STATISTICAL ANALYSIS PLAN

Study Title: **A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with hereditary angioedema**

Investigational Medicinal Product: CSL312 (Factor XIIa Antagonist Monoclonal Antibody)

Protocol Number: CSL312_2001

Version: 2.0 FINAL

Version Date: 19-JUN-2020

Sponsor:

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
1.0	01/APR/2020		N/A – First Version
2.0	19/JUN/2020	PPD	Incorporation of Protocol Amendment 2; Assignment of concomitant medication; COVID-19 related modifications; combination of 2nd and 3rd interim analysis; editorial changes.

2 List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
CCI	CCI
AESI	AE of Special Interest
CCI	CCI
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}tau}$	Area under the concentration-time curve in one dosing interval
BMI	Body Mass Index
C4	Complement Component 4
CDISC	Clinical Data Interchange Standards Consortium
CL_{tot}	Total Systemic Clearance
C_{max}	Maximum Concentration
COVID-19	Corona Virus Disease 2019
CI	Confidence Interval
CSR	Clinical Study Report
EMA	European Medicines Agency
ESP	External Service Provider
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FXII(a)	(Activated) Factor XII
HAE	Hereditary Angioedema
CCI	CCI
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
CCI	CCI
IRT	Interactive Response Technology
ISR	Injection Site Reaction
ITT	Intent-to-Treat Population
IV	Intravenous(ly)
MCMC	Markov-Chain Monte Carlo
CCI	CCI

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
PK	Pharmacokinetic
PP	Per-Protocol Population
PT	Preferred Term
CCI	CCI
q2wk	Administered Every 2 Weeks
q4wk	Administered Every 4 Weeks
SAE	Serious AE
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
CCI	CCI
SOC	System Organ Class
$T_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
TEE	Thromboembolic Event
TFL	Tables, Figures, and Listings
T_{max}	Time of C_{max}
V_z	Volume of Distribution During the Elimination Phase
CCI	CCI

3 Purpose

This SAP provides a detailed and complete description of the planned statistical analyses for the Independent Data Monitoring Committee (IDMC), the interim, and final analysis of the study CSL312_2001 to support the Clinical Study Report (CSR). Mock tables, figures, and listings (TFL) shells will be provided in separate supporting document.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the following study documents:

- Study Protocol Amendment 2 (dated 20 March 2020);
- Electronic Case Report Form (eCRF) (dated 11 May 2020).

The "Guideline on Missing Data in Confirmatory Clinical Trials" (European Medicines Agency [EMA] dated 2 Jul 2010) is relevant for analysis methodologies for missing data for the primary efficacy comparison.

Further detailed Pharmacokinetic (PK)-CCI analyses will be described in the Modeling and Simulation Analysis Plan.

All decisions regarding the IDMC, interim, and final analysis of the study results, as defined in SAP 1.0 document, have been made within 2 months after the first subject will be entered the Run-in period.

SAP 2.0 was issued following Protocol Amendment 2.

4 Study Design

4.1 Study Design

This is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study to investigate the clinical efficacy, PK, and safety of CSL312 as prophylaxis to prevent hereditary angioedema (HAE) attacks in subjects with C1-esterase inhibitor (C1-INH) deficiency HAE or HAE with normal C1-INH and factor XII or plasminogen gene mutation (FXII/PLG). As presented in Figure 1, the study consists of a Screening Period, a Run-in Period, 2 treatment periods, and a Follow-up Period.

The following interim analyses are planned, with the sequence depending on subject recruitment:

- after the last C1-INH subject who participated in the blinded part of the study has completed Treatment Period 1;
- after the last C1-INH subject who participated in the open-label part receiving [redacted] mg CSL312 and the last FXII/PLG subjects of the study have completed Treatment Period 1

All available data will be reported in each of the interim analyses. For details on the interim analyses see Section 4.6.1.

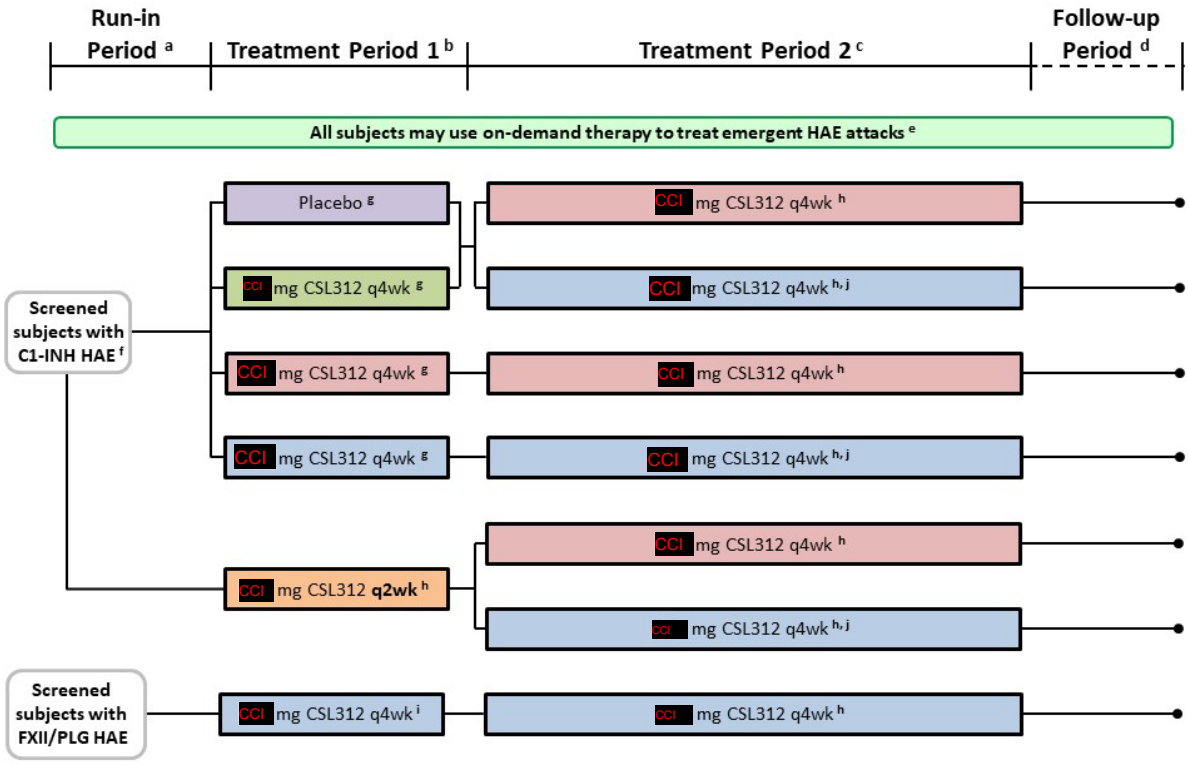
Three IDMC analyses are planned around following time points:

- First IDMC: December 2018;
- Second IDMC: end of February 2019;
- Third IDMC: end of May 2019 or beginning of June 2019.

Further IDMC analyses during Treatment Period 2 will be conducted with the first one planned after the last subject will have entered Treatment Period 2 and will have completed 3 months in Treatment Period 2. Subsequent IDMC analyses will be planned around every 4 months.

The IDMC intervals may be adjusted during the study depending on the enrolment rate. IDMC meetings may also be conducted upon request.

Figure 1 Study Overview



Abbreviations: q2wk = administered every 2 weeks; q4wk = administered every 4 weeks.

Footnotes:

[a] An overview of the Run-in Period is presented in protocol section 3.1.2.

[b] An overview of Treatment Period 1 is presented in protocol section 3.1.3.

[c] An overview of Treatment Period 2 is presented in protocol section 3.1.4.

[d] An overview of the Follow-up Period is presented in protocol section 3.1.5.

[e] Subjects may use the medication of their choice to treat HAE attacks experienced during the study if that medication has previously been shown to be effective. Investigators should ensure that participating subjects are capable of managing their HAE attacks.

[f] C1-INH HAE subjects will be assigned to receive [redacted] mg CSL312 q2wk, only after 32 subjects with C1-INH HAE are first randomly assigned to receive placebo or [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk.

[g] Subjects will receive treatment with investigational product in a blinded manner. These subjects will receive an initial intravenous (IV) loading dose of investigational product in Treatment Period 1 before receiving investigational product q4wk.

[h] Subjects will receive treatment with CSL312 in an open-label manner.

[I] Subjects will receive treatment with CSL312 in an open-label manner. These subjects will receive an initial IV loading dose of investigational product in Treatment Period 1 before receiving investigational product q4wk.

[j] All C1-INH HAE subjects receiving the [redacted] mg dose will have their dose reduced to [redacted] mg q4wk SC at their next scheduled study visit.

4.1.1 Run-in Period

After Screening, eligible subjects will enter the Run-in Period which will last at least 4 and up to 8 weeks. The HAE attacks recorded during Run-in will serve as subject's comparator to the number of attacks which occur under treatment.

Subjects are not permitted to use routine prophylaxis to prevent HAE attacks during the Run-in Period; however, subjects may use on-demand HAE therapy to treat emerging HAE attacks if that medication has previously been shown to be effective.

To enter Treatment Period 1 subjects must have participated in the Run-in period for a minimum of 4 weeks, and among other inclusion and exclusion criteria (see Protocol section 4.1.3) during that time:

- experienced ≥ 2 HAE attacks within a consecutive 4-weeks period during Run-in (subjects with C1-INH HAE);
- experienced ≥ 1 HAE attack during Run-in (subjects with FXII/PLG HAE).

4.1.2 Treatment Period 1

Subjects who are eligible should enter Treatment Period 1 no later than 14 days after Week 9 (Day 57) of the Run-in Period.

Treatment Period 1 will last for around 13 weeks. Subjects may complete the study after Treatment Period 1.

Subjects with C1-INH HAE

The first 32 eligible subjects with C1-INH HAE will be randomly assigned to receive treatment (cci mg CSL312 q4wk; cci mg CSL312 q4wk; cci mg CSL312 q4wk; placebo q4wk) with investigational product in a ratio of 1:1:1:1 during Treatment Period 1 as described in detail in Section 4.4. Subjects will receive a single intravenous (IV) loading dose of investigational product followed by three subcutaneous (SC) doses, depending on the randomized treatment arm in the following way:

- A single loading dose of cci mg CSL312 IV followed by cci mg CSL312 administered every 4 weeks (q4wk) (SC).
- A single loading dose of cci mg CSL312 IV followed by cci mg CSL312 q4wk SC.
- A single loading dose of cci mg CSL312 IV followed by cci mg CSL312 q4wk SC.

- A single loading dose of placebo IV followed by placebo q4wk SC.

For these first 32 subjects with C1-INH HAE, Treatment Period 1 will be conducted in a blinded manner, and the investigational product will be volume-normalized to maintain the blind.

After the first 32 subjects with C1-INH HAE are randomly assigned to study treatment, up to an additional 8 subjects with C1-INH HAE will be assigned to receive CCI mg CSL312 administered every 2 weeks (q2wk). CCI [redacted]. For these C1-INH HAE subjects, Treatment Period 1 will be conducted in an open-label manner and the investigational product will not be volume-normalized.

Subjects with FXII/PLG HAE

Up to 10 eligible subjects with FXII/PLG HAE will be assigned to receive a single loading dose of CCI mg CSL312 IV followed by CCI mg CSL312 q4wk. For these FXII/PLG subjects, Treatment Period 1 will be conducted in an open-label manner and the investigational product will not be volume-normalized.

4.1.3 Treatment Period 2

All subjects who participated in Treatment Period 1 may participate in Treatment Period 2. Treatment Period 2 will last for at least 44 weeks, or until another CSL312 study is opened for subjects to join, or until the current study is discontinued. Treatment Period 2 will be conducted in an open-label manner for all subjects. Subjects will be re-randomized or continue the treatment received in Treatment Period 1 as described in detail in Section 4.4.

Dose modification details for Treatment Period 2 are presented in Section 4.3.2. All C1-INH HAE subjects receiving the CCI mg dose will have their dose reduced to CCI mg q4wk SC at their next scheduled study visit, effective with Amendment 2.

4.1.4 Post-Treatment Follow-up Period

Subjects will attend a Follow-up Visit ~2 weeks after each subject's final treatment period visit; however, the Follow-up Visit may be waived in place of a telephone contact, at the discretion of the investigator.

4.2 Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective of this study is to evaluate the efficacy of CSL312 in the prevention of HAE attacks in subjects with C1-INH HAE.	Time-normalized number of HAE attacks.
Secondary	
1. To further evaluate the efficacy of CSL312 in subjects with C1-INH HAE. 2. To evaluate the PK of CSL312 in subjects with C1-INH HAE. 3. To evaluate the safety and tolerability of CSL312 in subjects with C1-INH HAE.	1. Responder subjects; HAE attack-free subjects; HAE attacks; HAE attacks treated with on-demand HAE medication. 2. CSL312 PK in plasma: • Maximum concentration (C_{max}); • Area under the concentration-time curve in 1 dosing interval ($AUC_{0\text{-}tau}$); • Time of maximum concentration (T_{max}); • Terminal elimination half-life ($T_{1/2}$); • Total systemic clearance (CL_{tot}); • Volume of distribution during the elimination phase (V_z). 3. Subjects experiencing: • Adverse events (AEs); • Serious AEs (SAEs); • AEs of special interest (AESIs), (i.e. anaphylaxis, thromboembolic events [TEEs], and bleeding events); • Injection site reactions (ISRs); • Inhibitory antibodies to CSL312; • Clinically significant abnormalities in laboratory assessments reported as AEs.

Objectives	Endpoints
CCI	
CCI	CCI The time-normalized number of uses of on-demand HAE medication per month. CCI • CCI CCI • CCI (CCI); CCI

Objectives	Endpoints
	CCI [redacted]

The endpoints will be evaluated separately for Treatment Period 1 and 2. Treatment Period 1 and Treatment Period 2 will be analyzed together for subjects who receive continuously the same dose of CSL312 during both treatment periods. For C1-INH subjects having a planned dose reduction from CCI mg to CCI mg in Treatment Period 2, only data until the date and time of the planned dose reduction will be included.

4.2.1 Primary Study Hypothesis

To test for a difference in the primary efficacy endpoint between [redacted] mg CSL312 q4wk or [redacted] mg CSL312 q4wk and placebo q4wk, pairwise comparisons will be performed by testing the hypotheses using a two-sided Mann-Whitney test.

To account for multiple testing, the alpha level of 5% will be evenly split between the two hypotheses tested. Details are given in Section 10.1.

4.3 Study Treatments

CSL312 will be supplied as a sterile, preservation-free solution for injection ([redacted] mL per vial with a concentration of [redacted] mg per [redacted] mL). The active substance is FXIIa antagonist monoclonal antibody. The mode of administration is IV or SC. CSL312 will be manufactured in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

The placebo will be the same as the CSL312 formulation buffer and supplied in the same way as CSL312 but will not contain the active substance (FXIIa antagonist monoclonal antibody). All study administration for the blinded part in Treatment Period 1 will be volume-normalized by diluting them to the volume of the [redacted] mg dose as further explained below in Section 4.4.

4.3.1 On-demand HAE Therapy

Subjects must be assessed by an investigator to be capable of managing their HAE attacks during participation in the study. This must be documented by the investigator in an individual acute action plan.

Subjects may use the on-demand medication of their choice that has previously been shown to be effective to treat HAE attacks experienced during the study.

4.3.2 Dose Modification

No dose modification is planned in Treatment Period 1.

Subjects in Treatment Period 2 at dose of [redacted] mg CSL312 q4wk who experience ≥ 3 HAE attacks within an 8-week period are eligible to have their CSL312 dose increased to [redacted] mg CSL312 q4wk. All CSL312 dose increases will be made in eligible subjects at the discretion

of the investigator in consultation with CSL. All C1-INH HAE subjects receiving the CCI mg dose will have their dose reduced to CCI mg q4wk SC at their next scheduled study visit, after the subject has signed informed consent to Amendment 2.

4.4 Randomization Procedures and Blinding

Randomization will be conducted using an interactive response technology (IRT).

Treatment Period 1

In Treatment Period 1, subjects will be randomized using block randomization with fixed block size by means of centralized IRT to 1 of 4 blinded treatment arms:

- The first 32 subjects with C1-INH HAE who are assigned to treatment in Treatment Period 1 will be randomized in a 1:1:1:1 ratio to receive placebo, CCI mg CSL312, CCI mg CSL312, or CCI mg CSL312 q4wk.

For the four blinded treatments above, the 32 C1-INH HAE subjects will be blinded to their treatment assignment. Except for the unblinded pharmacist (or delegate), all investigational site staff including the investigator will also be blinded to the treatment assignment of the 32 subjects with C1-INH HAE in Treatment Period 1. The unblinded personnel will prepare the investigational product but will not administer it to the subjects or assess the subjects. Representatives from CSL (or their delegates) with direct interaction with the study sites or subjects will be blinded to treatment assignment throughout Treatment Period 1. A physical blind (CCI) will be employed so that blinded study personnel or subjects are unable to detect any difference between CSL312 or placebo. Furthermore, the IV and SC doses will be volume-normalized so that irrespective of the randomized dose, the same volume will be infused or injected to each subject. The assigned IV loading doses will be diluted so that each is the same volume for administration as a dose of CCI mg (i.e., CCI mL). The assigned SC doses of CSL312 will be diluted so that each is the same volume for administration as a dose of CCI mg (i.e., CCI mL).

In addition, laboratory results which may reveal the treatment allocation will not be available to subjects, study site personnel, or CSL (and delegates) blinded to treatment assignment.

The following laboratory tests may reveal the treatment allocation:

Laboratory Category	Laboratory Test	Comments
Coagulation	[redacted]	Blinded in eCRF
	[redacted]	
	[redacted]	Blinded in eCRF
	[redacted]	
	[redacted]	
Immunogenicity	Inhibitory and non-inhibitory antibodies specific to FXIIa antagonist monoclonal antibody	
PK	CSL312 concentration	
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

Up to 8 additional subjects with C1-INH HAE who are assigned to treatment in Treatment Period 1 after the first 32 subjects (above) will receive [redacted] mg CSL312 q2wk in an unblinded open-label manner.

Up to 10 subjects with FXII/PLG HAE who are assigned to treatment in Treatment Period 1 will receive [redacted] mg CSL312 q4wk in an unblinded open-label manner.

Treatment Period 2

In Treatment Period 2, subjects will be re-randomized using block randomization with fixed block size by means of a centralized IRT to receive either [redacted] mg or [redacted] mg CSL312 q4wk.

- For subjects with C1-INH HAE, randomization will be stratified by Treatment Period 1 treatment assignment: subjects on placebo q4wk, subjects on [redacted] mg CSL312 q4wk, and subjects on [redacted] mg CSL312 q2wk:
    - Subjects on placebo q4wk and subjects on [redacted] mg CSL312 q4wk will be randomized in a 1:1 ratio to receive either [redacted] mg CSL312 q4wk or [redacted] mg CSL312 q4wk in Treatment Period 2.
    - Subjects on [redacted] mg CSL312 q2wk will be randomized in a 1:1 ratio to receive either [redacted] mg CSL312 q4wk or [redacted] mg CSL312 q4wk in Treatment Period 2.

- Subjects with C1-INH HAE on CCI mg CSL312 q4wk in Treatment Period 1 will continue to receive CCI mg CSL312 q4wk in Treatment Period 2.
- Subjects with C1-INH HAE on CCI mg CSL312 q4wk in Treatment Period 1 will continue to receive CCI mg CSL312 q4wk in Treatment Period 2.
- Subjects with FXII/PLG HAE will continue to receive CCI mg CSL312 q4wk in Treatment Period 2.

Treatment Period 2 will be conducted in an open-label manner.

4.5 Determination of the Sample Size

Subjects with C1-INH HAE

Seven subjects assigned to each treatment (placebo, or CCI mg, or CCI mg CSL312 q4wk) are needed to reach a power of ~82% for the comparisons of CCI mg CSL312 q4wk against placebo q4wk and CCI mg CSL312 q4wk against placebo q4wk in Treatment Period 1.

This is based on the following assumptions:

- Alpha is 2.5% for each of the 2 two-sided Mann-Whitney tests of CCI mg CSL312 q4wk or CCI mg CSL312 q4wk against placebo q4wk.
- The time-normalized number of HAE attacks is 2.9 attacks per month during treatment with placebo. This number was derived from CSL study CSL830_3001, using the lower bound of the distribution-free 95% confidence interval (CI) for the median of the first placebo treatment period.
- The time-normalized number of HAE attacks is 0.6 attacks per month during treatment with CCI mg or CCI mg CSL312 q4wk. The number was derived from CSL study CSL830_3001, using the upper bound of the distribution-free 95% CI for the median of the combined active treatment periods.
- For the time-normalized number of HAE attacks during CSL321 treatment and placebo a Poisson distribution is assumed. The lower bound and the upper bound, respectively, of the CIs for the medians are chosen for the rate parameters.
- Randomization allocation between CSL321 treatment and placebo which are compared are equal.

CCI [redacted]. The sample size of 7 subjects for this arm is not driven by an

efficacy comparison, but instead, by consistency with other treatment arms and for maintenance of the blinding of the study. No testing for efficacy of the CCI mg CSL312 dose against placebo is planned and no power calculation has been done.

An additional subject will be added to each of these 4 treatment arms to account for dropouts during Treatment Period 1, resulting in 8 subjects required in each treatment arm.

Up to 7 subjects with C1-INH HAE will be assigned to receive CCI mg CSL312 q2wk. This arm is included for informational purposes, and therefore no testing against placebo is planned and no power calculation has been done. An additional subject will be added to this arm to account for dropouts during Treatment Period 1, resulting in up to 8 subjects in this treatment arm.

Overall, a total of up to 40 subjects with C1-INH HAE will be assigned to treatment in Treatment Period 1.

Subjects with FXII/PLG HAE

Up to 10 subjects with FXII/PLG HAE will take part in the study. The sample size for this arm is not driven by statistical considerations, but instead, by the expectations what number of subjects with FXII/PLG HAE is feasible to be enrolled in the study.

4.6 Planned Interim Analyses and Reviews

4.6.1 Interim Analyses

A first interim analysis will be conducted after all C1-INH HAE subjects who received placebo or CCI mg, CCI mg, or CCI mg CSL312 q4wk have completed Treatment Period 1 using data from all subjects available at this time. The confirmatory test of CCI mg or CCI mg CSL312 q4wk against placebo q4wk will not be performed for any dry run. It will only be performed for the interim analysis.

A second interim analysis will be conducted after all subjects with C1-INH HAE who received CCI mg CSL312 q2wk and subjects with FXII/PLG HAE have completed Treatment Period 1 using data from all subjects available at this time. This interim analysis will include subjects with C1-INH HAE and with FXII/PLG HAE with all available data collected up to this time point.

No separate interim analysis will be conducted after subjects with FXII/PLG HAE have completed Treatment Period 1.

The interim analyses should provide information about the efficacy, safety and PK/CCI of CCI mg, CCI mg, and CCI mg CSL312 q4wk (CCI) and CCI mg CSL312 q2wk.

Each interim analysis will be presented as outlined in Section 7 and will include the following analyses:

- The time-normalized number of HAE attacks presented descriptively by treatment.
- Pairwise comparisons by using a two-sided Mann-Whitney test for a difference in the time-normalized number of HAE attacks between CCI mg CSL312 or CCI mg CSL312 q4wk for subjects with C1-INH HAE and placebo q4wk (the test will only be applied to the interim analysis after all subjects completed the blinded part of Treatment Period 1).
- Mann-Whitney test for the difference in the time-normalized number of HAE attacks between the 2 treatments CCI mg and CCI mg CSL312 q4wk for subjects with C1-INH HAE (the test will only be applied to the interim analysis after all subjects completed the blinded part of Treatment Period 1).
- By-subject listing for primary efficacy.
- CCI .
- The number and percentage of responders and non-responders with corresponding 95% CI and corresponding by-subject listing.
- CCI
- The number and percentage, and the fraction of subjects who do not experience a HAE attack at certain time points as well as the median time of being attack-free and corresponding by-subject listing.

- The total number and percentage of mild, moderate, or severe HAE attacks as well as the time-normalized number per month and the number of subjects having at least 1 mild, moderate, or severe HAE attack and corresponding by-subject listing.
- The number, the time-normalized number, and the percentage of treated and untreated attacks overall and by severity. The number and percentage of subjects with at least 1 treated attack, the number and percentage of subjects with only treated attacks, the number and percentage of subjects with attacks but without treated attacks, the number and percentage of subjects with no attacks at all, and the number and percentage of attacks treated per subject and corresponding by-subject listing.
- Summary of subjects with AEs (number with any AE, with AEs occurring within 24 hours of investigational product injection, with SAE, with related AEs, with AEs leading to study discontinuation, AEs within each of the intensity categories, and AEs within each of the outcome categories).
- Summary of subjects with SAEs (number with any SAE, with SAEs occurring within 24 hours of investigational product injection, with related SAE, with SAEs leading to study discontinuation, SAEs within each of the intensity categories, and SAEs within each of the outcome categories).
- Incidence of subjects with AEs by system organ class (SOC) and preferred term (PT)
- Incidence of subjects with TEEs by SOC and PT.
- Incidence of subjects with bleeding events by SOC and PT.
- Incidence of subjects with anaphylaxis by SOC and PT.
- By-subject listings of TEAEs, SAEs, AESIs
- Summary of CSL312 concentrations by planned time point and corresponding by-subject listing showing individual CSL312 concentrations by actual sampling time.
- Summary of PK parameters and corresponding by-subject listing.
- CCI [redacted]

Further details to the analysis above can be found in the corresponding sections (Section 10.1, 11.2, 12.2, 0, 13.1, 13.2).

Further interim analyses may be conducted on an as-needed basis to support regulatory activities.

4.6.2 IDMC Reviews

Output provided for the IDMCs will be unblinded and will be distributed only to IDMC members and unblinded CSL personnel. The outputs will be stored in access restricted folders to which only unblinded CSL personnel will have access (see further details to unblinded CSL personnel in the IRT Project Communication Plan). The output will be presented in the format as described in Section 7.

The IDMC will monitor safety, efficacy, and PK/[redacted] at regular intervals. The following outputs will be provided for the IDMCs:

First IDMC Review: Overview of Study Initiation Visits, Health Authorities feedback, number of subjects screened, enrolled, and entered Run-In Period. No analysis outputs will be produced.

Second IDMC Review: The following outputs as specified in this SAP will be produced:

- Subject Disposition (table);
- HAE History (table);
- Overall AE Summary (table);
- Overall SAE Summary (table)
- Treatment-emergent AE (TEAE) Summary by SOC and PT (table);
- Subject profiles showing HAE attacks and treatments on a timeline (figure).
- Listings:
  - SAEs;
  - [redacted]
  - [redacted]

Third IDMC review: The following outputs as specified in this SAP will be produced:

- Outputs listed above for the second IDMC review;
- Tables of
  - Time-normalized Number of HAE Attacks;
  - Responder Subjects;
  - HAE Attack-free Subjects;
  - HAE Attacks;
  - HAE Attacks Treated With On-demand HAE Medication;
  - [redacted]

- CCI ;
- CCI ;
- CCI ;
- CCI ;
- CCI ;
- CCI ;
- CCI .

5 Changes in the Conduct of Planned Analyses

Changes after finalization of this SAP will either be described in a protocol amendment or in an update to the SAP. They will be clearly indicated in the CSR.

Changes in the analysis following Amendment 2 are as follows:
Efficacy analysis: the planned treatment for the efficacy analysis is the randomized treatment. Following Amendment 2, for subjects randomized to CCI mg CSL312 q4wk in Treatment Period 2 their planned treatment will be reduced to CCI mg CSL312 q4wk. The subjects will be reported under this treatment after the planned dose reduction. For subjects who receive continuously the same dose of CSL312 during both treatment periods, data will be included in the analysis until the planned dose reduction following Amendment 2.

Safety analysis: the actual treatment will be used for the Safety analysis. Subjects with planned or unplanned dose reduction or allowed dose increase will be reported under the treatment they actually received. For subjects who receive continuously the same dose of CSL312 during both treatment periods, data will be included in the analysis until any dose change.

The second and third interim analysis will be combined into one.

6 Study Analysis Populations

6.1 Screening Population

The Screening population will consist of all subjects who provide written informed consent and who undergo any study screening procedure.

Technical Note: Subjects with informed consent date available and any assessments labelled as Screening Visit available will be included.

6.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all subjects who provide informed consent, undergo any study screening procedure, and who are assigned to treatment in Treatment Period 1 or to treatment in Treatment Period 2, regardless of whether they receive the investigational product. The ITT population will be analyzed using the treatment to which the subject was assigned in Treatment Period 1, in Treatment Period 2 at Week 13, or CCI mg after dose reduction from CCI mg following Amendment 2 in Treatment Period 2 (only applicable for C1-INH HAE subjects), regardless of the actual treatment received.

Technical Note: Subjects who belong to the Screening population and have randomization date available for Treatment Period 1 or Treatment Period 2 will be included for the corresponding Treatment Periods. Thus, the ITT will be assigned within treatment period.

6.3 Safety Population

The Safety population will consist of all subjects who provide informed consent, are assigned to treatment in Treatment Period 1 or to treatment in Treatment Period 2 and receive at least1 dose or partial dose of the investigational product and will be based on the actual treatment received.

Technical Note: Subjects who belong to the ITT population and have at least one non-missing volume of study medication entered in the eCRF will be included.

6.4 Per-Protocol Population

The per-protocol (PP) population will consist of all subjects in the ITT population, excluding subjects who have a significant protocol violation. Protocol violations which will lead to exclusion from the PP population will be reviewed and agreed prior to conducting each of the interim analyses and before database lock.

Technical Note: Subjects who belong to the ITT population and who do not have significant protocol violations which lead to exclusion from PP as decided during the Data Review Meeting will be included.

6.5 Pharmacokinetic Population

The PK population will consist of all subjects in the Safety population for whom at least 1 measurable concentration of CSL312 is reported.

6.6 CCI

CCI

7 General Considerations

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards, and data will be displayed according to reporting standards in this SAP and TFL formats.

SAS version 9.3 or higher will be used to perform all data analyses and to generate TFLs.

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

Depending on the analysis populations defined, all data from a subject or a subset of data may be excluded from certain analyses (e.g., analyses based on the PP population) as defined in Section 6.

Continuous variables will be described by the number of observations, mean values with their 95% CIs, standard deviation (SD), 25th percentile, median (50th percentile), 75% percentile, and range (minimum to maximum). The geometric coefficient of variation will be expressed as a percentage for PK and CCI data and will be calculated as 100*sqrt(exp(SD_{log}^2)-1). The geometric mean and its 90% CI will be calculated for PK and CCI data. 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% CI of the log-transformed data, and subsequently back transforming the mean and the lower and upper limits. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

Summary statistics of location parameters (mean, median, quartiles) will be reported to one more decimal place than the collected data. Summary statistics of variability (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 data from Treatment Period 1 and Treatment Period 2 will be analyzed separately. For subjects who received continuously the same dose of CSL312 during both treatment periods, the two treatment periods will also be analyzed together. For C1-INH subjects having a dose change in Treatment Period 2, only data until the date and time of the dose change will be included in these summaries over both treatment periods for the safety analyses. For efficacy analyses, data until the date and time of the planned dose reduction will be included in these summaries over both treatment periods.

In Treatment Period 1, subjects with C1-INH HAE who are treated with placebo, CCI mg, CCI mg, or CCI mg CSL312 q4wk will be analyzed separately from subjects with C1-INH HAE who are treated with CCI mg CSL312 q2wk. In both treatment periods, subjects with FXII/PLG HAE will be analyzed separately from subjects with C1-INH HAE.

Summaries will be reported by treatment period and treatment in the following order:

- Treatment Period 1 FXII/PLG HAE: CCI mg CSL312 q4wk;
- Treatment Period 2 FXII/PLG HAE: CCI mg CSL312 q4wk;
- Treatment Period 1 & 2 FXII/PLG HAE:CCI mg CSL312 q4wk;
- Treatment Period 1 C1-INH HAE: placebo, CCI mg, CCI mg, and CCI mg CSL312 q4wk, Total Blinded Part and Total CSL312 (no totals will be populated for efficacy; for PK, CCI only Total CSL312);
- Treatment Period 1 C1-INH HAE: CCI mg CSL312 q2wk;
- Treatment Period 2 C1-INH HAE: CCI mg (initial and after down-titration), [CCI mg in the Safety analysis], CCI mg CSL312 q4wk, and Total (no total will be populated for efficacy);
- Treatment Period 1 & 2 C1-INH HAE: CCI mg, CCI mg CSL312 q4wk, and Total (no total will be populated for efficacy) – only data included until dose change (Safety analysis) or planned dose reduction (Efficacy analysis).

The by-subject listings will include treatment period, treatment, subject number, and basic demographics (sex, age, body mass index [BMI]), and the information specific to that listing. The laboratory normal reference ranges will be provided and clinical laboratory test results outside the normal reference range will be flagged in the laboratory data listings.

The by-subject listings will be sorted by the treatment which the subjects will be assigned to in Treatment Period 1 in combination with the treatment they will be assigned to in Treatment Period 2, subject number, and then by visit / date and time. The planned dose reduction

following Amendment 2 or dose increase according to the protocol and any unplanned dose reductions will happen on an individual base and will be reported in the listings. The dose changes will not affect the treatment sequences. The treatment sequences for sorting will be as follows:

Treatment Period 1	**Treatment Period 2**
Subjects With C1-INH HAE	
Placebo q4wk	none
Placebo q4wk	CCI mg CSL312 q4wk
Placebo q4wk	CCI mg CSL312 q4wk
CCI mg CSL312 q4wk	none
CCI mg CSL312 q4wk	CCI mg CSL312 q4wk
CCI mg CSL312 q4wk	CCI mg CSL312 q4wk
CCI mg CSL312 q4wk	none
CCI mg CSL312 q4wk	CCI mg CSL312 q4wk
CCI mg CSL312 q4wk	none
CCI mg CSL312 q4wk	CCI mg CSL312 q4wk
CCI mg CSL312 q2wk	none
CCI mg CSL312 q2wk	CCI mg CSL312 q4wk
CCI mg CSL312 q2wk	CCI mg CSL312 q4wk
Subjects With FXII/PLG HAE	
CCI mg CSL312 q4wk	none
CCI mg CSL312 q4wk	CCI mg CSL312 q4wk

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 pre-specified planned times will be used in the summaries, statistical analyses, and calculations of any derived parameters; unscheduled assessments will be included in the listings.

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

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

7.1 Multicenter Studies

Data from all participating sites will be pooled prior to analysis. The site identifier will be populated in the listings along with the subject number.

7.2 Treatment Descriptors

C1-INH HAE: Treatment Period 1 Blinded			
Placebo q4wk	CCI mg CSL312 q4wk	CCI mg CSL312 q4wk	CCI mg CSL312 q4wk

C1-INH HAE Treatment Period 1 Open-label
CCI mg CSL312 q2wk

C1-INH HAE: Treatment Period 2 Open-label		
[redacted] mg CSL312 q4wk	[redacted] mg CSL312 q4wk	[redacted] mg CSL312 q4wk

[redacted] mg CSL312 will be included only for the Safety analysis; [redacted] mg will include planned (for Efficacy and Safety analysis) and unplanned dose reduction for Safety analysis.

FXII/PLG HAE: Treatment Period 2 Open-label
[redacted] mg CSL312 q4wk

7.3 Multiple Comparisons and Multiplicity

See Section 10.1 for details.

8 Data Handling Conventions

8.1 Missing Data

8.1.1 Imputation of Non-Date Missing Data

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

Only missing values for the primary efficacy endpoint (i.e., time-normalized number of HAE attacks) during Treatment Period 1 will have an impact on the analyses of the pairwise comparison between [redacted] mg CSL312 q4wk versus placebo q4wk and [redacted] mg CSL312 q4wk versus placebo q4wk in Treatment Period 1. The time-normalized number of HAE attacks will only be missing for subjects receiving investigational product q4wk and q2wk who drop out before Day 6 and Day 15, respectively, of Treatment Period 1.

Imputation methods based on Markov-Chain Monte Carlo (MCMC) techniques assume a certain distribution of the data and sample from this distribution values which are imputed to replace the missing values. With only 8 subjects per treatment, MCMC methods are not expected to yield reliable estimates. Instead a systematic approach (Enhanced Tipping Point

analysis [Liublinska and Rubin, 2014]) will be applied to investigate the robustness of the study's conclusion to the assumed missingness pattern. For details see Section 10.1.1.

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 "Yes". There will be no other imputation for missing data.

8.1.2 Imputation of Partial Dates

If the start or end date of an event is missing, then the duration of the event will naturally also be missing.

There will be no imputation of partially or completely missing dates. See Section 11.2 for the handling of partially or completely missing AE start dates. See Section 0 for the handling of partially or completely missing start and end dates of concomitant medication.

8.2 Derived Variables

The following sections provide a general description of the derived variables for data analyses. Analysis dataset specifications in a separate document will provide full details on data derivations and transformations.

8.2.1 Reference Dates

Reference dates are used to assign study periods relative to treatment.

Because age is an eligibility criterion, the reference date for age will be the date of Screening.

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

The efficacy reference date will be the start date of the efficacy evaluation period.

8.2.2 Study Day for Safety and Efficacy Measures

If the date of interest occurs on or after the safety or efficacy reference date, then the study day will be calculated as (date of interest – safety or efficacy reference date) + 1. If the date of interest occurs before the safety or efficacy reference date, then the study day will be calculated as (date of interest – safety or efficacy reference date). There will be no Day 0.

8.2.3 Durations

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

- End date and time (if available) – start date and time (if available) + 1.

CCI

To transform durations or CCI which are calculated in days into months, divide the number of days by 30.4375; to transform to weeks divide the number of days by 7; to transform to 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 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.

Age will be taken from the data base.

8.2.4 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to or on the first study treatment dose date.

8.2.5 Change from Baseline

Change from baseline can only be calculated for measures that have baseline and post-baseline records and will be calculated as:

- Value at respective visit – baseline value.

Percentage change from baseline will be calculated as:

- (change from baseline / baseline value) * 100

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

8.2.6 Multiple Assessments

All data will be reported according to the nominal visit date at which it was assessed (that is, no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the

protocol). If multiple assessments for the same visit occur, it will be distinguished why this is the case. 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.

8.2.7 Actual Treatment

The subject's actual treatment will be derived from exposure data. If a subject is either up-titrated or down-titrated during Treatment Period 2, the actual treatment will be the initial treatment until dose change and the modified treatment after dose change. The subject will be reported in the initial treatment until dose change and in the modified treatment beginning with the dose change. If a subject receives a treatment different from the planned it will be decided during the Data Review Meeting on an individual base what is considered the actual treatment.

8.2.8 Study Periods Relative to Treatment

The following definitions for the evaluation 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. It is not intended to re-assign assessments made during scheduled visits based on these definitions. Scheduled visits will not be re-labelled based on subject's study days irrespective of whether the visit takes place in the planned time window.

The Study Completion Date Visit in this study is at the end of Treatment Period 1 or Treatment Period 2 or at the time of premature study discontinuation. This visit is followed by the Follow-up Visit which may be waived in place of a telephone contact.

Efficacy Analysis: The evaluation periods will be:

Run-in Period (all subjects): From Week 1 Day 1 of the Run-in Period until the date / time of the Week 1 Day 1 Visit of Treatment Period 1 (the date / time of the first administration of

investigational product in Treatment Period 1) or the Study Completion Visit date and time (whichever occurs earlier). The duration (days) of the Run-in period will be:

Week 1 Day 1 Visit date and time of Treatment Period 1 or Study Completion Visit date and time – Week 1 Day 1 Visit date and time of Run-in + 1.

Treatment Period 1 (subjects who receive an IV loading dose of investigational product): From Week 1 Day 6 Visit of Treatment Period 1 (the date / time of the first SC administration of investigational product in Treatment Period 1) until the date / time of the Week 13 Day 91 Visit (the date / time of the first administration of investigational product in Treatment Period 2) or the Study Completion Visit date and time (whichever occurs earlier). The duration (days) of the efficacy evaluation period for Treatment Period 1 will be:

Week 13 Day 91 Visit date and time or Study Completion Visit date and time – Week 1 Day 6 Visit date and time + 1.

Treatment Period 1 (CCI): From Week 3 Day 15 Visit of Treatment Period 1 (the date / time of the second SC administration of investigational product in Treatment Period 1) until the date / time of the Week 13 Day 85 Visit (the date / time of the first administration of investigational product in Treatment Period 2) or the Study Completion Visit date and time (whichever occurs earlier). The duration (days) of the efficacy evaluation period for Treatment Period 1 will be:

Week 13 Day 85 Visit date and time or Study Completion Visit date and time – Week 3 Day 15 Visit date and time + 1.

Treatment Period 2 (subjects assigned to CCI mg CSL312 and FXII/PLG HAE subjects): Treatment Period 2 will start after it is assumed that all subjects have achieved steady-state under CSL312. From Week 21 Day 147 Visit of Treatment Period 2 (the date / time of the third administration of investigational product in Treatment Period 2) until the date / time of the Study Completion Visit. The duration (days) of the efficacy evaluation period for Treatment Period 2 will be:

Study Completion Visit date and time – Week 21 Day 147 Visit date and time + 1.

Treatment Period 2 (C1-INH HAE subjects assigned to CCI mg CSL312): Treatment Period 2 will start after it is assumed that all subjects have achieved steady-state under CSL312.

- CCI mg portion: From Week 21 Day 147 Visit of Treatment Period 2 (the date / time of the third administration of investigational product in Treatment Period 2) until the

date / time of the Study Completion Visit OR the date / time of the planned dose reduction to CCI mg (following Amendment 2), whatever occurs first. The duration (days) of the efficacy evaluation period for CCI mg in Treatment Period 2 will be:

(Study Completion Visit date and time or Date and time of planned dose reduction, whichever occurs first) – Week 21 Day 147 Visit date and time + 1;

- CCI mg portion: From the date / time of the planned dose reduction to CCI mg (following Amendment 2) until the Study Completion Visit date / time. The duration (days) of the efficacy evaluation period for CCI mg in Treatment Period 2 will be: Study Completion Visit date and time – Date and time of planned dose reduction.

Treatment Period 1 and 2 (subjects who receive an IV loading dose of investigational product and who participate in Treatment Period 2): From Week 1 Day 6 Visit of Treatment Period 1 (the date / time of the first SC administration of investigational product in Treatment Period 1) until the date / time of the Study Completion Visit or the date / time of planned dose reduction, whichever occurs first. The duration (days) of the efficacy evaluation period for Treatment Period 1 and 2 will be:

Study Completion Visit date and time or Date and time of planned dose reduction, whichever occurs first – Week 1 Day 6 Visit date and time + 1.

After planned dose reduction, data will not be included in the summary tables.

HAE attacks with start dates outside the above specified efficacy evaluation periods will not be included in the efficacy analysis but will only be listed:

- HAE attacks with a start date between the first and second administrations of the investigational product in Treatment Period 1,
- HAE attacks with a start date between Week 13 Day 85/91 and Week 21 Day 147,
- HAE attacks with start date between date of last treatment period visit and Follow-up.

Safety Analysis Exposure: The duration in days of the evaluation periods will be:

Treatment Period 1 (subjects who participate in Treatment Period 2):

Week 13 Day 85/91 Visit date and time – 1 – date and time of first administration of study treatment + 1.

Treatment Period 1 (subjects who do NOT participate in Treatment Period 2):

Study Completion Visit date and time – date and time of first administration of study treatment + 1.

Treatment Period 2 (subjects without dose change):

Study Completion Visit date and time –Week 13 Day 85/91 Visit date and time + 1.

Treatment Period 2 (subjects with dose change):

Portion before dose change:

Date and time of dose change – Week 13 Day 85/91 Visit date and time + 1.

Portion after dose change:

Study Completion Visit date and time – Date and time of dose change.

Treatment Period 1 and 2 (subjects without dose change):

Study Completion Visit date and time – date and time of first administration of study treatment + 1.

Treatment Period 1 and 2 (subjects with dose change):

Portion before dose change:

Date and time of dose change – date and time of first administration of study treatment + 1.

Portion after dose change:

Data will not be included in the summary tables.

Safety Analysis AEs: The duration in days of the evaluation periods will be:

Treatment Period 1 (subjects who receive an IV loading dose of investigational product and who participate in Treatment Period 2):

Week 13 Day 91 Visit date and time – 1 – Week 1 Day 6 Visit of Treatment Period 1 date and time (the date / time of the first SC administration of investigational product in Treatment Period 1) + 1.

Treatment Period 1 (subjects who receive an IV loading dose of investigational product and who do NOT participate in Treatment Period 2):

Follow-up or Study Completion Visit date and time (whichever occurs later) – Week 1 Day 6 Visit of Treatment Period 1 date and time (the date / time of the first SC administration of investigational product in Treatment Period 1) + 1.

Treatment Period 1 (CCI [redacted]):

Week 13 Day 85 Visit date and time – 1 – Week 1 Day 1 Visit of Treatment Period 1 date and time (the date / time of first SC administration of investigational product in Treatment Period 1) + 1.

Treatment Period 1 (CCI [redacted]):

Follow-up or Study Completion Visit date and time (whichever occurs later) – Week 1 Day 1 Visit of Treatment Period 1 date and time (the date / time of first SC administration of investigational product in Treatment Period 1) + 1.

Treatment Period 2 (subjects without dose change):

Follow-up or Study Completion Visit date and time (whichever occurs later) – Week 13 Day 85/91 Visit date and time + 1.

Treatment Period 2 (subjects with dose change):

Portion before dose change:

Date and time of dose change – Week 13 Day 85/91 Visit date and time + 1.

Portion after dose change:

Follow-up or Study Completion Visit date and time (whichever occurs later) – Date and time of dose change.

Treatment Period 1 and 2 (subjects without dose change):

Follow-up or Study Completion Visit date and time (whichever occurs later) – date and time of first SC administration of study treatment + 1.

Treatment Period 1 and 2 (subjects with dose change):

Portion before dose change:

Date and time of dose change – date and time of first SC administration of study treatment + 1.

Portion after dose change:

Data will not be included in the summary tables.

Date and time of first SC administration of study treatment is Week 1 Day 6 or Week 1 Day 1 for those with CCI [redacted] an IV loading dose, respectively.

8.3 Laboratory Parameters

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

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are clinically relevant, even if the absolute values are within the reference range.

9 Study Population

9.1 Disposition of Subjects

Subject disposition will be summarized using all subjects who provided informed consent.

The following will be presented in summary tables by treatment as specified in Section 7. The results will be presented over all subjects and for subjects with C1-INH and FXII/PLG HAE. Percentages will be based on the Screening population:

- Number of subjects who provided informed consent;
- Number and percentage of subjects who underwent Screening;
- Number and percentage of subjects who entered the Run-in Period;
- Number and percentage of subjects still in the Run-in Period (only for interim analysis);
- Number and percentage of subjects who were not assigned to study treatment;
- Number and percentage of subjects who were assigned to study treatment in Treatment Period 1;
- Number and percentage of subjects who were assigned to study treatment in Treatment Period 2;
- Number and percentage of subjects still in Treatment Period 1 (only for interim analysis);

- Number and percentage of subjects still in Treatment Period 2 (only for interim analysis);
- Number and percentage of subjects who have a planned dose reduction from CCI mg to CCI mg in Treatment Period 2 (following Amendment 2);
- Number and percentage of subjects who completed Treatment Period 1;
- Number and percentage of subjects who completed Treatment Period 2;
- Number and percentage of subjects still in the study (only for interim analysis);
- Number and percentage of subjects who completed the study;
- Number and percentage of subjects who discontinued the study in the Run-in Period with reason for discontinuation (percentages based on the number who discontinued);
- Number and percentage of subjects who discontinued the study in Treatment Period 1 with reason for discontinuation (percentages based on the number who discontinued);
- Number and percentage of subjects who discontinued the study in Treatment Period 2 with reason for discontinuation (percentages based on the number who discontinued);
- Number and percentage of subjects who discontinued the study in any period with reason for discontinuation (percentages based on the number who discontinued).

A by-subject listing for all available data with the information as described in Section 7 and in addition screening status (failed or qualified), reason for screening failure (in- or exclusion criterion numbers), date and time of informed consent, date of eligibility for Run-in, reasons for non-eligibility for Run-in, date of eligibility for Treatment Period 1, date and time of randomization, reason for non-eligibility for randomization, date and time of first IV, first SC, and last treatment, date of study completion or discontinuation, and reason for study discontinuation will be presented. Another listing for all available data will present the individual visit dates for all visits (scheduled and unscheduled) which the subject attended.

9.2 Protocol Violations

Protocol violations are those protocol deviations which may identify subjects who should be excluded from one or more analysis population(s). Listings showing subjects with protocol deviations will be generated prior to each interim and the final analysis to identify subjects who may have these protocol violations. During the Data Review Meetings, the subject assignment to analysis populations will be discussed in detail based on the consolidated protocol deviations from the CCI along with the listings of the potential protocol violations specified below. It cannot be ruled out that during the discussion of protocol deviations, additional violations which are not listed below will be considered to

have a significant impact and will thus lead to exclusion of subjects from analysis population(s). The decisions made during the Data Review Meetings will be documented in detail in the Data Review Meeting minutes and may modify the specifications in the list below. The Data Review Meeting minutes will be agreed upon prior to each interim and final analysis.

Potential Protocol Violations	**Potential Exclusion From Analysis Population**
Subject did not provide informed consent (informed consent date missing)	Screening, Safety, ITT, PP, PK, CCI
Subject randomized but not treated with study treatment	Safety, PP, PK, CCI
Subjects treated with incorrect study treatment	PP, potentially PK, CCI
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 CCI measurement	CCI
Subject randomized and treated but without primary efficacy assessment	PP
Subject randomized and treated but violated inclusion or exclusion criteria	PP, potentially also PK, CCI
Subject randomized and treated but compliance outside 80-120%	PP, potentially also PK, CCI
Subject randomized and treated but received prohibited concomitant medication	PP, potentially also PK, CCI

Protocol deviations caused by the Corona Virus Disease 2019 (COVID-19) pandemic will be documented throughout the entire study. They will be assigned as a separate protocol deviation category “COVID-19”, will be listed, and discussed during the Data Review Meetings. They will be summarized separately from the other protocol deviations and will also be discussed in the CSR.

Prior to each 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/[redacted] analysis or with the efficacy analysis will be flagged.

A summary table with the number and percentages of subjects with

- Inclusion and exclusion protocol violations;
- All significant protocol violations including inclusion and exclusion violations

will be provided. Number and percentage of subjects in the Screening, Safety, ITT, PP, PK, and [redacted] population will be provided.

The following by-subject listings for all available data with the information as described in Section 7 and in addition information as listed below will be provided:

- Randomized and actual treatment;
- All inclusion and exclusion protocol deviations;
- All other protocol deviations with an indication whether this is a significant violation or minor deviation and from which analysis population the subject will be excluded;
- COVID-19 protocol deviations.

9.3 Demographic and Baseline Characteristics

Demographic and baseline subject characteristics will be summarized for the ITT and PP populations.

BMI will be defined as body weight [kg]/height [m^2]

The following summaries will be provided:

- Demographic characteristics: sex, race, ethnicity, age, height and body weight at Screening, and BMI. As only adults will be included, no age groups will be formed.
- HAE history: HAE type (C1-INH Type I, C1-INH Type 2, FXII HAE, PLG HAE), number of HAE attacks before Screening for subjects without prophylactic HAE therapy (C1-INH HAE: over a consecutive 2-month period during the 3 months before Screening; FXII/PLG HAE: during the 3 months before Screening), number and percentage of subjects who took prophylactic HAE therapy, number of HAE attacks before the start of prophylactic therapy (C1-INH: over any consecutive 2-months period during 3 months before the start of prophylactic HAE therapy; FXII/PLG: during the 3 months before the start of prophylactic therapy).

- Medical history will be presented by SOC and PT – include medical history terms with end date / evidence for end date prior to informed consent date.
- Concomitant diseases will be presented by SOC and PT – include medical history terms with end date / evidence for end date after informed consent date or flagged "Ongoing" or end date missing.

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 with the information as described in Section 7 will be provided for:

- Demographic data (sex, age, race, ethnicity, height at Screening, body weight at Screening, and BMI);
- Disease characteristics (HAE type, number of HAE attacks before Screening, prophylactic HAE therapy [Yes, No], number of HAE attacks before the start of prophylactic HAE therapy);
- Medical history and concomitant diseases (medical history term, SOC, PT, start and end date or ongoing flag);
- Reproductive system findings (childbearing potential, method of birth control, date and time of pregnancy test, and pregnancy test result).

9.4 Concomitant Medications

Prior and concomitant medication will be summarized for the Safety population. 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. For the "Any Medication" entry, the virtual ATC class "On-demand HAE Medication" will be excluded to avoid counting the medication twice.

Concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) B3 version March 2018 or more recent. The summary of concomitant medications will show the number and percentage of subjects taking

concomitant medications by Anatomical Therapeutic Chemical (ATC) class and PT. ATC Level 4 will be used for the summary tables and listing unless coding is not available at level 4. In these cases, level 3 ATC name will be used. Similarly, if the level 3 ATC name is not available then the level 2 ATC name will be used and if the level 2 ATC name is not available then the level 1 ATC name will be used. These replacements will only be made for missing ATC level 4. ATC Level 1 information will be included in the dataset created but will not appear in the listing or summary except when all other levels are not available.

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

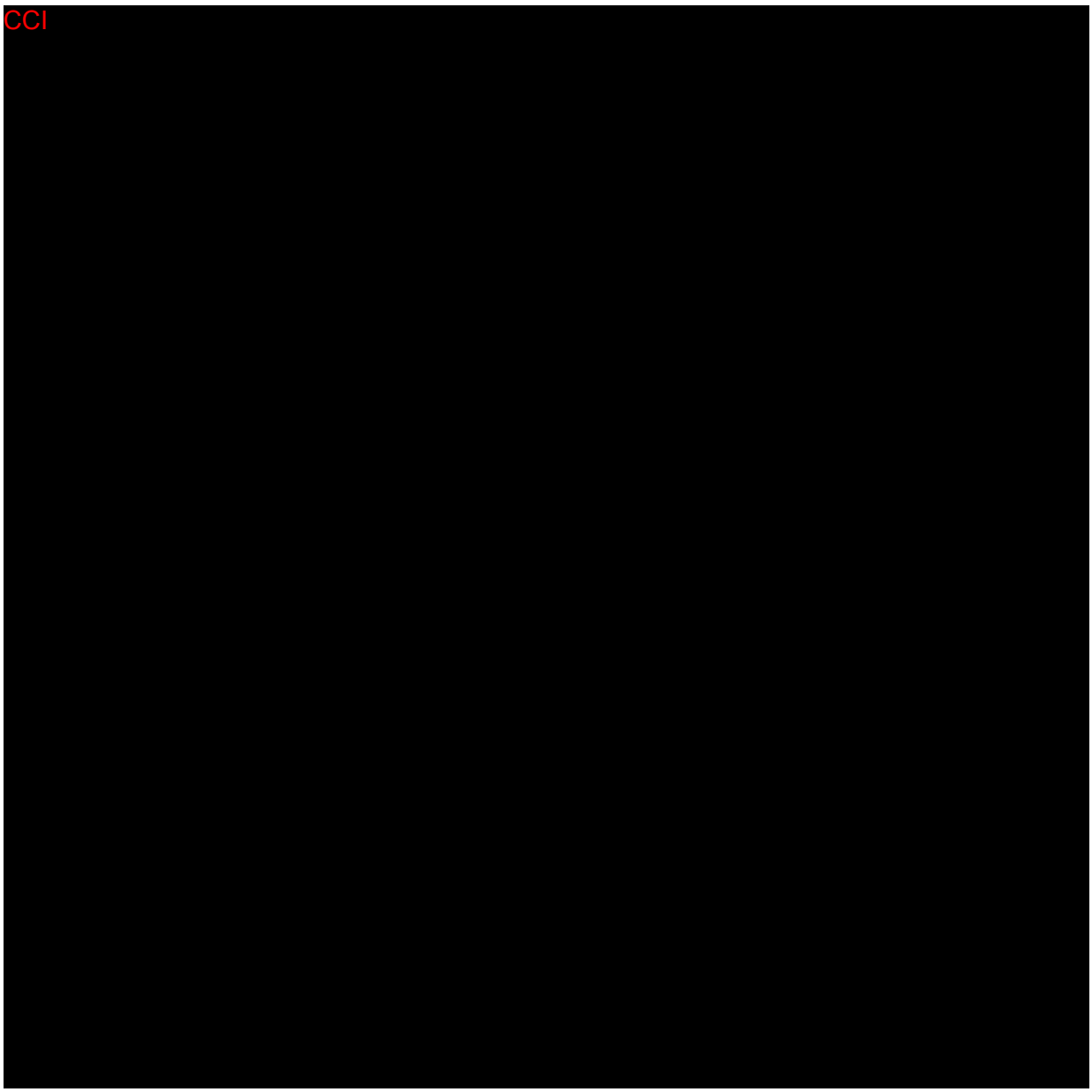
- Assign to 'Prior Only' if the concomitant medication start date and end date is prior to study treatment start date of the respective treatment period; if the subject has not taken any study treatment; or the concomitant medication start date is missing and the concomitant medication end date is before the study treatment start date of the respective treatment period;
- Assign to 'Prior and Concomitant' if the concomitant medication start date is prior to study treatment start date of the respective treatment period and the concomitant medication end date is on or after study treatment start date of the respective treatment period or ongoing treatment;
- Assign to 'Concomitant Only' if the concomitant medication start date is on or after the study treatment start date of the respective treatment period.

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

For medications which are considered ‘Prior and Concomitant’ or ‘Concomitant Only’ in Treatment Period 2 or in both treatment periods, the dose change needs to be considered. It should be noted that the medication flags will no longer be exclusive. The same medication may be “Concomitant Only” for Treatment Period 1 and for both treatment periods, but “Prior Only” for Treatment Period 2.

The following flags will be assigned:

CCI



In the summary of concomitant medications, each subject will be counted once within each PT (Any Medication, ATC Class, and PT). For example, if a subject takes Amoxycillin on two separate occasions, the subject will be counted only once under the medication "Amoxycillin", once in the corresponding ATC class, and once for "Any Medication". The number and percentages of subjects based on the Safety population along with the number of reports will be presented for 'Prior'. For 'Prior and Concomitant' the number and percentage of subjects will be presented together with 'Concomitant Only' medications.

A by-subject listing for all available data with the information as described in Section 7 and in addition medication/treatment, start and end date or ongoing, dose, route, frequency, primary indication for the concomitant medication, AE identifier if applicable, medical history identifier if applicable, and concomitant medication flag (Prior Only [P1, P2], Prior and Concomitant [PC1, PC2, PC2_after, PC12], Concomitant Only [C1, C2, C2_after, C12]) will be provided.

10 Efficacy

The primary efficacy endpoint will be summarized for the ITT and PP populations. CCI

Tables will be presented by treatment as described in Section 7.2 and treatment period. The planned treatment will be used. This is the randomized treatment before planned dose reduction following Amendment 2. After planned dose reduction following Amendment 2, the planned treatment is the reduced dose (CCI mg) for the C1-INH HAE subjects randomized to CCI mg in Treatment Period 2. Unplanned dose reductions or dose increase to CCI mg CSL312 q4wk will not be considered for the Efficacy analysis.

10.1 Primary Efficacy: Analysis of Time-Normalized Number of HAE Attacks in Treatment Period 1 (Blinded Part)

The ITT population will be used for the primary analysis and the PP will be used as the secondary.

As outlined in Section 8.2.8, HAE attacks with a start date not falling into the efficacy evaluation period will not be included in the analyses of efficacy but will be presented in a listing only.

Subjects will enter HAE symptoms into their eDiary and the start and end date and time, the interference of HAE symptom(s) with daily activities, and location(s) of the HAE symptom(s). Investigator-reported HAE attacks will be based upon review of subject diaries, relevant interval medical history, and physician judgment. The investigator may ask clarifying questions to assist in his/her assessment of whether or not an HAE attack occurred. If an attack occurred, then the investigator will record an attack in the eCRF, the start/end date, the attack location(s), and the severity of the attack based on the most severe symptoms. For every visit, the Investigator will report all HAE attacks that have occurred in the interim since the last visit the subject attended.

For the analyses, a HAE attack is defined based on the HAE attacks reported by the investigator using the HAE attack eCRF.

In the primary analysis, only subjects with C1-INH HAE who receive q4wk SC dosing (after an IV loading dose) in a blinded manner will be included. The evaluation periods are defined in Section 8.2.8.

The time-normalized number of HAE attacks per month during Treatment Period 1 for a subject will be calculated as:

(number of HAE attacks / length of subject's evaluation period in days) * 30.4375

where the length of subject's evaluation period is defined in Section 8.2.8.

The time-normalized number of HAE attacks per month will be summarized descriptively including median (primary) and mean (secondary) with corresponding 95% CIs by blinded treatment (i.e., placebo, or [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk).

To test for a difference in the primary efficacy endpoint between CCI mg CSL312 q4wk or CCI mg CSL312 q4wk and placebo q4wk, pairwise comparisons will be performed by testing the hypotheses using a two-sided Mann-Whitney test.

To account for multiple testing, the alpha level of 5% will be evenly split between the hypotheses tested. Therefore, the CCI mg CSL312 q4wk or CCI mg CSL312 q4wk CSL312 doses will each be evaluated against placebo q4wk at alpha = 0.025:

$H_{01}: a_1 = 0$ versus $H_{11}: a_1 \neq 0$
and
$H_{02}: a_2 = 0$ versus $H_{12}: a_2 \neq 0$

In the above hypotheses, the term "a_1" is the shift between the 2 distributions of CCI mg CSL312 q4wk and placebo q4wk and the term "a_2" is the shift between the distributions of CCI mg CSL312 q4wk and placebo q4wk, respectively.

For the difference in the primary endpoint between the 2 treatments CCI mg and CCI mg CSL312 q4wk in Treatment Period 1, a comparison will be performed as an CCI using a two-sided Mann-Whitney test at alpha = 0.05:
$H_{03}: a_3 = 0$ versus $H_{13}: a_3 \neq 0$
where the term "a_3" is the shift in the 2 distributions of the 2 CSL312 doses compared against each other.

There will be no testing of the CCI mg CSL312 q4wk dose against placebo q4wk. The time-normalized number of HAE attacks will be presented descriptively only.

A by-subject listing will be generated as specified in Section 7 and in addition showing the subject reported HAE symptoms, the HAE attack identifier as entered by the investigator with start and end date and time and duration (days), HAE attack location(s), and severity. HAE attacks with a start date falling into the efficacy evaluation period and HAE attacks treated with on-demand treatment for HAE attacks will be flagged. Details of the on-demand treatment will be provided in another by-subject listing. Derived efficacy variables such as number of HAE attacks and the time-normalized number of HAE attacks per month for each treatment period and for both treatment periods for subjects who received the same dose will be presented in another by-subject listing.

10.1.1 Sensitivity Analysis for Primary Efficacy: Missing Values for the Time-normalized Number of HAE Attacks in Treatment Period 1

To assess the impact of missing data for the primary efficacy variable a systematic approach will be applied. Imputation techniques based on MCMC methodology are considered inappropriate for this study with very small sample size.

For each treatment (i.e., placebo q4wk, CCI mg, or CCI mg CSL312 q4wk), 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. For the two comparisons of active treatment versus placebo all possible combinations from the subdivided ranges will be imputed to replace the missing values and the data will be analyzed using the Mann-Whitney test. 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) and depicted in a table and 2 graphs where the x-axis presents the subdivided range for placebo and the y-axis the subdivided range for the active treatment. The different outcomes will be distinguished by different symbols. This will only be applied to the ITT population.

10.1.2 Supporting Analysis: Time-normalized Number of HAE Attacks in Treatment Period 1 and 2 (Open-label Part)

In addition to the primary analysis, the time-normalized number of HAE attacks per month will also be summarized descriptively for the CCI mg and CCI mg CSL312 q4wk regimens for the following:

- Treatment Period 2 evaluation period (alone).
- Treatment Period 1 and Treatment Period 2 evaluation periods (combined) for subjects who received the same dose continuously during both treatment periods (data will only be included until the date of the planned dose reduction following Amendment 2 in Treatment Period 2).

The time-normalized number of HAE attacks per month will also be summarized descriptively for the CCI mg CSL312 q2wk regimen for subjects with C1-INH HAE for the efficacy evaluation period of Treatment Period 1 and for the CCI mg CSL312 q4wk regimen for subjects with FXII/PLG HAE for the efficacy evaluation periods of Treatment Period 1, Treatment

Period 2, and combined Treatment Period 1 and Treatment Period 2 (only applicable for subjects with FXII/PLG HAE).

The efficacy evaluation periods are defined in Section 8.2.8.

There will be no testing of the of CCI mg CSL312 q2wk dose against placebo q4wk or the CCI mg CSL312 q4wk dose against placebo q4wk for subjects with FXII/PLG HAE.

Subjects profiles will be generated for each subject. Subjects will be grouped by treatment sequence as for the by-subject listings as described in Section 7. The x-axis will show the Run-in Period, Treatment Period 1 and Treatment Period 2. The different subject IDs will be plotted on the y-axis. CCI

Subject profiles will be reviewed to detect possible patterns of missing values due to drop-outs, e.g., due to many attacks.

10.1.3 CCI

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10.1.4 CCI

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10.1.5 CCI

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10.2 Secondary Efficacy

Secondary efficacy endpoints will be analyzed for Treatment Period 1 and Treatment Period 2 separately. In addition, both treatment periods will be analyzed together for subjects who received the same dose continuously during both treatment periods (data will only be included until the date of the planned dose reduction following Amendment 2 in Treatment Period 2). The evaluation periods are defined in Section 8.2.8.

10.2.1 Analysis of Responders

A subject is classified as a responder if the percentage reduction in time-normalized number of HAE attacks per month is ≥ 50% as compared to the Run-in Period. The percentage reduction is calculated within a subject as:

$$100 * [1 - (\text{TNA CSL312} / \text{TNA Run-in})]$$

where TNA CSL312 is the time-normalized number of HAE attacks per month during treatment with CSL312 and TNA Run-in is the time-normalized number of HAE attacks per month during the Run-in Period.

The number and percentage of subjects classified as responders and non-responders will be presented along with 95% CI.

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In Treatment Period 2, the comparison between CCI mg and CCI mg CSL312 q4wk will only include data collected prior to the planned dose reduction following Amendment 2.

A by-subject listing will be provided as specified in Section 7 with the response classification and the degree of reduction in time-normalized number of HAE attacks per month.

10.2.2 **Analysis of Attack-free Subjects**

The number and percentage of subjects who do not experience a HAE attack will be presented.

10.2.3 **Analysis of 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 per month. The number and percentage of subjects experiencing at least 1 mild, moderate, or severe HAE attack will also be presented.

The severity of HAE attacks will be included in the by-subject listing (see Section 10.1).

10.2.4 Analysis of HAE Attacks Treated With On-demand HAE Medication

A treated HAE attack is defined as a HAE attack which started during the corresponding evaluation period for Treatment Period 1 or 2 and during which (start and end date including) on-demand medication to treat HAE attacks was taken (i.e., has been started).

The number and percentage and the time-normalized number of treated and untreated HAE attacks per month overall and by severity will be presented. A summary table will be provided with

- Number and percentage of subjects with at least 1 treated HAE attack;
- Number and percentage of subjects with only treated HAE attacks;
- Number and percentage of subjects with HAE attacks but without treated attacks;
- Number and percentage of subjects with no attacks at all (attack-free subjects);
- Descriptive statistics for the number and percentage of treated attacks per subject.

This analysis will be repeated for moderate or severe HAE attacks only.

A by-subject listing will be provided as specified in Section 7 and with the additional information of type of on-demand HAE medication (Berinert, Firazyr, Ruconest, Kalbitor, Cinryze, or Other), start date and time of the on-demand HAE medication, dose (unit), route, frequency, the date and dose of the last and next CSL312 (or placebo) administration, HAE attack identifier, start and end date and time of the HAE attack, location(s), and severity.

10.2.5 PK Analysis of CSL312 in Subjects With C1-INH

Please refer to Section 12.

10.2.6 Analysis of Safety and Tolerability of CSL312 in Subjects With C1-INH

Please refer to Sections 11.3, 11.4, 11.5, 11.6, 11.7, 11.8.

10.3 CCI [redacted]

CCI [redacted]

10.3.1 CCI [redacted]

CCI [redacted]

10.3.2 Analyses of Time-normalized Uses of On-demand HAE Medication per Month

Only for subjects with C1-INH HAE, the time-normalized number of uses of on-demand HAE medication per month will be summarized descriptively.

On the "Acute HAE Treatment" eCRF page, it will be entered if on-demand treatment for a HAE attack is needed and if so, what medication was used (Berinert, Firazyr, Ruconest, Kalbitor, Cinryze, or Other), the dose, route, and frequency administered, and the start date and time as well as the HAE attack identifier.

On-demand medications for treatment of a HAE attack during the efficacy evaluation period which will be administered during a HAE attack, will be included in the calculation of the time-normalized number of uses of on-demand medication for the treatment of a HAE attack. The start date and time of the administration of the on-demand medications will be compared with the start and end dates of the HAE attacks described in Section 10.1. Only if the date of an administration of an on-demand medication is between the start (including) and end date (including) of a HAE attack, the on-demand medication will be included in the calculation of the time-normalized number of uses of on-demand HAE medication per month.

The time-normalized number of uses of on-demand HAE medication per month will be calculated as:

$$\text{(number of uses of on-demand HAE medication / length of subject's evaluation period)} * 30.4375$$

where the length of subject's evaluation period is defined in Section 8.2.8.

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10.3.3 CCI

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10.3.4 CCI

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10.3.5 CCI

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10.4 Treatment Compliance

Compliance will be summarized for the ITT population for the SC injections in each treatment period and both periods together for subjects who received the same dose continuously during both treatment periods (data will only be included until the date of the planned dose reduction following Amendment 2 in Treatment Period 2). The IV infusions will not be included in the compliance analysis. The administered volume of each injection will be taken from the data base. The study medication has a concentration of CCI mg per CCI mL. To maintain the blind, the doses in the blinded part of Treatment Period 1 will be volume-normalized. It is planned that all SC injections will contain CCI mL. If in the blinded study part, the subject is randomized to CCI mg CSL312, the CCI mL injection will contain purely the study medication. For the CCI mg and the CCI mg CSL312 group, the study

medication will be diluted in a CCI and CCI ratio, respectively. For the derivation of the actual dose, it is assumed that the dilution will take place as planned. For the open-label part, the study medication is not diluted.

From the actual volume of an injection as in the database and considering the randomized dose, the actual dose will be derived as:

Actual dose (mg) = (actual volume [mL] / K [mL/mg]) * 100,

where K = CCI or CCI mL/mg for CCI mg, CCI mg, or CCI mg CSL312 q4wk in the blinded arm and CCI for the open-label arms.

Compliance for dose (mg) will be calculated as

Compliance (%) = [total cumulative actual dose / total planned dose)]*100,

where the total planned dose will be derived from the subject's exposure and planned treatment schedule (q2wk or q4wk) as

(duration of exposure in days / (7 * X)) * planned dose + planned dose

where (duration of exposure in days) is rounded down to the nearest integer which can be divided by 7 and X = 2 or 4 corresponds to q2wk or q4wk, respectively.

Only the administered doses will be considered for the total cumulative actual dose which are identical to the planned treatment. The planned treatment is the randomized treatment in Treatment Period 1 and in Treatment Period 2 prior to the planned dose reduction following Amendment 2. For C1-INH HAE subjects randomized to CCI mg CSL312 in Treatment Period 2, the planned treatment after dose reduction changes to CCI mg CSL312. Exposure duration will depend on the treatment period and subject's course of the study. Definitions are provided in Section 8.2.8.

The following summaries will be provided:

- Descriptive statistics for compliance (%) over the entire treatment period, for Treatment Period 1 plus the first three doses of Treatment Period 2 (administration on site), and for Treatment Period 2 after the first three doses (administration at home);
- Number and percentage of subjects in the compliance categories < 80%, 80 – 120%, and > 120% and < 90%, 90 - 110%, and > 110% for the periods specified above.

A by-subject listing as specified in Section 7 and with the following additional information will be provided:

- Randomized, planned and actual treatments;

- Compliance in Treatment Period 1 plus the first three doses of Treatment Period 2, after the first three doses in Treatment Period 2, and over the entire study.

11 Safety Analyses

Safety data will be summarized using the Safety population. Evaluation periods for the Safety analysis are defined in Section 8.2.8.

The summary tables will be presented by actual treatment. Due to the dose increase allowed in Treatment Period 2 for subjects randomized to CCI mg CSL312, the unplanned dose reduction, and the planned dose reduction for C1-INH HAE subjects randomized to CCI mg CSL312 following Amendment 2, the same subject may occur in different dose groups in Treatment Period 2. The Total column will report each subject only once. Thus, the treatment columns will no longer sum up to the Total column. This applies to all Safety summary tables.

11.1 Extent of Exposure

Duration of exposure (days) will be calculated as specified in Section 8.2.8 for the duration of the safety evaluation periods. Descriptive statistics will be provided for each treatment period in which a subject participated and for the subject's exposure over the entire study.

Number and percentages of subjects who received 0 or 1 IV infusions and descriptive statistics for the number of SC injections will also be presented.

A by-subject listing will be provided as specified in Section 7 and with the following additional information:

- Duration of exposure (days) for each treatment period in which the subject participated and subject's exposure over the entire study;
- Number of IV infusions and SC injections;
- Time point and level of dose modifications.

11.2 Dose Modification

The number and percentage of subjects (based on the Safety population) with dose change in Treatment Period 2 will be summarized. It will be differentiated between subjects randomized to CCI mg or CCI mg CSL312 and planned or unplanned dose changes. A by-subject listing will be provided as specified in Section 7 and with date and level of dose change.

11.3 Adverse Events

TEAEs are AEs which start on or after the date and time of the first administration of study treatment. TEAEs with a start date and time on or after the administration of the IV loading dose and before the first administration of SC investigational product will be analyzed separately from TEAEs with start date and time on or after the first administration of SC investigational product.

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 treatment. 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 treatment, 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 treatment, the AE will be considered non-treatment-emergent.

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

TEAEs occurring until the Follow-up Visit will be summarized. All AEs regardless of when they were reported will be listed.

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. Percentages for subject incidence rates will be based on the Safety population.

CCI [redacted]. 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.

The tables referring to TEAEs on or after first SC injection will comprise two parts: one – indicated in the numbering by x.1 – containing the number of subjects, percentage of subjects, and number of events, and the other – indicated in the numbering by x.2 – containing the event rates per administration and per subject year. The tables referring to TEAEs on or after the IV loading dose and before the first SC injection will comprise only the first part (number and percentage of subjects and number of events) as described above and no rates.

AE rates per SC injection for each safety evaluation period will be calculated as follows:

- AE Rate per SC Injection = $\frac{\text{Number of events for a particular PT}}{\text{Number of SC injections}}$

where number of SC injections will be the sum of the SC injections that subjects received during the respective safety evaluation period.

- AE Rate per Subject SC Year = $\frac{\text{Number of events for a particular PT}}{\text{Subject SC years}}$

where subject SC years will be the sum of the time in years that subjects were exposed to study treatment administered by SC injections during the respective safety evaluation period (sum of the duration after SC injections of the respective safety evaluation period in years).

The safety evaluation periods (Treatment Period 1, Treatment Period 2, and overall) are defined for the Safety analysis in Section 8.2.8.

For TEAEs which started on or after the IV loading dose but before the first SC dose, a summary table as described below will be provided and a table of TEAEs by SOC and PT as described below.

An overview summary of TEAEs will be provided as specified in Section 7 for:

- Any TEAE;
- Any SAEs;
- Any SAEs caused by COVID-19;
- Any deaths;

- Any deaths caused by COVID-19;
- TEAEs occurring within 24 hours of investigational product administration;
- Relates TEAEs;
- TEAEs leading to study discontinuation;
- TEAEs leading to study discontinuation caused by COVID-19;
- TEAEs in each intensity category;
- TEAEs in each outcome category;
- TEAEs not resolved or resolved with sequelae caused by COVID-19.

The following summary tables will be provided as specified in Section 7 for:

- TEAEs by SOC and PT;
- TEAEs by intensity, SOC, and PT;
- Related TEAEs by SOC and PT;
- TEAEs leading to study discontinuation by SOC and PT;
- Non-serious TEAEs by SOC and PT;
- Laboratory Findings reported as AEs.

The relationship between MedDRA SOC, PT, and Verbatim Text will be listed.

TEAEs will be listed for the Safety population. AEs without specification for treatment-emergency will be listed for all data available. The listings will include the variables as specified in Section 7 and in addition MedDRA SOC, PT, and the verbatim, AE start and end date and time if available, duration of AE in days, intensity, serious (yes or no), relationship to treatment (yes or no), outcome, action taken, and AE flags (TEAE, SAE, temporal relationship within 24 hours, laboratory finding, AESI).

The following listings will be provided:

- Non-TEAEs – all data available;
- TEAEs on or after IV loading dose and before first SC dose – Safety population;
- TEAEs on or after first SC dose – Safety population;
- AEs related to laboratory findings – all data available;
- AEs caused by COVID-19;
- MedDRA SOC and PT with all AE verbatim – all data available.

11.4 Adverse Events of Special Interest

The AESIs are:

- TEE –Embolic and thrombotic events (Standardized MedDRA Query [SMQ]);
- Bleeding events –Haemorrhages (SMQ);
- Anaphylactic reaction–Anaphylactic reaction (SMQ)(broad).

Summaries by SOC and PT for each AESI will be provided separately.

In addition, AESIs will be listed separately in the format specified in Section 11.3.

CSL will provide CCI [redacted] with the MedDRA SMQs.

11.5 Deaths and Serious Adverse Events

There will be an entry in the overall summary table showing the number of subjects with treatment-emergent SAEs and the number of events. Another entry will show the number of treatment-emergent deaths. Treatment-emergent SAEs and deaths will be differentiated for caused by COVID-19.

An overview summary of treatment-emergent SAEs, including counts and percentages of subjects as well as the number of events, will be provided for:

- any treatment-emergent SAE;
- treatment-emergent SAEs caused by COVID-19;
- any treatment-emergent death;
- treatment-emergent death caused by COVID-19;
- treatment-emergent SAEs occurring within 24 hours of investigational product administration;
- Relates treatment-emergent SAEs;
- treatment-emergent SAEs leading to study discontinuation;
- treatment-emergent SAEs leading to study discontinuation caused by COVID-19;
- treatment-emergent SAEs in each intensity category;
- treatment-emergent SAEs in each outcome category;
- treatment-emergent SAEs not resolved or resolved with sequelae caused by COVID-19.

For treatment-emergent SAEs a summary table by SOC and PT as specified in Section 11.3 will be provided.

Deaths will be listed for all available data. An additional by-subject listing for SAEs (including deaths) will be produced for all available data which will contain the information as specified in Section 7 and in addition information for criteria for SAE, hospitalization admission and discharge date, alternative cause for SAE not related to study treatment. SAEs and deaths caused by COVID-19 will be flagged.

11.6 Adverse Events Leading to Discontinuation of Study Treatment, Withdrawal from the Study, and Other Significant Adverse Events

For AEs leading to study discontinuation, a summary table by SOC and PT as specified in Section 11.3 will be provided. AEs leading to study discontinuation will also be listed. AEs leading to study discontinuation caused by COVID-19 will be flagged and displayed separately.

11.7 Adverse Drug Reactions

An adverse drug reaction is defined as either:

a. A TEAE, including local tolerability events, that began during or within 1 hour of the start of an administration, or

b. A TEAE reported as causally related to the administration of study treatment, or which the sponsor determined to be causally related to the administration of study treatment, or

c. A TEAE for which the investigator's causality assessment is missing or indeterminate, or

d. All TEAEs for which the exposure-adjusted incidence rate in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in exposure-adjusted incidence rates is 1% or more. This bullet point is only applicable for Treatment Period 1 (blinded and open-label part).

A summary table for adverse drug reactions by SOC and PT will be provided as well as a by-subject listing.

11.8 Public Disclosure of Clinical Trials Requirements

To support public disclosure requirements for clinical study, a summary of treatment-related SAEs will be provided.

Additionally, a summary of non-serious TEAEs by SOC and PT will be produced. A summary of the number of subjects with non-serious TEAEs that occurred at a frequency of more than 1%, 2%, 3%, 4%, and 5% will be produced following these steps for each frequency:

- Determine which subjects experienced any non-serious TEAE that occurred at a frequency higher than the frequency of interest.
- From that subset of subjects, sum the subjects who experienced at least one of the non-serious TEAEs that occurred at a frequency higher than the frequency of interest. Do not double count subjects who experienced 2 or more of those non-serious TEAEs.

11.9 Pregnancies

If a female subject becomes pregnant, she must discontinue treatment with the investigational product immediately, her participation in the study will be discontinued, and the procedure for discontinuation of a subject will be followed, as described in protocol Section 4.2.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If any subject becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.10 Clinical Laboratory Evaluations

Laboratory tests will be summarized descriptively by scheduled visit as specified in Section 7. For laboratory test 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 8.2.4. Laboratory tests with categorical values will be summarized by number and percentage of subjects in the respective categories (based on subjects of the Safety population with non-missing values at this time point). Summary tables will be provided for hematology, biochemistry, coagulation, and immunogenicity (inhibitory and non-inhibitory antibodies). All laboratory tests (scheduled and unscheduled) will be listed. The listings will include the variables as specified in Section 7 and in addition the laboratory

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.

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 number and percentage of subjects who experience antibodies (inhibitory and non-inhibitory) specific to FXIIa will be summarized as a secondary (for subjects with C1-INH HAE) and CCI in this study. Percentages will be based on subjects of the Safety population with non-missing values at each time point.

The number and percentage of subjects with abnormal laboratory values reported as AEs will be summarized by laboratory test and visit and for all laboratory tests combined as a further secondary (for subjects with C1-INH HAE) and CCI . The laboratory findings reported as AEs will be identified through the eCRF. Percentages will be based on subjects of the Safety population with non-missing values at each time point.

The laboratory tests will be presented in the following grouping and sequence as specified in Table 6 of the protocol. The test names used in the TFLs 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.

Hematology: Hemoglobin, Hematocrit, Erythrocytes (red blood cell count), Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Leukocytes (white blood cell count), Neutrophils (% and absolute), Lymphocytes (% and absolute), Monocytes (% and absolute), Eosinophils (% and absolute), Basophils (% and absolute), and Platelet count.

Biochemistry: Sodium, Potassium, Chloride, Carbon dioxide, Albumin, Alkaline phosphatase, Direct bilirubin, Total bilirubin, Aspartate aminotransferase, Total protein, Calcium, Alanine aminotransferase, Creatinine, Phosphate, Blood urea nitrogen, Glucose.

Coagulation: CCI [redacted].

Immunogenicity: Binding antibodies (inhibitory and non-inhibitory) specific to FXIIa antagonist monoclonal antibody.

Urinalysis: Bilirubin, Occult blood, Erythrocytes, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific gravity, Urobilinogen.

11.11 Other Safety Measures

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

11.11.1 Vital Signs

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

The following summaries of descriptive statistics will be provided for scheduled visits as specified in Section 7:

- Measured values of vital signs by scheduled visit;
- Change from baseline by scheduled visit.

A by-subject listing will also be provided. The listing will also include unscheduled assessments.

12 Pharmacokinetic Analyses

The PK analysis will be performed using the PK population.

CCI [redacted]

CCI

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

Derivation of PK parameters will be conducted using actual infusion durations, actual doses administered and actual sampling times relative to the start of the dose infusion.

12.1 Plasma PK Endpoints

The PK parameters derived by CCI will include

- C_{max};
- $AUC_{0\text{-}tau}$;
- T_{max};
- $T_{1/2}$;
- CL_{tot};
- Vz.

The PK parameter derivation including imputation of the values below the lower limit of quantification (BLQ) and missing data will be conducted in accordance to PK-GDL-01 which gives guidance on how to derive PK parameters in the presence of missing data.

12.2 Summary of CSL312 Plasma Concentrations

The handling and imputation of BLQ values for PK parameter derivation is described in PK-GDL-01. The imputation rules below will be used for summary statistics of CSL312 plasma concentrations. The summaries will be given by sampling time point (planned time points) and treatment group.

- The sampling time of pre-dose samples relative to start of the dose infusion will be treated as zero;
- Concentration values below BLQ in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- Post-dose one or more consecutive BLQ concentrations flanked by quantifiable concentrations will be set to missing;

- Post-dose BLQ concentrations after the last quantifiable point will be set to missing for mean presentations of plasma concentrations.
- The mean/median value at a time-point where one or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the lower limit of quantification (BLQ) of the assay;
- Zero mean or median values will be included in summary tables.

It should be noted that a high proportion of BLQ values may affect the SD; if more than 50% of the values are imputed (i.e., BLQ), then the SD will not be displayed.

Summary statistics for concentration-time data will include the percentage of BLQ values relative to the total number of observations

> %BLQ = 100 * (number of subjects who have BLQ values / total number of subjects within each treatment group at each time point)

and the coefficient of variation (CV) % in addition to the statistic parameters outlined in Section 7.

Two mean plots for CSL312 plasma concentrations (one on linear and one on log-linear scale) versus nominal (planned) time will be provided. All CSL312 treatment groups will be overlaid in each mean plot. Error bars on mean values within the plot will represent +/- SD values. The plasma concentration for subjects who are down-titrated from CCI mg to CCI mg will stop for the CCI mg group when down-titration occurs. The plasma concentrations after down-titration will be included in the CCI mg group starting at the time point of down-titration.

Individual PK plots (one linear and one log-linear scale) for all subjects within the same active treatment (with dose level specified) combined on one graph and plotted versus actual time of the samples will be provided. For subjects who are down-titrated, a vertical line will indicate the time point when the CCI mg dose was administered.

A by-subject listing of CSL312 plasma concentrations with the concentrations flagged that have been excluded from the derivation of the PK parameters will support the summaries.

12.3 Summary of CSL312 Pharmacokinetic Parameters

PK parameters will be summarized by treatment group.

Variable	Statistical Parameters:
C_{max}, $AUC_{0\text{-}tau}$, CL_{tot} and Vz	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%
$T_{1/2}$	n, arithmetic mean, SD, CV%, minimum, median, and maximum
T_{max}	n, minimum,Q1, median, Q3, and maximum

A by-subject listing of CSL312 PK parameters will be provided.

CCI [redacted]

13 CCI [redacted]

13.1 CCI [redacted]

CCI [redacted]

13.2 CCI [redacted]

CCI [redacted]

14 Pharmacokinetic - CCI [redacted] Analyses

A population PK-CCI analysis using the CCI population will be conducted by Clinical Pharmacology at CSL. CCI [redacted]. This work will be presented in a separate analysis plan and report.

15 References

Liublinska, V and Rubin, DB (2014) Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial, Statistics in Medicine Vol 33 (24) 4170-4185.

PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring.

Signature Page

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Signed By	Date (GMT)
PPD	01-Jul-2020 11:32:03
Approved-PPD Approval	
PPD	19-Jun-2020 20:28:42
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