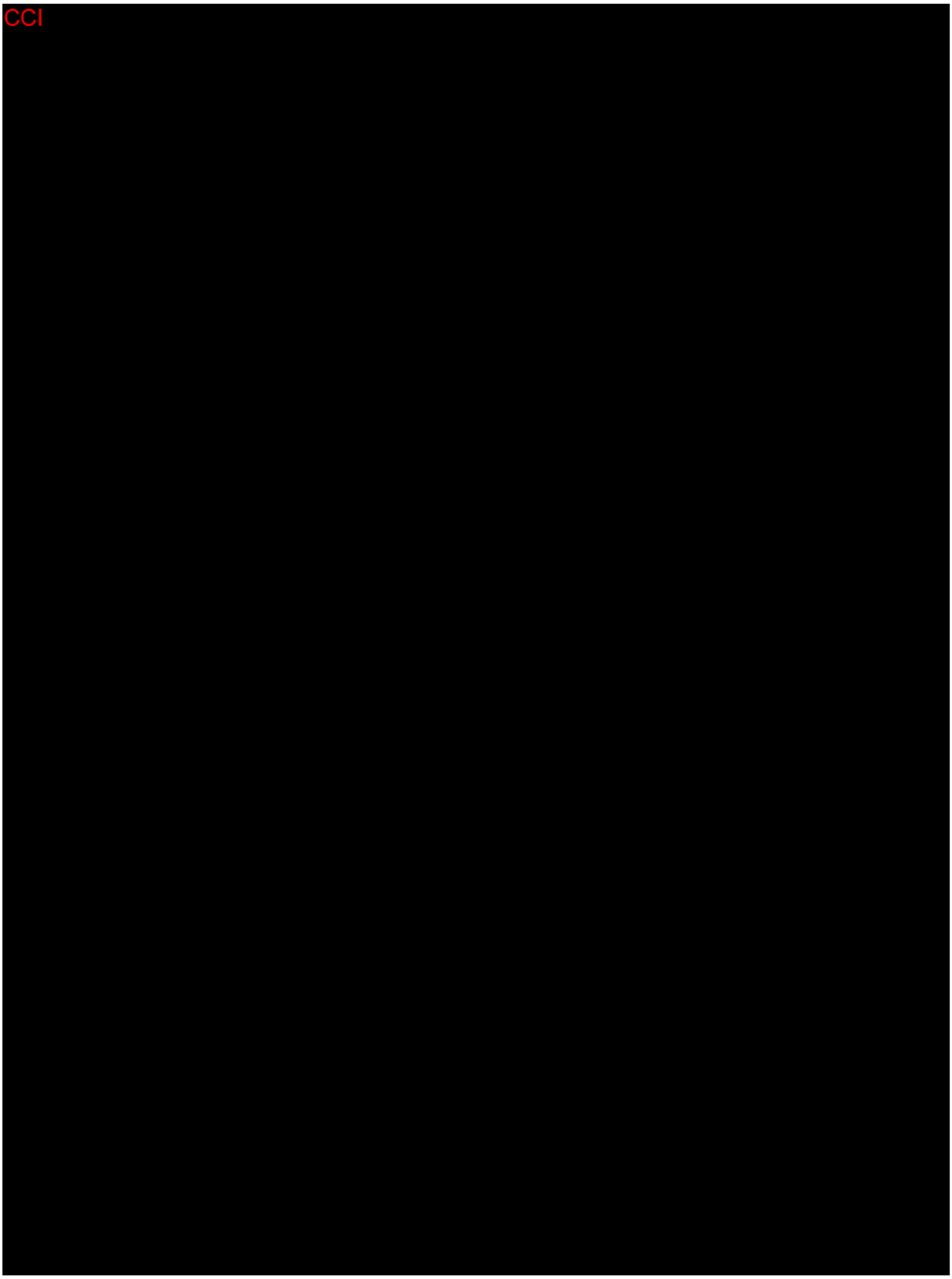
HAE attacks

The number and percentage of mild, moderate, and severe HAE attacks will be presented as well as the time-normalized number of mild, moderate, and severe HAE attacks during Run-in Period and Treatment Period.

A by-subject listing will show all details per HAE attack sorted by treatment arm, subject-ID and HAE Attack ID including: nominal visit, start and end date:time, anatomical location, severity, on demand treatment taken, potential trigger for this HAE attack.

An additional listing will present absolute number and time-normalized number of all, mild, moderate, and severe HAE attacks per Run-in Period and Treatment Period, duration of Run-in Period and Treatment Period as used for time-normalization for each subject.

CCI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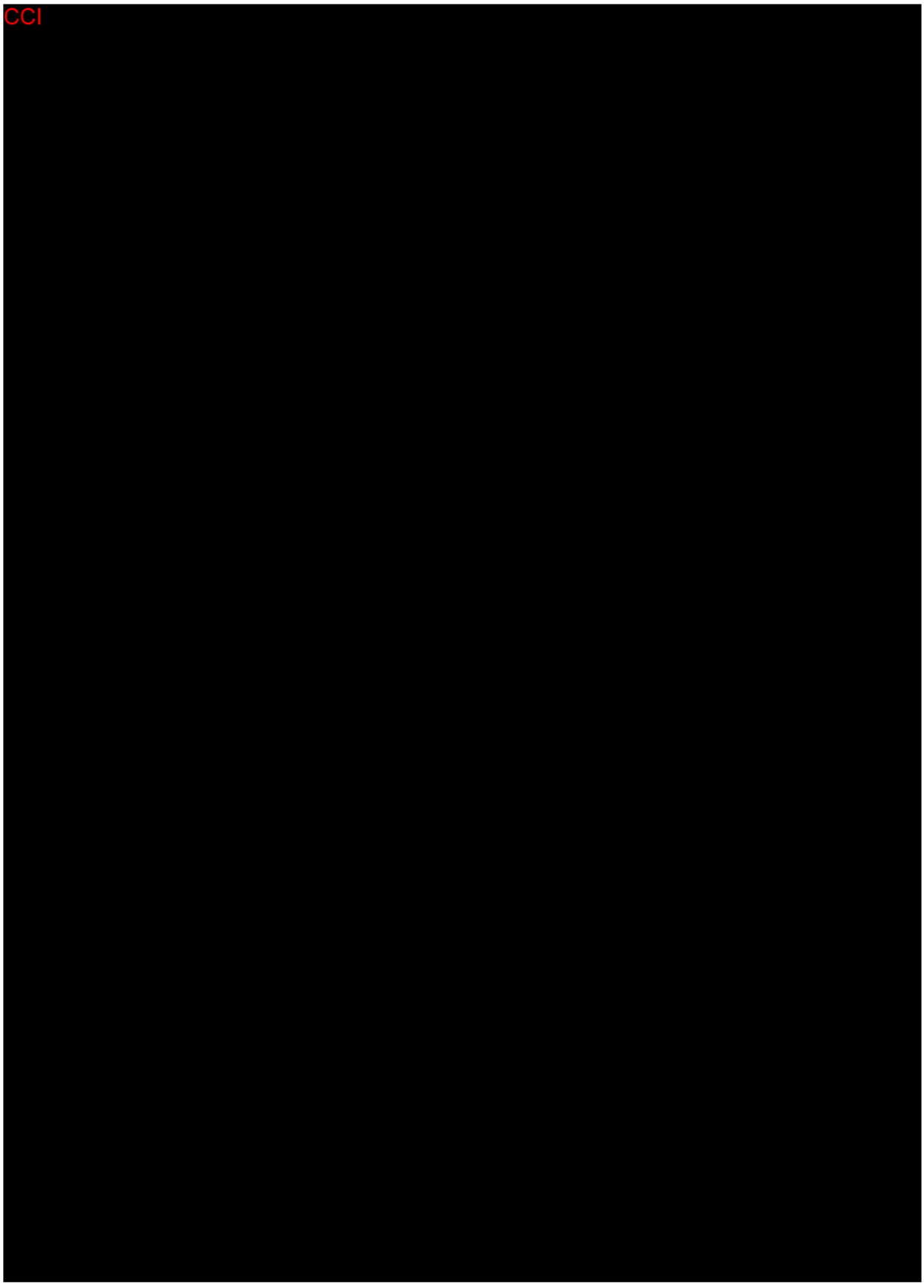

Time to first HAE attack after Day 1 and after Day 15 during Treatment Period

Time to first HAE attack after Study Day 1 and after Study Day 15 during Treatment Period will be analyzed using the Kaplan-Meier method. Time to first HAE attack after Day 1 will be derived as:

Date of first HAE attack after Study Day 1 – Date of Study Day 1,

and Time to first HAE attack after Day 15 will be derived as:

Date of first HAE attack after Study Day 15 – [Date of Study Day 1 + 14].

Subjects with no HAE attack will be censored at Visit Day 182 or at End of Study Visit (whatever is first). Kaplan-Meier (KM) curves with 95% CI will be plotted by treatment arm showing the percentage of subjects having no attack (subjects under risk) over study days. The corresponding life table will be presented. The median time, the 25% and 75% percentile times until the first HAE attack will be calculated for each treatment arm based on the KM approach. The median time ratio will be calculated for CSL312 against placebo. Summary table will further include minimum and maximum times to the first attacks.

10.5 Multiple Comparisons and Multiplicity

Four test one for the primary endpoint (H01) and 3 for the 3 secondary endpoints (H02, H03, H04) will be performed in a hierarchical order with an 2-sided alpha of 5% each, see Section 4.2. Four null hypotheses are defined:

- H01: the time-normalized number of HAE attacks in the first 6-month time period of the Active Arm and in the Placebo Arm period are equal.
- H02: the percentage reduction in means of the time-normalized number of HAE attacks for the 6-months of the Active Arm compared to the 6-month Placebo Arm period are equal.
- H03: the number of subjects who do not experience a HAE attack in the first 3 months of the Active Arm and the first 3-months of the Placebo Period are equal.
- H04: the percent of subjects with good or excellent responses to the CCI at the end of Treatment Period (Day 182) are equal for subjects treated with CSL312 and placebo.

The general process flow of the hypothesis testing is as follows:
the null hypothesis associated with the primary endpoint H01 will be tested first. If and only if the resulting 2-sided p-value is < 0.05, testing of H02 will be performed. If and only if H02 can be rejected (2-sided p-value < 0.05), H03 is tested at 2-sided alpha of 5%. If and only if H03 can be rejected (2-sided p-value < 0.05), H04 is tested at 2-sided alpha of 5%.

This hierarchical testing procedure controls for the overall alpha level of 5%. All other tests will be performed with 2-sided alpha of 5% in an exploratory manner.

10.6 Treatment Compliance

Compliance will be summarized for the Safety Analysis Set for all injections administered during the Treatment Period.

The 1.2 mL prefilled syringes contain 200 mg garadacimab (CSL312) at a concentration of 170 mg per 1 mL. A loading does will be administered by the use of two pre-filled syringes and every subsequent dose will be administered by use of one pre-filled syringe. In eCRF only the information is collected if one or two syringes have been administered and if the full volume of the study drug for that injection was administered (Yes, No). The actual administered mL is not documented.

Technical Note: The loading dose will be treated as one injection for all calculations defined in this SAP even though the administration will require the use of two syringes and will have two kit numbers recorded in the CRF.

Thus, treatment compliance will be based on number injection with 'was the full volume of the study drug administered' answered with 'Yes' in relation to the planned number of injections.

Treatment compliance for each subject will be derived for the Treatment Period as:

Treatment compliance (%) = 100 × (Number of injections with full volume administered / Total planned number of injections),

with Total planned number of injection is 6 per CSP (once per month within 6-month Treatment Period).

Treatment Compliance as well as details for device malfunctions or other errors will be summarized using descriptive statistics along with further exposure data (see Section 11.1).

11 Safety Analyses

Safety data will be summarized using the Safety Analysis Set.

11.1 Extent of Exposure

Exposure and Treatment Compliance (see Section 10.6) will be descriptively summarized by treatment arm:

- Number of SC injections received,
- Treatment Compliance (%),
- Treatment Compliance categories (<80%, 80 - 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.

Listings of individual subject data will present all injection records for Safety Analysis Set.

11.2 Adverse Events

AEs will be coded using the MedDRA dictionary. Treatment-emergent AEs (TEAEs), defined as AEs starting on or after the date (and time if available) of the first study drug administration, will be summarized. All AEs regardless of whether they were treatment-emergent or not will be listed.

AEs with completely or partially missing date or time 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 drug. AEs with completely missing start dates will be considered treatment-emergent. If only the day is missing, and the start month and year of the

AE is before the start month and year of the first administration of study drug, the AE will be considered non-treatment-emergent. If day and month are missing and the start year of the AE is before the year of the first administration of study drug, the AE will be considered non-treatment-emergent.

Summaries of TEAEs will count the number of subjects, that is, subjects with multiple occurrences of the same TEAE will be counted once in the total of those experiencing this PT. Similarly, a subject with 1 or more PT in a SOC will be counted once in the total of those experiencing PTs in that SOC.

Injection site reactions (ISRs) will be summarized by SOC and PT forming a virtual SOC "Injection Site Reactions". To decide which PTs will be considered ISRs, CSL will be provided a list in Excel format of all PTs found in the data base. CSL will review this list and mark the PTs considered ISRs in a column of this Excel sheet. The PTs summarized as ISRs will also be reported in their original MedDRA SOC. For the "Any TEAE" entry, the ISR will be reported once; they will not be counted in both their original and virtual SOC. ISRs will be presented as first "SOC" following the "Any TEAE" entry. The MedDRA SOCs and PTs will be presented in descending frequency of the overall CSL312 category. Within the same frequency, SOCs and PTs will be ordered alphabetically.
Overview summaries of TEAEs will be provided by treatment arm and total summarizing:

- Any TEAEs;
    - TEAEs related to study drug;
    - TEAEs leading to study discontinuation;
    - TEAE temporally related (onset within 24h after start of study drug administration);
    - TEAEs by severity (Mild, Moderate, Severe);
    - TEAEs by outcome (Death, Not Recovered or Not Resolved, Recovered or Resolved, Recovered or Resolved with Sequelae, Recovering or Resolving, Unknown);
    - TEAE identified as Injection Site Reaction (ISR);
        - ISRs related to study drug;
        - ISRs by severity;
- Any Serious TEAEs (SAEs);
    - SAEs related to study drug;
    - SAEs leading to study discontinuation;
    - SAE temporally related;
    - SAEs by severity (Mild, Moderate, Severe);
    - SAEs by outcome (Death, Not Recovered or Not Resolved, Recovered or Resolved, Recovered or Resolved with Sequelae, Recovering or Resolving, Unknown).

The following summary tables will be provided:

- All TEAEs by SOC and PT,
- All TEAEs leading to study discontinuation by SOC and PT,
- All TEAEs by severity and by SOC and PT,
- All TEAEs related to study drug by SOC and PT,
- All AESI by SOC and PT,
- All ISRs by SOC and PT,
- All SAEs by SOC and PT,
- All Non-serious TEAEs by SOC and PT,
- Laboratory Findings reported as AEs,
- All AEs caused by COVID-19 (see Section 7.1),
- TEAEs occurring 7 days of COVID-19 vaccine administration (see Section 7.1),
- All TEAES excluding TEAEs occurring within 7 days of COVID-19 vaccine administration.

Summaries will include the number and percentage of subjects, the number of TEAEs, and the number of TEAEs per injection and per subject year (where applicable) derived as:

$$\text{TEAE rate per SC Injection (AERI)} = \frac{\text{Number of Events for particular SOC/PT}}{\text{Number of SC Injections}};$$

$$\text{and TEAE rate per Subject SC Year (AERS)} = \frac{\text{Number of Events for particular SOC/PT}}{\text{Subject SC years}}.$$

where subject SC years will be the sum of the time in years that subjects were exposed to study drug administered by SC injections derived as:

[date of Study Completion or date of study discontinuation [whatever is first] – the date of Study Visits Day 1 within Treatment Period +1] / 365.25.

All AEs (treatment-emergent and non treatment-emergent) will be listed including MedDRA SOC, PT and verbatim, AE start and end date:time, duration of AEs in days, intensity, serious status, relationship to study drug, outcome, action taken, and AE flags (TEAES, SAE, AESI, clinically significant laboratory finding, temporal relationship).

The following listings will be provided:

- All Non-TEAEs,
- All TEAEs,
- All TEAEs leading to study discontinuation,
- All TEAEs related to laboratory findings,
- All TEAEs caused by COVID-19,

- All SAEs,
- All SAEs with fatal outcome,
- All TEAEs occurring within 7 days of COVID-19 vaccine administration.

11.3 Clinical Laboratory Evaluations

Laboratory tests will be summarized descriptively by scheduled visit and treatment arm. For laboratory tests with continuous values, descriptive statistics for the measured values and for change from baseline will be presented. Definition of the baseline assessment can be found in Section 8.2.3. Laboratory tests with categorical values will be summarized by number and percentage of subjects in the respective categories (based on subjects of the Safety Analysis Set with non-missing values at this Study Visit). Summary tables will be provided for hematology, biochemistry, coagulation, and immunogenicity (binding antibodies: inhibitory and non-inhibitory; specific to FXIIa inhibitor monoclonal antibody, anti-CSL312) and urinalysis. All laboratory test results (scheduled and unscheduled) will be listed.

The listings 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.

The laboratory tests will be presented in the following grouping and sequence as specified in Table 4 of the CSP. The test names used in the TFL outputs may differ depending on the terminology used by the central laboratory. The test names and units as provided in the laboratory data transfer will be used.

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

11.4 Other Safety Measures

11.4.1 Vital Signs

Systolic and diastolic blood pressure, respiratory rate, pulse rate, temperature, height, and body weight will be collected as vital signs.

Vital Signs will be presented in standard units and in alphabetical order. Summaries to be produced will be:

- descriptive statistics for vital signs at each scheduled visit and change from baseline (visit value – baseline value).

Listings to be produced are:

- vital signs results and change from baseline by nominal visit, visit date and time.

11.4.2 ECG

All ECG findings will be summarized by treatment arm and listed by subject including nominal visits, assessment date and time, clinically significant and abnormal status (Yes, No) and related AE ID.

11.4.3 Physical Examination

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

12 Pharmacokinetic Analyses

Plasma samples for CSL312 concentrations will be collected during Treatment Period at the following study visits: Day 1, Day 31, Day 61, Day 91, Day 121, Day 151, Day 182 and Day 242 (if applicable).

All analyses in this section will be based on the PK Analysis Set and will be only conducted for subjects treated with CSL312.

12.1 Drug Concentration Measures

The summaries will be given by nominal time points (planned time points) with descriptive statistics: mean, SD, percent coefficient of variation, median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean and its respective 90% CI.

The geometric coefficient of variation will be expressed as a percentage and will be calculated as $100*\text{sqrt}(\exp(SD_{log}^2)-1)$. The geometric mean and its 90% CI will be calculated by log-transforming the data, calculating the mean and the lower and upper limits of the 90% Wald CI of the log-transformed data, and subsequently back transforming the mean and the lower and upper limits.

The summaries for CSL312 concentrations will be also stratified according to the following:

- Age (adolescent [12 to ≤ 17 years] and adult [>17 years] subjects),
- Region (Japanese and non-Japanese subjects).

Below lower Limit of Quantification (BLQ) of CSL312 plasma concentrations will be handled as follows:

- pre-dose BLQ results (prior first study drug administration) will be treated as zero;
- all other post-dose BLQ results will be set to missing.

If in total more than 50% of the values at a nominal time point are imputed (i.e., BLQ) or missing, then the summary statistics will not be displayed.

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

All concentrations results will be listed by subject, including actual sampling date and time, nominal time point and actual time from end of previous injection. BLQ results will be listed as "BLQ".

13 Pharmacodynamic and Biomarkers Analyses

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

13.1 Pharmacodynamic Analyses

Samples for FXII concentrations and FXIIa-mediated kallikrein activity will be collected during Treatment Period at the following study visits: Day 1, Day 31, Day 61, Day 91, Day 121, Day 151, Day 182 and Day 242 (if applicable).

The summaries will be given by nominal time points (planned time points) and by treatment arm with descriptive statistics: mean, SD, percent coefficient of variation, median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean and its respective 90% CI. All PD concentration results will be listed by subject, including actual sampling date and time, nominal time point and actual time from end of previous injection.

Mean (± SD) concentration/activity-time profiles will be plotted using nominal (planned) time. FXIIa-mediated kallikrein activity % of Baseline values will also be provided in the listings, summaries, and figures.

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

13.2 Biomarker Analyses

Samples collected during Treatment Period at the following study visits: Day 1, Day 31, Day 61, Day 91, Day 121, Day 151, Day 182 and Day 242 (if applicable) will be stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion of the study.

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

14 Pharmacokinetic/Pharmacodynamic Analyses

PK / PD modelling will be explored, as feasible, for further time-dependent characterization of PK versus PD endpoints and / or safety / efficacy endpoints and reported separately.

Additional information on PK / PD analyses will be provided separately in the Modeling and Simulation Analysis Plan.

15 References

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Signature Page

CSL312_3001 - Statistical Analysis Plan - V1.0 - 21Apr2021

Signed By	Date (GMT)
PPD	22-Apr-2021 08:20:41
Approved-PPD Approval	
PPD	22-Apr-2021 10:57:28
Approved-Clinical Development Physician Approval	

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