CLINICAL STUDY PROTOCOL

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

Study Number:	CSL312_3002
Study Product:	CSL312 (Factor XIIa inhibitor monoclonal antibody)
Development Phase:	3
Short Title:	Study of the long-term safety and efficacy of CSL312 (garadacimab) in the prophylactic treatment of hereditary angioedema attacks
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Amendment 1
EudraCT Number:	2020-003918-12
IND Number:	139936
Protocol Date:	27 October 2022
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki, and all applicable national and local regulations.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL Behring (or delegate) and provided to the study sites as needed.

REVISION HISTORY

Date	Version	Summary of Changes
12 October 2020	Original	Not applicable
27 October 2022	Amendment 1	High-level description of changes: • Removal of brand names of permitted and prohibited treatments for HAE attacks during the study (on-demand medication) and emphasis that on-demand medication must be used in accordance with standard of care in the region and with the product label; text added that Berinert will not be supplied to study sites in Japan as a study medication. • Language added about conduct of study conforming with principles in the Declaration of Helsinki. • Follow-up Visit format (telephone call only) and window updated. • Autoinjector to be used in place of needle safety device for administration of CSL312. • Overall study duration and possibility for stopping early updated. • "Injection rate" removed from overdose text. • Changes made to frequency of QoL assessments, urinalysis, hematology / biochemistry / coagulation sample collection, and biomarker sample collection. • Changes made to assessments performed at EOT Visit and Follow-up Visit. • Details added regarding consent to continue with treatment under Amendment 1.

		• Clarification added that blood draws are performed on the same day of CSL312 administration (on visit days). • Benefits and risks text updated (including name of section heading), including removal of TEEs and abnormal bleeding. • Maximum attack-free time added as an exploratory efficacy endpoint. • Relevant items added for Czech Republic sites only (from country specific administrative amendment). • Administration location updated for the needle safety device. • Clarification added that CSL312 may be self-administered by subject or caregiver. • Details about recording the dose and date of CSL312 administration updated. • Access to investigational product will not be provided after end of study. • Erythrocytes removed from urinalysis procedures. • Adverse events of special interest language updated. • Updated language added to describe how the impact of COVID-19 pandemic will be handled in the statistical analysis. • CSL312 description changed from “antagonist” to “inhibitor.” • Clinical experience text updated with recent information / data.

		• Dosing modifications to no longer be permitted during the study. • Method of measuring body temperature and requirement for consistency of method removed. • Clarification added about allowing remote assessments / procedures under extenuating circumstances. • Updates made to the description of CSL312. • Subjects may switch to an HAE prophylaxis medication during the Follow-up Period. • Text about device malfunctions added. • Prothrombin fragment (pF1+2) assessment removed from the coagulation panel. • Description of investigational medical device revised. • Minor corrections and clarifications, including word modifications and administrative changes

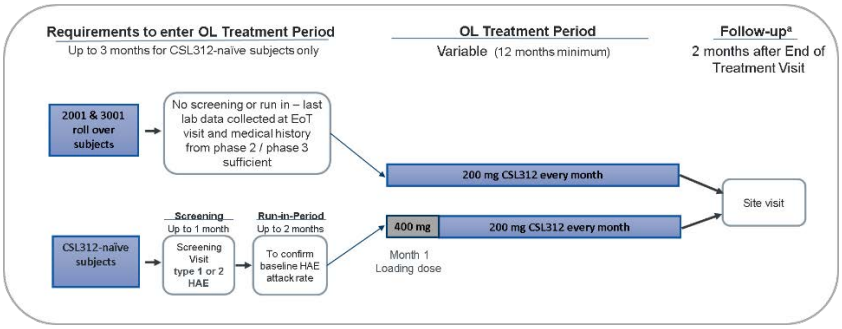
Clinical Study Protocol Synopsis

Title	An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema
Study Number	CSL312_3002
Sponsor	CSL Behring, LLC
Development Phase	3
Study Product	CSL312 (Factor XIIa inhibitor monoclonal antibody)
Indication	Treatment of hereditary angioedema (HAE)
Study Summary and Overview	This phase 3b study will evaluate long-term safety and efficacy of CSL312 (also known as garadacimab) when administered subcutaneously (SC) once monthly for at least 12 months. Subjects entering CSL312_3002 will be from 3 sources: • Subjects who participated in Study CSL312_2001 • Subjects who participated in Study CSL312_3001 • CSL312-naïve HAE subjects who have not participated in either of the above studies The study will consist of screening, run-in (for CSL312-naïve subjects), open label treatment, and follow-up periods. For subjects naïve to CSL312, there will be up to 1 month Screening Period followed by a Run-In Period, which may last at least 1 month and up to 2 months. CSL312-naïve subjects who meet all eligibility criteria during the Run-In Period will then enter the at least 12-month Treatment Period. Subjects rolling over from Studies CSL312_2001 or CSL312_3001 will enter directly into the Treatment Period.

Study Summary and Overview (continued)

Subjects who reach the end of treatment or terminate the study early will have a follow-up telephone call 2 months after the End of Treatment Visit (End of Treatment Visit is 1 month after the last dose of CSL312). Subjects may switch to an HAE prophylaxis medication during the Follow-up Period.

The study schematic is shown below.



EoT = End of Treatment; HAE = hereditary angioedema; OL = open-label.

[a] The Follow-up Visit will be conducted via telephone call.

A Pharmacokinetic (PK) subgroup analysis will be conducted in adult CSL312-naïve subjects to further characterize the PK of CSL312 following the SC loading dose. A target number of 12 CSL312-naïve adult subjects will be included in the subgroup analysis.

Per Amendment 1, subjects or caregivers will subcutaneously administer CSL312 200 mg autoinjector (AI) instead of CSL312 200 mg needle safety device (NSD). The AI is a device that contains the same prefilled syringe already being used in the NSD since the start of the study. The purpose of using an AI is to further facilitate the administration of CSL312. The dose and dosing regimen will continue to be 200 mg once monthly. Subjects who decline switching to CSL312 200 mg AI and who have participated in the study for at least 12 months will receive 1 more dose of CSL312 200 mg NSD at the time of the scheduled site visit and subsequently proceed with the End of Treatment

	Visit 1 month later, as well as a Follow-up Visit 2 months after the End of Treatment Visit, as per the original protocol.
Primary Objective(s)	The primary objective of the study is to evaluate the long-term safety of SC administration of CSL312 in the prophylactic treatment of subjects with C1-INH HAE.
Primary Endpoint(s)	The primary safety endpoint is treatment-emergent adverse events (TEAEs).
Secondary Objective(s)	The secondary objectives of this study are to evaluate the long-term efficacy, safety and patient reported assessment of response to therapy.

Secondary Endpoint(s)

The secondary efficacy endpoints are:

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

The secondary safety endpoints are:

- Serious adverse events (SAEs)
- Deaths
- Related TEAEs
- TEAEs leading to study discontinuation
- TEAEs by severity
- Anti-CSL312 antibodies
- Laboratory findings reported as adverse events (AEs)
- Adverse events of special interest (AESIs) (ie, thromboembolic events [TEEs], abnormal bleeding events, severe hypersensitivity, including anaphylaxis events)
- TEAEs (for nC1-INH subjects only)

The secondary endpoint for the reported assessment of response to therapy is:

- Subject's Global Assessment of Response to Therapy (SGART)

Study Duration	Per Amendment 1, the duration of treatment for an individual subject is estimated to be a minimum of 12 months. The treatment duration for each subject will be variable. In addition, the study may be stopped in a specific country either after garadacimab obtains regulatory approval or it becomes commercially available in the respective country. The Sponsor reserves the right to stop the study at any time.
Number of Subjects	The study plans to enroll approximately 150 subjects. At least 100 subjects should receive treatment for a minimum of 12 months.

Study Population and Main Criteria for Eligibility

The main eligibility criteria for the **Run-in Period** are:

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements and / or the subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent / assent as appropriate.
2. Male or female.
3. Aged ≥ 12 years at the time of providing written informed consent or assent for minors.
4. Diagnosed with clinically confirmed C1-INH HAE
    a. Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
    b. C1-INH antigen concentration and / or functional activity ≤ 50% of normal concentration as documented in the subject's medical record, and
    c. C4 antigen concentration below the lower limit of the reference range as documented in the subject's medical record.
5. Experienced ≥ 3 HAE attacks during the 3 months before Screening, as documented in the subject's medical record.

Note: For subjects taking any prophylactic HAE therapy during the 3 months before Screening, ≥ 3 HAE attacks may be documented over 3 consecutive months before commencing the prophylactic therapy.

The main eligibility criteria for the **Treatment Period** are:

1. Participated in the Run-in Period for at least 1 month (CSL312-naïve subjects only).
2. Experienced at least an average of 1 HAE attack per month during the Run-in Period (ie, experienced a total of at least 2 HAE attacks).
3. Do not have laboratory clinical abnormalities assessed as clinically significant by the investigator in results of

	hematology, chemistry, or urinalysis assessments performed during Screening. **Note**: Subjects with ≥ 2 times the upper limit of normal for aspartate aminotransferase (AST) and / or alanine aminotransferase (ALT) may be eligible for participation if there is an explanation for this laboratory result and if the results are not clinically significant.
Study Product Dose, Dosing Regimen and Administration	CSL312 will be administered as 1 dose (200 mg) SC once monthly for a total minimum of 12 doses (ie, 12 months of treatment). For CSL312-naïve subjects, a loading dose of 400 mg (two 200 mg doses) will be administered SC on the first month, then 200 mg once monthly for at least 11 months. Per Amendment 1, CSL312 will be administered as 1 injection (200 mg) SC once monthly using an AI instead of the NSD. The AI is a device that contains the same prefilled syringe already being used in the NSD since the start of the study. The purpose of using an AI is to further facilitate the administration of CSL312.
Comparator Product, Dose, Dosing Regimen and Administration	Not applicable
Efficacy Assessments	At each subject's study visit, the investigator will assess and document the occurrence of HAE attacks in the Case Report Form (CRF) based on subject electronic diary (eDiary) data.
Safety Assessments	Safety will be assessed by all AEs, TEAEs, vital signs, physical examinations, hematology, biochemistry, urinalysis, coagulation parameters, and anti-drug antibodies.

Pharmacokinetics	Plasma samples will be collected for assessment of CSL312 concentrations. From a PK subgroup analysis in CSL312-naive adult subjects, CSL312 PK parameters (maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the concentration-time curve from 0-30 days [$AUC_{0\text{-}30days}$]) will be derived.
Pharmacodynamics	Plasma samples will be collected for assessment of FXIIa-mediated kallikrein activity.
Other Assessments	Other assessments to evaluate quality of life and response to treatment will be obtained using the Angioedema Quality of Life (AE-QoL) questionnaire, the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire, the Treatment Satisfaction for Medication Questionnaire version II (TSQM II), and the Subject and Investigator Global Assessment of Response to Treatment (SGART and IGART).

Statistical Analyses

A minimum of 100 subjects are planned to receive treatment for a minimum of 12 months. This is a single arm study without a control arm. The sample size for this study is not based on a formal statistical sample size calculation but on the guideline E1A issued by the International Conference on Harmonisation, March 1995. The sample size of 100 subjects allows observation of ≥ 1 AE with a probability of 3% at 95% confidence.

The primary endpoint, TEAEs for all C1-INH HAE subjects receiving CSL312 once monthly, independent of the use of CSL312 200 mg AI or CSL312 200 mg NSD, will be summarized using the Safety Analysis Set, defined as all subjects who receive at least 1 dose of CSL312. The TEAEs will be assessed overall and by the use of CSL312 200 mg AI or CSL312 200 mg NSD. TEAEs are AEs that start on or after the date and time of the first administration of study treatment until the Follow-up Visit. TEAEs 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.

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

TEAE rates per injection will be calculated as follows:

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

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

TEAE rates per subject years will be calculated as follows:

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

where subject years will be the sum of the time in years that subjects were exposed to study treatment during the respective safety evaluation period.

Schedule of Assessments: Screening and Run-in Period (CSL312-naïve Subjects Only)

Study Period		Screening	Run-in Period [A]				
Day		-30 to 1	1	15	30	45	60 [B]
Window (Days)				± 4	± 4	± 4	± 4
Study center visit		X [C]					
Telephone contact				X	X	X	X
Written informed consent [D]		X					
Demographics		X					
Relevant medical history [E]		X					
Inclusion / exclusion criteria		X					
Physical examination [F]		X					
Vital signs including body weight		X					
Urine collection for urinalysis (central lab)		X					
Blood Draws (central lab)	Hematology / Biochemistry / Coagulation	X					
	C1-INH and C4 [G]	X					
Pregnancy test [H]		X					
Individual acute treatment plan [I]		X					
eDiary training		X					
Open eDiary access / review eDiary instructions with subject			X				
Review eDiary data and assess / document HAE attacks				X	X	X	X
Close eDiary access and collect device [J]							X
Confirm access to on-demand HAE medication [K]			X	X	X	X	X
Prior / concomitant medications and therapies		←	—	—	—	→	
Adverse events		←	—	—	—	→	

Abbreviations: C1-INH = C1-esterase inhibitor; C4 = complement C4; eDiary = electronic diary; HAE = Hereditary angioedema.

Footnotes to the Schedule of Assessments: Screening and Run-in Period [All Subjects]

[A:] Subjects must complete at least 1 month of the Run-in Period. Subjects may enter the Treatment Period once they experience at least 2 HAE attacks.

[B:] If a subject is unable to enter the Treatment Period after Day 60, then the Sponsor approval is required for the subject to extend the Run-in Period for another month to enter the Treatment Period within 3 months. Day 60 (extended Run-in Day 90) will conclude the study for a subject who has entered the Run-in Period and is subsequently not eligible to enter the Treatment Period. Eligible subjects will proceed to the Day 1 visit of the Treatment Period.

[C:] The first day of the Run-in Period may occur on the same day as the Screening Visit if the subject meets the criteria for entering the Run-in Period.

[D:] Written informed consent must be provided before any study-specific assessments or procedures are performed.

[E:] Include C1-INH functional activity and antigen, and C4 antigen concentration history, recording of overall health within the 3 months before Screening; HAE history including type, age of diagnosis, medical records to support diagnosis (ie, attack frequency, history of laryngeal attacks, prior prophylaxis therapy and on-demand treatment medication) within the 3 months before Screening, and contraception method (for female subjects of childbearing potential only).

[F:] A physical examination will be conducted per the investigator's standard procedure and will also include assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

[G:] Blood sample for C1-INH functional activity and antigen concentration, and C4 antigen concentration will be collected during the Screening Period for confirmation of historical laboratory values contained in the subject's medical record. If a subject requires the use of on-demand medication to treat an HAE attack within 120 hours (ie, 5 days after C1-INH administration) before Screening, then that subject may return to the study site within the first 2 weeks of the Run-in Period for a second blood draw to assess C1-INH antigen concentration and functional activity, and C4 antigen concentration.

[H:] A urine test for beta-human chorionic gonadotropin will be performed for women of childbearing potential. A serum pregnancy test will be performed if urine result is inconclusive.

[I:] An individual acute treatment plan will be developed by the investigator to ensure that participating subjects are capable of managing their HAE attacks during the study. The action plan will be reviewed with subjects.

[J:] Access to the eDiary should be closed at the Day 60 Telephone Contact for subjects who are not eligible to enter the Treatment Period. eDiary should be returned.

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

Schedule of Assessments: Treatment Period (All CSL312_3001 Subjects and CSL312-naïve Subjects)

Study Period		Treatment Period										End of Treatment[A]	Final Visit[B] / Follow-up (2 months after End of Treatment Visit)
Month			1	2	3	6	9	12	18	24	30		
Visit Day		1	31	61	91	181	271	361	541	721	901		
Visit Window (Days)			±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]		±7d
Study center visit		X	X	X	X	X	X	X	X	X	X	X	
Written informed consent for subjects rolling over from Study CSL312_3001		X											
Confirm eligibility for Treatment Period[D]		X											
Physical examination[E]		X	X	X	X	X	X	X	X	X	X	X	
Vital signs including body weight and height[F]		X	X	X	X	X	X	X	X	X	X	X	
SGART and IGART[G]								X		X			
TSQM II (subjects ≥ 18 yrs), AE-QoL (subjects ≥ 18 yrs) & WPAI:GH (subjects ≥ 16 yrs)[H]		X			X	X	X	X	X	X			
Urine collection for urinalysis (central lab)		X				X		X	X	X	X	X	
Blood Draws[I] (central lab)	Hematology/Biochemistry/Coagulation	X			X	X		X	X	X	X	X	
	Retention sample for HAE biomarkers[J]	X	X	X	X	X	X	X	X	X	X	X	
	Pharmacokinetics /Pharmacodynamics	X	X	X	X	X	X	X	X	X	X	X	
	Immunogenicity	X				X		X		X		X	
Pregnancy test[K]		X	X	X	X	X	X	X	X	X	X	X	
PRO / eCOA tablet training		X											
Review of eDiary instructions with subject		X											
Review eDiary data and assess / document HAE attacks		X	X	X	X	X	X	X	X	X	X	X	X
eDiary deactivation[L]													X
Confirm access to on-demand HAE medication[M]		X	X	X	X	X	X	X	X	X	X		
IRT CSL312 kit assignment		X	X	X	X	X	X	X	X	X	X		
Accountability of CSL312		X	X	X	X	X	X	X	X	X	X	X	
Administration of CSL312 at site[N,O]		X	X	X	X								

Study Period	Treatment Period										End of Treatment[A]	Final Visit[B] / Follow-up (2 months after End of Treatment Visit)
Month		1	2	3	6	9	12	18	24	30		
Visit Day	1	31	61	91	181	271	361	541	721	901		
Visit Window (Days)		±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]	±4d[C]		±7d
Concomitant medications and therapies	←	—	—	—	—	—	—	—	—	—	→	
Adverse events	←	—	—	—	—	—	—	—	—	—	→	

Abbreviations: AE-QoL = Angioedema Quality of Life; eCOA = electronic clinical outcomes assessment; eDiary = electronic diary; HAE = hereditary angioedema; IGART = Investigator's Global Assessment of Response to Therapy; IRT = interactive response technology; PRO = patient reported outcome; SC = subcutaneous; SGART = Subject's Global Assessment of Response to Therapy; TSQM II = Treatment Satisfaction for Medication Questionnaire version II; WPAI:GH = Work Productivity and Activity Impairment: General Health; yrs = years.

Footnotes to the Schedule of Assessments: Treatment Period [All CSL312_3001 and CSL312-naïve Subjects]

A: End of treatment is 1 month after the last administration of CSL312.

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

C: Treatment Period visits have ± 4 day window, with a maximum of 34 days between any 2 doses (see Section 5.1.3).

D: CSL312-naïve subjects must complete at least 1 month of the Run-in Period and may enter the Treatment Period once they experience at least an average of 1 HAE attack per month during the Run-in Period (ie, at least 2 HAE attacks in total), and do not have laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments performed during Screening (see Section 4.1.1.2). For CSL312-naïve subjects, C1-INH functional activity and antigen, and C4 antigen concentration levels should be confirmed before entry into the Treatment Period. Eligibility to be confirmed before entry into the Treatment Period and any study assessments are performed.

E: A physical examination will be conducted per the investigator's standard procedure, and will also include assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

F: Height is collected at Day 1 only.

G: Investigator completes IGART in Rave. Subjects complete SGART.

H: Subjects rolling over from Study CSL312_3001 who have completed the AE-QoL and WPAI:GH as part of the last visit of Study CSL312_3001 will only need to complete the TSQM II at Day 1.

I: Blood draws should be completed before study drug administration on the same day.

J: Blood samples for potential future assessment of HAE biomarkers will be obtained during the Treatment Period. These samples will be stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion of the study or used for future research on HAE. These samples will not be collected in adolescents.

K: The urine test for beta-human chorionic gonadotropin will be performed for women of childbearing potential only. A serum pregnancy test will be performed by the site if urine result is inconclusive. Female subjects of childbearing potential will perform home urine testing on months for which there is no onsite visit.

L: The eDiary will be collected and deactivated for all subjects. For subjects who terminate the study early, the eDiary should be deactivated and collected either on date of early termination or at the Follow-up Visit as applicable. If the Follow-up Visit is conducted remotely, the device should be returned to the site.

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

N: For CSL312 naïve subjects, the first dose of CSL312 will be a loading dose consisting of 2 SC injections of 200 mg CSL312 each for a total of 400 mg CSL312. Subjects rolling over from the CSL312_3001 study will not receive a loading dose. Subjects will be trained in CSL312 self-administration at Baseline, Months 1, 2 and 3 visits. Starting at Month 4, all subjects will self-administer at home monthly.

O: Subjects will complete the Medication Dosing Diary on the eDiary at site visits (ie, Day 1, Months 1, 2, and 3) and then monthly at home through the End of Treatment Visit.

Schedule of Assessments: Treatment Period (CSL312_2001 Subjects)

Study Period		Treatment Period							End of Treatment[A]	Final Visit[B] /Follow-up (2 months after End of Treatment Visit)
Month			3	6	12	18	24	30		
Visit Day		1	91	181	361	541	721	901		
Visit Window (Days)			±4d[C]	±4d[C]	±4[C]	±4d[C]	±4d[C]	±4d[C]		±7d
Study center visit		X	X	X	X	X	X	X	X	
Written informed consent		X								
Confirm eligibility for Treatment Period [D]		X								
Physical examination [E]		X	X	X	X	X	X	X	X	
Vital signs, body weight, and height [F]		X	X	X	X	X	X	X	X	
SGART and IGART					X		X			
TSQM II (subjects ≥ 18 yrs), AE-QoL (subjects ≥ 18 yrs), WPAI:GH (subjects ≥ 16 yrs)[G]		X		X	X	X	X			
Urine collection for urinalysis (central lab)		X		X	X	X	X	X	X	
Blood Draws[I] (central lab)	Hematology / Biochemistry / Coagulation	X		X	X	X	X	X	X	
	Retention sample for HAE biomarkers[H]	X	X	X	X	X	X	X	X	
	Pharmacokinetics / Pharmacodynamics	X	X	X	X	X	X	X	X	
	Immunogenicity	X		X	X		X		X	
Pregnancy test [J]		X	X	X	X	X	X	X	X	
PRO / eCOA tablet training		X								
Review of eDiary instructions with subject		X								
Review eDiary data and assess / document HAE attacks			X	X	X	X	X	X	X	X
eDiary deactivation [K]										X
Confirm access to on-demand HAE medication [L]		X	X	X	X	X	X	X		
IRT CSL312 kit assignment		X	X	X	X	X	X	X		
Accountability of CSL312		X	X	X	X	X	X	X	X	
Administration of CSL312 at site [M,N]		X								
Concomitant medications and therapies		←	———	———	———	———	———	———	→	
Adverse events		←	———	———	———	———	———	———	→	

Abbreviations: AE-QoL = Angioedema Quality of Life; eCOA = electronic clinical outcomes assessment; eDiary = electronic diary; HAE = hereditary angioedema; IGART = Investigator's Global Assessment of Response to Therapy; IRT = interactive response technology; PRO = patient reported outcome; SGART = Subject's Global Assessment of Response to Therapy; TSQM II = Treatment Satisfaction for Medication Questionnaire version II; WPAI:GH = Work Productivity and Activity Impairment:General Health.

Footnotes to the Schedule of Assessments: Treatment Period [CSL312_2001 Subjects]

A: End of treatment is 1 month after the last administration of CSL312.

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

C: Treatment Period Visits have ± 4 day window, with a maximum of 34 days between any 2 doses.

D: Subjects must meet all inclusion/exclusion criteria. Subjects who successfully completed CSL312_2001 may roll over directly from treatment in CSL312_2001 and start this study at Treatment Day 1.

E: A physical examination will be conducted per the investigator's standard procedure, and will also include assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

F: Height is collected at Day 1 only.

G: Subjects rolling over from Study CSL312_2001 who have completed the AE-QoL and WPAI:GH as part of the last visit of Study CSL312_2001 will only need to complete the TSQM II at Day 1.

H: Blood samples for potential future assessment of HAE biomarkers will be obtained during the Treatment Period. These samples will be stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion of the study or used for future research on HAE. These samples will not be collected in adolescents.

I: Blood draws should be completed before study drug administration on the same day.

J: The urine test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum pregnancy test will be performed by the site if urine result is inconclusive. Female subjects of childbearing potential will perform home urine testing on months for which there is not an onsite visit.

K: The eDiary will be collected and deactivated for all subjects. For subjects who terminate the study early, the eDiary should be deactivated and collected either on date of early termination or at the Follow-up Visit as applicable. If the Follow-up Visit is conducted remotely, the device should be returned to the site.

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

M: Subjects will be dispensed study medication for at home self-administration. Only first administration will be at site.

N: Subjects will complete the Medication Dosing Diary on the eDiary at Day 1 site visit and then monthly at home through the End of Treatment Visit.

Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1

Study Period		Treatment Period						End of Treatment[A]	Final Visit / Follow-up Telephone Call[B] (2 months after End of Treatment Visit)
Month		12	18	24	30	36	42		
Visit Day		361	541	721	901	1081	1261		
Visit Window (Day)[C]		±4d	±4d	±4d	±4d	±4d	±4d	±4d	-14d
Study center visit		X	X	X	X	X	X	X	
Written informed consent for Amendment 1 and switch to CSL312 200 mg AI[D]		1st day under Amendment 1							
Physical examination [E]		X	X	X	X	X	X	X	
Vital signs including body weight		X	X	X	X	X	X	X	
SGART and IGART [F]		X		X		X			
TSQM II (subjects ≥ 18 yrs), AE-QoL (subjects ≥18 yrs) & WPAI:GH (subjects ≥ 16 yrs) [G]		1st day under Amendment 1							
Urine collection for urinalysis (central lab) [H]		1st day under Amendment 1							
Blood Draws (central lab) [I]	Hematology / biochemistry / coagulation [J]	X		X		X		X	
	Retention sample for HAE biomarkers [K]	1st day under Amendment 1							
	Pharmacokinetics / Pharmacodynamics	X	X	X	X	X		X	
	Immunogenicity	X		X		X		X	
Pregnancy test [L]		X	X	X	X	X	X	X	
Review eDiary / assess / document HAEattacks		X	X	X	X	X	X	X	X[M]
eDiary deactivation [N]								X	
Confirm plan for managing potential attack [O]		X	X	X	X	X	X		
IRT CSL312 kit assignment		X	X	X	X	X	X		
CSL312 accountability		X	X	X	X	X	X	X	
Administration of CSL312 [P]		X	X	X	X	X	X		
Concomitant medications and therapies		X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X

Abbreviations: AI = autoinjector; HAE = hereditary angioedema; IGART = Investigator's Global Assessment of Response to Therapy; IRT = interactive response technology; NSD = needle safety device; PRO = patient reported outcome; QoL = Quality of Life; SGART = Subject's Global Assessment of Response to Therapy; TSQM II = Treatment Satisfaction for Medication Questionnaire version II; WPAI:GH = Work Productivity and Activity Impairment: General Health; yrs = years.

Footnotes to the Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1

A: End of Treatment can replace any of the planned site visits (eg Visit Month 36) and should occur 1 month after last dose of CSL312 but no later than September 2025. The End of Treatment Visit may vary per individual subject depending on the end of study in their respective country as per Section 3.4. Any visit beyond Month 36 requires approval from the Sponsor.

B: Follow-up Visit will be conducted via telephone call only.

C: Treatment Period visits have ± 4 day window, with a maximum of 34 days between any 2 doses.

D: The specific site visit to consent into Amendment 1 and to switch to CSL312 200 mg AI may vary per individual subject. Consent into Amendment 1 and switching to CSL312 200 mg AI may occur starting at the Month 12 Visit. An unscheduled visit to accommodate consent into Amendment 1 and switching to CSL312 200 mg AI (with no other assessments performed at this visit) may be scheduled as needed at dates planned for home doses; this unscheduled visit should be performed according to the dosing schedule. The first administration with CSL312 200 mg AI will always occur at the site. Subjects who decline switching to CSL312 200 mg AI and who have participated in the study for at least 12 months will receive 1 more dose of CSL312 200 mg NSD at the time of the scheduled site visit and subsequently proceed with the End of Treatment Visit 1 month later, as well as a Follow-up Visit 2 months after the End of Treatment Visit, as per the original protocol.

E: A physical examination will be conducted per the investigator's standard procedure and will also include assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

F: Investigator completes IGART in Rave. Subjects complete SGART in tablet.

G: PRO QoL assessments will be completed for the last time at the visit that the subject consents to Amendment 1 (ie, Month 12, Month 18, Month 24, or Month 30). If consent into Amendment 1 and switching to CSL312 200 mg AI is performed at an unscheduled visit after the Month 12 Visit, the last data for PRO QoL assessments will be from the last visit prior to the unscheduled visit (under the original protocol).

H: Urine collection for urinalysis will be collected for the last time at the visit that the subject consents to Amendment 1 (ie, Month 12, Month 18, Month 24, or Month 30). If consent into Amendment 1 and switching to CSL312 200 mg AI is performed at an unscheduled visit after the Month 12 Visit, the last data for urinalysis will be from the last visit prior to the unscheduled visit (under the original protocol).

I: On a visit day, blood draws should be completed on the same day of CSL312 administration.

J: Per Amendment 1, collection of blood sample for hematology / biochemistry / coagulation analysis will be required every 12 months starting from the Month 12 Visit.

K: Blood samples for potential future assessment of HAE biomarkers will be obtained for the last time at the visit that the subject consents to Amendment 1 (ie, Month 12, Month 18, Month 24, or Month 30). If consent into Amendment 1 and switching to CSL312 200 mg AI is performed at an unscheduled visit after the Month 12 Visit, the last collection of HAE biomarkers will be from the last visit prior to the unscheduled visit (under the original protocol). These samples will be stored for potential future assessment of HAE biomarkers and will be destroyed within 5 years after completion of the study. These samples will not be collected in adolescents.

L: The urine test for beta-human chorionic gonadotropin will be performed only for women of childbearing potential. A serum pregnancy test will be performed by the site if urine result is inconclusive. Female subjects of childbearing potential will perform home urine testing on months for which there is no onsite visit.

M: At the Follow-up Visit (conducted via telephone call), HAE attacks will be reported verbally, as the eDiary is deactivated at the End of Treatment Visit.

N: The eDiary will be collected and deactivated for all subjects at the End of Treatment Visit. For subjects who terminate the study early, the eDiary should be deactivated and collected either on the date of early termination or at the End of Treatment Visit, as applicable.

O: Subjects may use the on-demand medication of their choice (in accordance with the standard of care in the region) to treat HAE attacks experienced during the study.

P: Subjects / parents and caregivers will be trained in CSL312 self-administration with CSL312 200 mg AI on the site visit date they consent into Amendment 1. The first administration with CSL312 200 mg AI will occur at the site. Subsequent to onsite administration with CSL312 200 mg AI, all subjects will self-administer at home (or with the help of a caregiver). Additional CSL312 200 mg AI administration training at subsequent scheduled onsite visits may be provided if it is requested. Subjects will complete the Medication Dosing Diary on the eDiary at site on the visit they consent to Amendment 1 and then monthly at home through the End of Treatment Visit. Any device malfunctions should be reported as a suspected Product Technical Complaint. Refer to the Site Investigational Product Manual for additional information.

Schedule of Additional Assessments for Pharmacokinetic Subgroup Analysis in a Subset of CSL312-naïve Adult Subjects (Treatment Period)

Study Period	**Treatment Period**			
Sampling Time[A]	+7 days (±2 days) after Visit Day 1	+14 days (±2 days) after Visit Day 1	+21 days (±2 days) after Visit Day 1	+30 days (pre-dose for next dose)
Pharmacokinetics / Pharmacodynamics (Central Lab)	X	X	X	X

[A]: Post-dose blood draws to occur after the administration of the loading dose consisting of 2 subcutaneous injections of 200 mg CSL312 each for a total of 400 mg CSL312 at Visit Day 1.

Note: A target number of 12 CSL312-naïve adult subjects will be included in the subgroup.

Schedule of Assessments for Pharmacokinetic Sampling in all Adolescents (Treatment Period)

Study Period	**Treatment Period**				
Sampling Time[A,B,C]	+3 days (±1 day) after Month 3 (Visit Day 91) administration	+7 days (±2 days) after Month 3 (Visit Day 91) administration	+14 days (±2 days) after Month 3 (Visit Day 91) administration	+21 days (±3 days) after Month 3 (Visit Day 91) administration	+30 (days pre-dose for next dose after Visit Day 91)
Pharmacokinetics / Pharmacodynamics (Central Lab)	X	X	X	X	X

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

[A]: Post-dose blood draws to occur after the administration of the CSL312 at Month 3 (Visit Day 91).

[B]: Minimum of 3 of 5 post-dose blood draws may be collected from adolescent subjects.

[C]: Post-dose blood draws are in addition to the PK / PD collections described for Schedule of Assessments for CSL312-naïve subjects and for subjects who completed Study CSL312_3001.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Term
AE	Adverse event
AE-QoL	Angioedema Quality of Life
AESIs	Adverse events of special interest
AI	Autoinjector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	All Treated Subjects (analysis set)
$AUC_{0\text{-}30days}$	Area under the concentration-time curve from 0-30 days
BK	Bradykinin
CI	Confidence interval
C1-INH	C1-esterase inhibitor
COVID-19	Coronavirus disease 2019
CRF	Case Report Form (printed, optical, or electronic document)
CSL	CSL Behring
CV%	Percent coefficient of variation
eCOA	electronic Clinical Outcome Assessment
eDiary	electronic Diary
E-R	Exposure-response
FDA	Food and Drug Administration
FXII	Factor XII
FXIIa	Activated Factor XII
GCP	Good Clinical Practice
HAE	Hereditary angioedema
HMWK	High molecular weight kininogen
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGART	Investigator's Global Assessment of Response to Therapy
IRB	Institutional Review Board

Abbreviation	Term
IRT	Interactive response technology
IV	Intravenous
kDa	kilodalton
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
nC1-INH	Normal C1-esterase inhibitor
NSD	Needle safety device
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation
SGART	Subject's Global Assessment of Response to Therapy
SOC	System organ class
TEAE	Treatment-emergent adverse events
TEE	Thromboembolic event
T_{max}	Time to reach maximum concentration in plasma
TP1	Treatment Period 1
TP2	Treatment Period 2
TSQM II	Treatment Satisfaction for Medication Questionnaire version II
WPAI:GH	Work Productivity and Activity Impairment: General Health

List of Conventions

- The abbreviation “C1-INH HAE” is used in this clinical study protocol to include hereditary angioedema type 1 (quantitative decrease in C1-esterase inhibitor plasma concentrations) and hereditary angioedema type 2 (dysfunctional C1-esterase inhibitor present in normal or high plasma concentrations).
- CSL312 has been given the World Health Organization International Nonproprietary Names identification of garadacimab.

1 Introduction

1.1 Background

1.1.1 Factor XII

Factor XII (Hageman factor, FXII) is produced in the liver and is secreted into the plasma; the glycosylated 80 kilodalton (kDa) zymogen circulates with a concentration of ~30 µg / mL and a half-life of 50 to 70 hours [Björkqvist et al, 2014].

Factor XII is the principal initiator of the plasma contact system [Renné et al, 2012]. The contact system is a protease cascade involving the proteins FXII, factor XI (FXI), plasma prekallikrein, and the nonenzymatic cofactor high molecular weight kininogen (HMWK). Upon contact with a negatively-charged surface FXII is converted to activated Factor XII (FXIIa). Several biologic substances have been shown to support FXII activation in vivo, including heparin released from mast cells, misfolded protein aggregates, ribonucleic acid, and platelet polyphosphates [Kenne et al, 2015]. FXIIa triggers fibrin formation through activation of FXI, and also leads to the production of the inflammatory mediator bradykinin (BK) through the kallikrein-kinin pathway. Further cleavage of FXIIa releases the 30 kDa light chain containing the catalytic domain (βFXIIa), which can activate the classical complement pathway. Thus, activated forms of FXII have proinflammatory and procoagulant activities.

1.1.2 Factor XII and the Kallikrein-kinin Pathway

Activation of FXII (to FXIIa) also leads to the production of BK through the kallikrein-kinin pathway. In this pathway, prekallikrein is converted to kallikrein by FXIIa. Kallikrein plays a number of roles. First, it activates FXII zymogens by a positive feedback mechanism to amplify the cascade. Second, kallikrein cleaves HMWK to release the potent inflammatory mediator BK. The binding of BK to BK type 2 receptors activates various intracellular signaling pathways that dilate vessels, induce chemotaxis of neutrophils, and increase vascular permeability and fluid efflux [Björkqvist et al, 2013]. BK production is increased during acute hereditary angioedema (HAE) attacks and is the mediator of swelling in HAE [Nussberger et al, 1998; Nussberger et al, 1999].

1.1.3 Background of Disease

HAE is a rare autosomal dominant disease characterized by recurrent and unpredictable episodes of swelling of subcutaneous tissues throughout the body and / or submucosal edema in the upper airway or gastrointestinal tract. HAE affects approximately 1 in 50,000 individuals, with males and females equally affected. The mean age of onset is 10 years and most patients experience a worsening of symptoms at the time of puberty. Attacks are usually characterized by mild to severe tissue swelling at 1 or more sites in the body (typically the face, hands, feet, airways, and intestinal tract). The frequency and duration of HAE attacks are highly variable. On average, HAE attacks can occur every 1 to 2 weeks. If untreated, swelling is self-limited and usually resolves spontaneously in 2 to 5 days; however, laryngeal edema poses the risk of death due to asphyxiation [Bork, 2016].

HAE is classified into 3 disease types [Rosen et al, 1965; Bork et al, 2000]; types 1 and 2 involving deficiency or dysfunction of C1 esterase inhibitor (C1-INH) levels, and 1 type formerly known as type 3 with normal C1-INH (nC1-INH HAE). Type 1 HAE is the most common form, accounting for about 85% of HAE cases and type 2 accounts for approximately 15% of HAE cases [Zuraw 2010]. The prevalence of nC1-INH is currently unknown; however, it is estimated to be significantly less prevalent than C1-INH HAE [Cicardi and Zanichelli 2010; Nasr et al, 2016]. C1-INH is a broad-spectrum major serine protease inhibitor which regulates 4 proteolytic enzyme cascades: complement, contact, fibrinolytic, and coagulation pathways. C1-INH is a major inhibitor of the kallikrein-kinin system (contact pathway) by inactivating the FXIIa and kallikrein.

Clinically, attacks of all symptomatic HAE patients manifest as painful, potentially life-threatening swelling of subcutaneous tissues throughout the body and / or submucosal edema in the upper airway or gastrointestinal tract. These attacks recur with unpredictable frequency, intensity, and duration. Patients with sporadic attacks fear the next attack even during attack free times.

1.2 Information on CSL312

1.2.1 Overview

Throughout development, CSL312 (garadacimab) has been described as an FXIIa antagonist monoclonal antibody (mAb) and therefore that terminology has been used in all previous corresponding documentation and communications. CSL312 is a fully human

immunoglobulin G subclass 4 (IgG4) / lambda recombinant mAb which binds to the catalytic domain of the plasma protein FXIIa and potently inhibits its catalytic activity. As such, CSL312 blocks FXIIa protease activity by binding to its active site; it does not block the effects of an agonist binding to FXIIa. Therefore, it is scientifically more precise for CSL312 to be identified as an inhibitor. This revised terminology does not indicate any change in the activity of the product or a change in the understanding of the mechanism of action. The corrected description for CSL312 as an FXIIa inhibitor mAb is used herein. CSL312 is an affinity-matured variant of the parental antibody 3F7, which was isolated following screening against the active catalytic fragment of FXII (βFXIIa). CSL312 is produced in Chinese hamster ovary cells that have been characterized according to applicable international guidelines.

Factor XII is the principal initiator of the plasma contact system [Renné et al, 2012]. The contact system is a protease cascade involving the proteins FXII, factor XI (FXI), plasma prekallikrein, and the non-enzymatic cofactor HMWK. Upon contact with a negatively charged surface, FXII is converted to FXIIa. FXIIa can cleave both FXI and plasma prekallikrein, which leads to separate pathways that exert procoagulant and proinflammatory effects. Further cleavage of FXIIa releases the 30 kDa light chain containing the catalytic domain (βFXIIa), which can activate the classical complement pathway.

During acute HAE attacks, BK production is increased and is the mediator of swelling in HAE [Nussberger et al, 1998; 1999]. Acute and prophylactic treatments for HAE are based on blocking BK production through targeting different proteins in the kallikrein-kinin pathway. Plasma levels of FXIIa have been shown to increase in patients during acute HAE attacks compared to levels during remission [Csuka et al, 2015; Cugno et al, 1996]. Given the importance of FXIIa in the initiation of the plasma contact system, it is a novel target for the inhibition of the kallikrein kinin pathway and the excessive production of BK detected during HAE attacks.

The rationale for evaluating for prophylaxis to prevent HAE attacks with CSL312 relies on the strong inhibition of FXIIa catalytic activity by CSL312 resulting in the upstream blocking of the contact pathway that produces BK which feeds the central pathogenic mechanism of HAE.

The efficacy and safety of CSL312 in patients with HAE has been demonstrated in a phase 2 study. This phase 3b is to evaluate long-term safety and efficacy of CSL312 200 mg when administered once monthly for at least 12 months.

1.2.2 Nonclinical Evaluation

The nonclinical program conducted to support development of CSL312 included pharmacological, pharmacokinetic (PK), and toxicological studies performed in pharmacologically relevant species that are described in the CSL312 Investigator's Brochure.

1.2.3 Clinical Experience

1.2.3.1 Healthy Subjects

In healthy subjects, 2 phase 1 studies have been completed and 1 study is ongoing.

Study CSL312_1001, a phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study, was conducted in healthy volunteers. During this study, the safety, tolerability, and PK of escalating doses of CSL312 were assessed after single intravenous (IV) or subcutaneous (SC) injections of up to 10 mg/kg in healthy male subjects. CSL312 had an acceptable safety and tolerability profile. During the study, there were no serious adverse events (SAEs); no withdrawals due to adverse events (AEs); no thromboembolic events (TEEs), bleeding events, or cases of anaphylaxis; no clinically significant abnormal trends in hematology or clinical chemistry assessments. The majority of the AEs were of mild severity. Injection site reactions were more common with SC CSL312 than SC placebo, but there was no apparent dose dependence. Additionally, CSL312 exhibited linear PK with a half-life of approximately 19 days.

Additionally, a phase 1, single-ascending dose study to investigate the PK, pharmacodynamics (PD), safety, and tolerability of CSL312 in healthy Japanese and Caucasian subjects (Study CSL312_1003) was completed. Results from the safety and tolerability assessments demonstrated that CSL312 was well tolerated after a single SC infusion at doses of 200 or 600 mg in Japanese subjects or 200 mg in Caucasian subjects. There were no differences in the safety profiles between healthy Japanese and Caucasian subjects. No deaths, SAEs, adverse events of special interest (AESIs [ie, severe hypersensitivity including anaphylaxis, TEEs, or abnormal bleeding events]), or AEs leading to study discontinuation were reported.

Finally, Study CSL312_1004 is an ongoing phase 1 study to compare the PK of CSL312 administered subcutaneously via CSL312 200 mg autoinjector (AI) and via CSL312 200 mg needle safety device (NSD) in healthy subjects. No preliminary data are available yet; the study is expected to end in early 2023.

The study results are described in greater detail in the CSL312 Investigator's Brochure.

1.2.3.2 Subjects with Hereditary Angioedema

Three clinical studies with CSL312 have taken place in subjects with HAE; 2 studies are completed (CSL312_2001 and CSL312_3001), and 1 study is ongoing (CSL312_3002).

Study CSL312_2001

CSL312_2001 is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 dose-ranging (75 mg, 200 mg, and 600 mg) study to investigate the efficacy, PK, and safety of CSL312 SC administered every 4 weeks as prophylaxis to prevent HAE attacks in subjects with C1-INH HAE or FXII / Plasminogen HAE. The study consisted of a Screening Period, a Run-in Period, 2 Treatment Periods (Treatment Period 1 [TP1] [2 parts: 1 double-blind part and 1 open-label part] and open-label Treatment Period 2 [TP2]), and a Follow-up Period. After the Run-in Period, eligible subjects with C1-INH HAE were randomized to 1 of 4 treatment groups (placebo, or 75 mg, 200 mg, or 600 mg CSL312) in double-blind TP1. Subjects received a single IV loading dose of investigational product followed 1 week later by a single SC injection of investigational product once every 4 weeks for 12 weeks (for a total of 13 weeks). Additionally, further subjects were assigned to the open-label 400 mg CSL312 SC every 2 weeks treatment arm in TP1. In open-label TP2, subjects received a single SC injection of either 200 mg or 600 mg CSL312 every 4 weeks. Subjects receiving 600 mg CSL312 every 4 weeks in TP2 had their dose decreased to 200 mg CSL312 every 4 weeks effective with Protocol Amendment 2.

The study was conducted in 5 countries at 20 study sites; the first subject visit was on 29 October 2018. A total of 32 subjects with C1-INH type 1 or type 2 HAE were enrolled in the randomized double-blind treatment arms of TP1. Additionally, 6 subjects were assigned to the open-label 400 mg CSL312 SC every 2 weeks treatment arm in TP1. Of the 38 subjects who entered TP2, 36 subjects completed the study.

Among subjects with C1-INH HAE, in TP1, treatment with 200 mg or 600 mg CSL312 SC every 4 weeks resulted in a statistically significant reduction in the time-normalized number of HAE attacks per month when compared with placebo ($P < 0.001$ and $P < 0.001$, respectively). This represented a reduction in the mean time-normalized number of HAE attacks of 98.94% with 200 mg CSL312 and 91.68% with 600 mg CSL312, relative to placebo. In an exploratory analysis comparing the time-normalized number of HAE attacks in the 200 mg CSL312 treatment arm (mean [standard deviation (SD)]: 0.05 [0.127]) and the 600 mg CSL312 treatment arm (mean [SD]: 0.35 [0.407]), the difference was not statistically significant ($P = 0.082$). Of the 24 subjects randomized to blinded treatment with any dose of CSL312, 15 subjects were HAE attack-free during the efficacy evaluation period, including 7/8 (87.5%) subjects who were treated with 200 mg CSL312 and 3/7 (42.9%) subjects who were treated with 600 mg CSL312. No subjects who were treated with placebo were HAE attack-free during the same efficacy evaluation period. Of the 6 subjects in the 400 mg CSL312 every 2 weeks open-label treatment arm, 4/6 (66.7%) were HAE attack-free. All subjects receiving placebo had at least 1 HAE attack treated with on-demand HAE medication, compared with 3/9 (33.3%) subjects in the 75 mg CSL312 arm, 1/8 (12.5%) subjects in the 200 mg CSL312 arm, and 2/7 (28.6%) subjects in the 600 mg CSL312 arm. Subjects receiving CSL312 showed clinically meaningful improvements in the total score of the Angioedema Quality of Life questionnaire. Overall, the efficacy results for TP2 are consistent with TP1 and demonstrated a sustained treatment effect through TP2.

During TP1, blinded treatment with 75 mg, 200 mg, or 600 mg CSL312 SC every 4 weeks, as well as open-label treatment with 400 mg every 2 weeks, was safe and well tolerated. There were no safety signals or concerns, and no dose-dependent patterns in overall AE rates were noted. The percentage of subjects experiencing at least 1 AE during treatment with any dose of CSL312 was similar to placebo. All AEs were nonserious and were assessed as mild or moderate in intensity. There were no AESIs (ie, anaphylaxis, TEEs, or bleeding events), no AEs or SAEs leading to study discontinuation, and no deaths reported during TP1. Similar rates of AEs and no safety signals and concerns were observed in TP2.

Study CSL312_3001

Study CSL312_3001 is a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of 200 mg CSL312 administered SC once monthly as prophylaxis for 6 months to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with HAE. Sixty-four subjects were

randomized and entered the Treatment Period since April 2021; this study was recently completed. The study was conducted globally at 28 study sites.

Data from this study showed that in subjects with C1-INH HAE, CSL312 was safe and effective in the prevention of HAE attacks during the 6-month Treatment Period. The primary efficacy results demonstrated that treatment with SC CSL312 200 mg once monthly resulted in a statistically significant reduction in the time-normalized number of HAE attacks per month compared to placebo (first hierarchical test: $p < 0.001$, 2-sided Wilcoxon Test). Efficacy of CSL312 was consistently observed across different efficacy endpoints, and no safety signals or concerns were observed, consistent with previous studies.

Six adolescent subjects between the ages of 12 and 17 years were enrolled in the study (3 were male and 3 were female). Safety, PK, and efficacy were consistent with the adult population.

1.3 Study Overview

This is a multicenter, open-label, phase 3b study designed to investigate the clinical safety and efficacy of SC administered CSL312 in the prophylactic treatment of HAE. Section 3.1 presents a detailed overview of the study.

1.4 Benefit / Risk Assessment

Benefit assessment

Potential key benefits of CSL312 include prevention of HAE attacks, less frequent attacks, less severe attacks when attacks do occur, and less frequent use of on-demand medication for the treatment of acute attacks. The treatment, which is injected subcutaneously by the subject, can be conveniently administered at home once monthly. Data from CSL312_2001, a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 dose-ranging study, provide support that treatment with CSL312 results in a clinically meaningful reduction in attack frequency while being safe and well tolerated.

Data from CSL312_3001, a multicenter, randomized, placebo-controlled, parallel-arm, phase 3 study in adults and adolescents, provide confirmation of the results observed in the phase 2 study that treatment with CSL312 provides clinically meaningful reduction in HAE attacks while being safe and well tolerated.

Risk assessment

The following risks have not been observed in the development program of CSL312, but are potential risks based on the drug class and / or the mode of action:

Severe hypersensitivity, including anaphylaxis: Administration of therapeutic proteins including mAbs such as CSL312 may be associated with the risk of severe hypersensitivity and anaphylactic reactions, some of which can be serious and life threatening. To date, no severe hypersensitivity or anaphylactic-type reactions have been observed after repeated administration of CSL312 in the completed or ongoing clinical studies. Appropriate precautions will be taken when CSL312 is administered at the study site, with vigilant monitoring for potential severe hypersensitivity and anaphylactic reactions. For CSL312-naïve subjects, at least the first 3 doses will be performed at the site under medical supervision with immediate access to emergency equipment and medication for treatment of severe hypersensitivity adverse reactions including anaphylaxis. Subjects will be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

Immunogenicity (anti-drug antibodies): All protein therapeutics are potentially immunogenic. Because CSL312 is a protein, it has the potential to cause the development of neutralizing and non-neutralizing anti-drug antibodies. The development of anti-drug antibodies throughout the study will be monitored.

The important potential risks of TEEs and abnormal bleeding were removed from the CSL312 list of safety concerns following the review of recently accumulated clinical study data (CSL312_1001, CSL312_1003, CSL312_2001, and CSL312_COVID-19) together with nonclinical data and scientific literature; although TEEs and abnormal bleeding are no longer considered potential risks, safety surveillance and monitoring of these types of events as AESIs will continue in accordance with existing protocol provisions in the CSL312_3002 clinical study (additional information is provided in the CSL312 Investigator's Brochure).

Given the potential benefits of CSL312 for subjects with HAE, as well as the favorable safety data of CSL312 from phase 1 studies in healthy volunteers (CSL312_1001, CSL312_1003, and CSL312_1004), in the phase 2 and 3 studies in subjects with HAE (CSL312_2001, CSL312_3001, and CSL312_3002), and in the phase 2 study in subjects with severe COVID-19 (CSL312_COVID-19), and taking into account the implementation of procedures in the current study to closely monitor subject safety, the associated benefit / risk assessment is considered to be acceptable. Additional information on CSL312 is provided in the CSL312 Investigator's Brochure.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

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

2.1.2 Primary Endpoint

Endpoint	Summary Measure
Treatment-emergent Adverse Events	Number of subjects, percentage of subjects, and number of events as well as the event rates per injection and per subject year

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of this study are to evaluate:

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

2.2.2 Secondary Endpoints

Secondary Objective	Endpoint	Summary Measure(s)
Efficacy Endpoints		
1	Time-normalized number of HAE attacks	The time-normalized number (per month and year) of HAE attacks for the run-in and Treatment period.
1	The reduction in the attack rate during the Treatment Period compared to the Run-in Period	The percentage reduction and the number of subjects experiencing at least ≥ 50%, ≥ 70%, ≥ 90% or equal to 100% (attack free) reduction in the time-normalized number of HAE attacks on Treatment compared to Run-in Period.
1	The time-normalized number of HAE attacks requiring on-demand treatment	The time-normalized number (per month and year) of HAE attacks requiring on-demand treatment in subjects on treatment.
1	The time-normalized number of moderate and / or severe HAE attacks	The time-normalized number (per month and year) of moderate and / or severe HAE attacks in subjects on treatment.
1	SGART	Number and percentage of subjects rating their response to therapy as good or excellent.

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

AE = adverse event; AESI = adverse event of special interest; nC1-INH = normal C1-esterase inhibitor; SAE = serious adverse event; SGART = Subject's Global Assessment of Response to Therapy; TEAE = treatment-emergent adverse event.

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

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

2.3.2 Exploratory Endpoints

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

Exploratory QoL endpoints include the following:

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

The exploratory PK and PD endpoints are:

- CSL312 concentrations at scheduled time points
- FXIIa-mediated kallikrein activity at scheduled time points
- CSL312 PK parameters (maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the concentration-time curve from 0-30 days [$AUC_{0\text{-}30days}$])

3 Study Design and Oversight

3.1 Overall Design

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

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

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

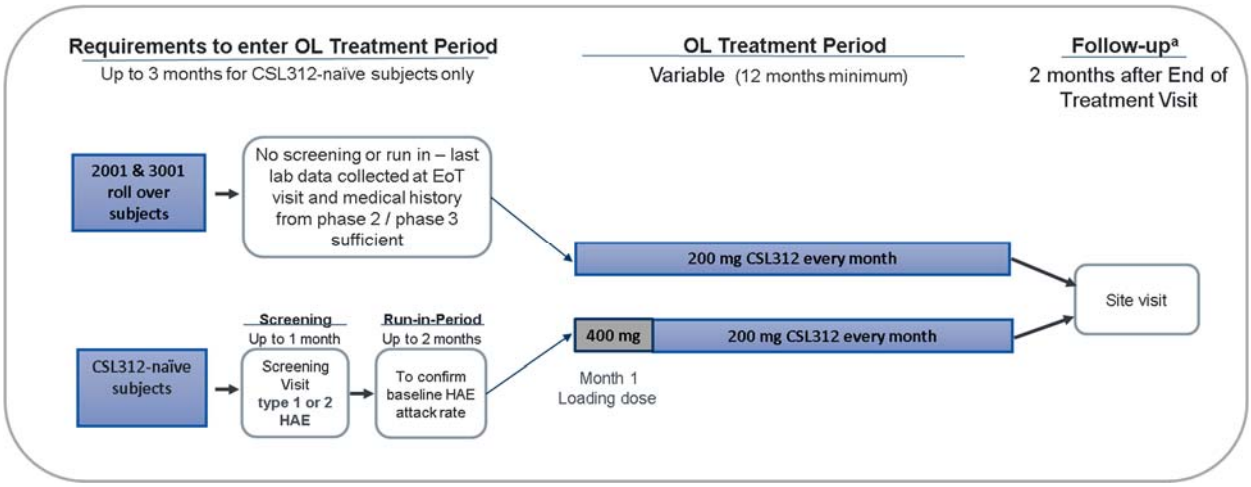
For subjects naïve to CSL312, there will be a Screening Period of up to 1 month followed by a Run-In Period, which may last at least 1 month and up to 2 months. CSL312-naïve subjects who meet all eligibility criteria during the Run-In Period will then enter the Treatment Period. Subjects who complete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

Per Amendment 1, subjects or caregivers will subcutaneously administer CSL312 200 mg AI instead of CSL312 200 mg NSD. The AI is a device that contains the same prefilled syringe already being used in the NSD since the start of the study. The purpose of using an AI is to further facilitate the administration of CSL312. The dose and dosing regimen will continue to be 200 mg once monthly. Subjects who decline switching to CSL312 200 mg AI and who

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

The study schematic is shown in Figure 1.

Figure 1 CSL312_3002 Study Schematic



EoT = End of Treatment; HAE = hereditary angioedema; OL = open-label.

[a] The Follow-up Visit will be conducted via telephone call.

3.1.1 Pharmacokinetic Subgroup

A PK subgroup analysis will be conducted in a sub-set of adult CSL312-naïve subjects to further characterize the PK of CSL312 following the SC loading dose. A target number of 12 CSL312-naïve adult subjects will be recruited from a subset of sites to be included in the subgroup.

3.1.2 Screening (CSL312-naïve subjects only)

Following informed consent, subjects will undergo a Screening Period of up to 1 month to determine eligibility for enrollment into the study. Screened subjects who meet all the inclusion criteria and none of the exclusion criteria will enter the Run-in Period. If a subject does not meet the criteria for entering the Run-in Period within 30 days, the subject may be rescreened with confirmation from the Sponsor. Rescreening is allowed once.

3.1.3 Run-in (CSL312-naïve subjects only)

After Screening, eligible subjects will enter the Run-in Period lasting at least 1 month and up to 2 months to confirm their underlying disease status and to assess their eligibility for participation in the Treatment Period. The first day of the Run-in Period may occur on the same day as Screening.

Subjects must complete at least 1 month of the Run-in Period. Additionally, subjects must experience at least 2 HAE attacks during the Run-In Period to be eligible to enter the Treatment Period. Subjects who experience at least 2 attacks during the required first month of the Run-In Period may enter the Treatment Period. Subjects who do not experience an HAE attack during the first month of the Run-in Period will remain in the Run-in Period up to 2 months during which time they would be required to experience at least 2 attacks to be eligible to enter the Treatment Period (Section 4.1.1.2).

Subjects are prohibited from using routine prophylaxis to prevent HAE attacks during the Run-in Period (Section 7.3); however, subjects may use on-demand HAE therapy to treat HAE attacks if that medication has previously been shown to be effective (Section 7.2).

Subjects who do not meet the minimum HAE attack rate during the Run-in Period, or are otherwise determined to be ineligible due to Screening assessments, will be considered Run-in failures and will not be allowed to be rescreened for participation in the study.

3.1.4 Treatment Period

Subjects meeting the eligibility criteria (Section 4.1.1.2) will enter the Treatment Period after the Run-in Period. If a subject is unable to enter the Treatment Period after Day 60, then CSL Behring (herein, “the Sponsor”) approval is required for the subject to enter the Treatment Period.

3.1.5 Follow-up

Subjects will be contacted 2 months after the End of Treatment Visit to complete final study assessments.

3.2 Dose and Dosing Regimen

CSL312 will be administered as 1 dose (200 mg) SC once monthly for a minimum of 12 doses (ie, 12 months of treatment). For CSL312-naïve subjects, a loading dose of 400 mg

(two 200 mg doses) will be administered SC on the first month, then 200 mg once monthly for at least 11 months.

Per Amendment 1, CSL312 will be administered as 1 injection (200 mg) SC once monthly using an AI instead of the NSD. The AI is a device that contains the same prefilled syringe already being used in the NSD since the start of the study. The purpose of using an AI is to further facilitate the administration of CSL312.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

This phase 3b, multicenter, open-label study is designed for the assessment of long-term safety and efficacy of CSL312 (200 mg once monthly) in HAE patients as established in earlier phase 2 and phase 3 studies.

The study will include a Screening Period (up to 1 month) to assess subject eligibility, a Run-in Period (up to 2 months) for confirmation of disease activity and determination of subjects' baseline HAE attack rate for CSL312-naïve subjects, a Treatment Period (minimum of 12 months) for confirmation of the safety and efficacy of the 200 mg CSL312 dose once monthly, and a Follow-up Visit (2 months after the End of Treatment Visit).

Amendment 1 will introduce the use of an AI to continue administration of 200 mg CSL312 once monthly. The Sponsor considers that the use of an AI to administer CSL312 will add convenience and is patient-centric. In addition, it will be intended for future commercial use.

3.3.2 Dose Rationale

The 200 mg dose is the dose used in Study CSL312_3001, the pivotal phase 3 study, and will continue to be evaluated in this study. The dose of 200 mg was selected based on the efficacy and safety observed in TP1 of Study CSL312_2001, CSL312 PK, inhibition of FXIIa-mediated kallikrein activity, and exposure-response (E-R) modeling.

The 200 mg dose was highly effective across various efficacy endpoints and had a favorable safety profile. In addition, the 200 mg dose resulted in ~50% inhibition of FXIIa-mediated kallikrein activity.

To support phase 3 dose selection, an E-R model was used to simulate HAE attack rates over a wide range of CSL312 concentrations that would be expected after different dosing

regimens. Based on the E-R model, the estimated daily average concentrations to achieve 50, 75, and 90% relative risk reduction in the baseline attack rate were 1.4, 3.3, and 7.8 µg/mL, respectively. The median predicted minimum daily average CSL312 concentrations ($C_{avg,min}$) at steady-state following 200 mg SC once monthly regimen corresponds to the 90% relative risk reduction in baseline attack rate in 73% of patients.

Additionally, the E-R model showed a cumulative effect of CSL312 concentration is evidenced in the reduction in the expected number of HAE attacks per month. The 200 mg SC once monthly regimen is predicted to reduce the mean attack rate by approximately 91% compared to placebo. Increasing the dose beyond 200 mg is not predicted to result in significant further reductions in HAE attacks.

Finally, the exposures at the 200 mg SC dose administered monthly are not expected to cause activated partial thromboplastin time prolongation in the majority of subjects in the phase 3 study.

Based on all the factors taken into consideration in selecting a dose for advancing the CSL312 clinical program, a 200 mg SC dose of CSL312 administered once monthly is expected to achieve clinically meaningful treatment effect and optimal benefit / risk ratio in subjects with HAE.

3.4 Planned Study Duration

The duration of the study for a **CSL312-naïve subject** is expected to be a minimum of 17 months. This estimation is based on:

- An up to 1-month Screening Period.
- An up to 2-month Run-in Period.
- A minimum of a 12-month Treatment Period.
- A 2-month Follow-up Period.

The duration of the study for a **previously treated CSL312 subject** is expected to be a minimum of 14 months in this study. This estimation is based on:

- A minimum of a 12-month Treatment Period.
- A 2-month Follow-up Period.

Per Amendment 1, the duration of treatment for an individual subject is estimated to be a minimum of 12 months. The treatment duration for each subject will be variable. In addition, the study may be stopped in a specific country either after garadacimab obtains regulatory approval or it becomes commercially available in the respective country. The Sponsor reserves the right to stop the study at any time.

3.5 Planned Number of Subjects

A minimum of 100 subjects having received treatment for a minimum of 12 months and approximately 150 subjects are planned to be enrolled into the study.

3.6 Definition of Start of the Clinical Study

The start of the clinical study is defined as the date of the first Screening Visit of the first potential subject at a study site.

3.7 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) is defined as the date of the last visit of the last subject.

3.8 Study Oversight

3.8.1 Data Monitoring Committee(s)

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

3.9 Study Halting Criteria

Individual Subject

If a subject meets any of the following criteria during participation in the study, then further administration of CSL312 to that subject will be halted (ie, temporarily paused) until an

assessment of that subject's safety is completed: Prolonged symptoms of severe hypersensitivity, including anaphylaxis, considered by the investigator and / or the Sponsor to be related to CSL312 administration; a confirmed diagnosis of TEE or a clinically significant abnormal bleeding event, irrespective of CSL312 causality; or any event or laboratory abnormality considered by the investigator and / or the Sponsor to pose an unacceptable risk to the subject in the study.

Study Level

If any of the following criteria are met, then all further administration of investigational product and further enrolment of new subjects will be halted (ie, temporarily paused) until an assessment of the overall safety of continuing the study is completed: 1 subject develops an SAE that results in death and is considered by the investigator, IDMC and / or the Sponsor to be related to the administration of CSL312; or 1 subject develops any event that is deemed to pose an unacceptable risk to other subjects in the study, and these events are considered by the investigator, IDMC and / or CSLB to be related to the administration of CSL312.

If any study halting criteria are met and the study is halted per IDMC recommendation, the Sponsor Global Safety Committees will conduct a safety assessment to establish if the study should be resumed or if the temporary halt should continue. The study can be resumed on the recommendation of the Sponsor's Global Safety Committees, in agreement with the IDMC, if the safety assessment concludes that no further study modifications, protocol amendments, or risk mitigation measures are necessary and it is safe to resume the study. Regulators (on a conditional basis) and the Independent Ethics Committee (IEC) will be notified of the temporary halt and subsequent resumption of the study. A substantial protocol amendment will be submitted to the Regulators and the IEC for approval if the safety assessment concludes that modifications to the protocol (including addition of new risk mitigation measures) are required to resume the study. If the risk assessment concluded that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the Sponsor Global Safety Committees will be involved in recommending a study stop. Regulators and the IEC will be notified of a study stop.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.1 Run-in Period

To enter the Run-in Period, **CSL312-naïve subjects** must meet all the following inclusion criteria:

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements and / or the subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent/assent as appropriate.
2. Male or female.
3. Aged ≥ 12 at the time of providing written informed consent or assent for minors.
4. Diagnosed with clinically confirmed C1-INH HAE:
   a) Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
   b) C1-INH antigen concentration and / or functional activity ≤ 50% of normal as documented in the subject's medical record, and
   c) C4 antigen concentration below the lower limit of the reference range as documented in the subject's medical record.
5. Experienced ≥ 3 HAE attacks during the 3 months before Screening, as documented in the subject's medical record.

   Note: For subjects taking any prophylactic HAE therapy during the 3 months before Screening, ≥ 3 HAE attacks may be documented over 3 consecutive months before commencing the prophylactic therapy.

4.1.1.2 Treatment Period

CSL312-naïve subjects will be eligible to exit the Run-in Period and enter the Treatment Period if they meet all the following criteria:

1. Participated in the Run-in Period for at least 1 month.

2. Experienced at least an average of 1 HAE attack per month during the Run-in Period (ie, experienced a total of at least 2 HAE attacks).
3. Do not have laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments performed during Screening.
4. C1-INH functional activity and antigen, and C4 antigen concentration levels have been verified at screening.

Note: Subjects with ≥ 2 times the upper limit of normal for aspartate aminotransferase (AST) and / or alanine aminotransferase (ALT) may be eligible for participation if there is an explanation for this laboratory result and if the results are not clinically significant.

Subjects who successfully complete Studies CSL312_2001 or CSL312_3001 according to their respective protocols may roll over directly from treatment in those trials and start this study at Treatment Day 1.

4.1.2 Exclusion Criteria

4.1.2.1 Run-in Period

Subjects must not enter the Run-in Period if they meet any of the following exclusion criteria:

1. Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema or recurrent angioedema associated with urticaria.
2. Use of C1-INH products, androgens, antifibrinolytics or other small molecule medications for routine prophylaxis against HAE attacks at least 2 weeks before the first day of the Run-in Period.
3. Use of mAbs such as lanadelumab (Takhzyro®) 3 months before the first day of the Run-in Period.
4. Female subjects' use of estrogen-containing medications with systemic absorption (eg, oral contraceptive or hormonal replacement therapy within 4 weeks prior to the Run-in Period).
5. Participation in another interventional clinical study during the 30 days before Screening or within 5 half-lives of the final dose of the IP administered during the previous interventional study, whichever is longer.

6. Known or suspected hypersensitivity to mAb therapy or hypersensitivity to CSL312 or to any excipients of CSL312.
7. Subject has any condition that in the judgement of the investigator or the Sponsor, may compromise their safety or compliance, impede successful conduct of the study, interfere with interpretation of the results, or would otherwise render the subject unsuitable for participation in the study, eg, clinically significant bleeding due to coagulopathy, thrombotic disorder, significant illnesses or major comorbidities.
8. Intention to become pregnant or to father a child at any time during the study.
9. Female or male subjects who are fertile and sexually active not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 3 months after receipt of the last dose of CSL312. Acceptable methods of contraception are defined in Section 7.4.

   Note: All female subjects are assumed to be of childbearing potential except:

   a) Subjects aged > 60 years.

   b) Subjects aged 45 to 60 years (inclusive) with amenorrhea for ≥ 1 year[1] with documented evidence of follicle-stimulating hormone level > 30 IU/L. If the follicle-stimulating hormone value is not available before first dose, a urine pregnancy test is required.

   c) Subjects who are surgically sterile for at least 3 months before providing informed consent.

   Note: All male subjects are assumed fertile except subjects who are surgically sterile for at least 3 months before providing informed consent
10. Pregnant, breastfeeding, or not willing to cease breastfeeding.
11. Currently receiving a therapy not permitted during the study, as defined in Section 7.3.
12. Involved in the planning and / or conduct of the study (applies to the Sponsor staff, staff at the study site, and third-party vendors).

[1] For Czech Republic sites only (per Administrative Amendment 1 dated 13 May 2021): Without an alternative medical cause.

4.2 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical study but who do not meet the eligibility criteria for participation in the study (see Section 4.1). A minimal set of information including demography, eligibility criteria, and screen failure details should be recorded for all individuals considered screen failures.

If a potential subject is not eligible for entry into the Run-in Period within 30 days after providing informed consent, then the subject may reconsent and may be screened again (for a maximum of 2 screening periods per subject) after consultation with the Sponsor. In the event that a potential subject is screened twice, all Screening assessments must be repeated during the second Screening Period.

4.2.1 Run-in Period Screen Failures

A Run-in Period screen failure is defined as those subjects who are not eligible to enter the Treatment Period. Subjects who enter the Run-in Period but are not eligible to enter the Treatment Period will be considered Run-in failures and may not be rescreened. If a subject is not eligible to enter the Treatment Period, the primary reason for Run-in failure must be documented.

4.3 Discontinuation of Study Treatment and Subject Withdrawal

4.3.1 Discontinuation of Study Treatment

Subjects may discontinue study treatment with CSL312 at any time at their own request, or at the discretion of the investigator or the Sponsor for safety, behavioral, or administrative reasons.

4.3.2 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or at the discretion of the investigator or the Sponsor for safety, behavioral or administrative reasons (eg, because of an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination). The investigator should record in the Case Report Form (CRF) and in the subject's medical records the reason and date of subject withdrawal.

In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) principles of Good Clinical Practice (GCP), the

investigator always has the option to advise a subject to withdraw from the study if the subject's safety or wellbeing is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

4.3.3 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document the End of Treatment Visit assessments. If the subject is withdrawn from the study after receiving CSL312, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

4.3.4 Subjects Lost to Follow-up

If a subject repeatedly fails to return for scheduled visits, the site must attempt to contact the subject and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and / or should continue in the study. All attempts to contact the subject should be documented in the subject’s medical record.

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Subjects lost to follow-up will be considered to have withdrawn from the study.

4.3.5 Replacement Policy

Subjects withdrawn from the study will not be replaced.

5 Study Interventions

5.1 Investigational Product(s)

5.1.1 Description of CSL312

CSL312 is supplied (1.2 mL per CSL312 200 mg NSD or CSL312 200 mg AI) as a sterile, preservative-free solution for injection, at pH 6.1. CSL312 is formulated in buffer containing 20 mM L-histidine, 150 mM L-arginine monohydrochloride, 140 mM L-proline, 0.02% w / v

polysorbate 80, and water for injection. Each prefilled syringe contains CSL312 at a concentration of 170 mg per 1 mL.

Substance name	CSL312
Active substance	Factor XIIa inhibitor monoclonal antibody
Trade name	Not applicable
International non-proprietary name:	Garadacimab
Storage	The recommended storage temperature is + 2 to + 8°C
Dosage form	1.2 mL 200 mg CSL312 at a concentration of 170 mg per 1 mL, either in CSL312 200 mg NSD or CSL312 200 mg AI

5.1.2 Description of Comparator Product

Not applicable.

5.1.3 Dosing and Administration of CSL312

The investigator (or delegate) will administer or dispense CSL312 only to subjects included in this study following the procedures set out in this study protocol. Information on the dosing characteristics of CSL312 is provided in Table 1.

Table 1 CSL312 Dosing Characteristics

Administration Parameter of CSL312 200 mg NSD	
Dose	200 mg once monthly
Route	Subcutaneous
Anatomical location	Abdomen, other (ie, upper arm, thigh)
Total infusion volume	1.2 mL

Administration Parameter of CSL312 200 mg AI	
Dose	200 mg once monthly
Route	Subcutaneous
Anatomical location	Abdomen, other (ie, upper arm, thigh)
Total infusion volume	1.2 mL

AI = autoinjector; NSD = needle safety device.

All subjects who meet the criteria to enter the study will be assigned to 1 dose, 200 mg, to be given SC once monthly. For CSL312-naïve subjects, a loading dose of 400 mg (two 200 mg doses) will be administered SC on Visit Day 1, then 200 mg once monthly in subsequent months. CSL312 SC administrations will be self-administered by the subjects or caregivers.

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

Per Amendment 1, subjects or caregivers will subcutaneously administer CSL312 200 mg AI instead of CSL312 200 mg NSD. The AI is a device that contains the same prefilled syringe already being used in the NSD since the start of the study. The purpose of using an AI is to further facilitate the administration of CSL312. The first administration with CSL312 200 mg AI will be on site, and training will be provided for subjects and caregivers. Additional

CSL312 200 mg AI administration training at subsequent scheduled onsite visits may be provided if it is requested. Subsequent administrations with CSL312 200 mg AI will occur at home (either self-administered or with the help of a caregiver). The dose and dosing regimen will continue to be 200 mg once monthly. Subjects who decline switching to CSL312 200 mg AI and who have participated in the study for at least 12 months will receive 1 more dose of CSL312 200 mg NSD at the time of the scheduled site visit and subsequently proceed with the End of Treatment Visit 1 month later, as well as a Follow-up Visit 2 months after the End of Treatment Visit, as per the original protocol.

Any device malfunctions should be reported as a suspected Product Technical Complaint. Refer to the Site Investigational Product Manual for additional information.

Detailed information on the preparation and administration of CSL312 is provided in the Site Pharmacy Manual.

5.1.3.1 Dosing Modification

Per Amendment 1, no dosing modifications will be permitted.

5.1.3.2 Treatment Compliance

The subject will record the dose and date of CSL312 administration in the eDiary. Compliance will be assessed using the administration details entered into the eDiary.

5.1.3.3 Overdose

Overdose is defined as the administration of any dose (single or cumulative) of a product that is considered excessive. The highest studied single dose was 10 mg/kg IV and SC and multiple doses at 600 mg SC without clinically relevant side effects. The effects of potential overdose with CSL312 have not been studied. In case of overdose, the subject should be closely monitored, and supportive treatment should be administered as needed.

Any overdose that occurs in association with an adverse sign or symptom must be entered into the CRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.3).

Details (ie, volume, location of injection) of overdose of CSL312 must be recorded in the study treatment administration CRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication CRF.

See Section 9.6.5 for overdose reporting requirements.

5.1.4 Description of Investigational Medical Device Constituent(s)

The 1.2 mL CSL312 is supplied in a 2.25 mL ready-to-use staked-in-needle prefillable syringe with rigid needle shield and syringe plunger. The prefilled syringe is assembled with a plunger rod and embedded in an NSD and an extended finger flange which are not in contact with the liquid.

Per Amendment 1, the 1.2 mL CSL312 is supplied in an AI. The administration parameters of the CSL312 200 mg AI for this study are detailed in Table 1.

The CSL312 200 mg AI does not require assembly or preparation before use. Injection of a single fixed SC dose is triggered by push-on-skin activation after pulling off the protective cap. Injection is done automatically and takes up to 15 seconds. An integrated needle safety locking feature is activated after the CSL312 200 mg AI is lifted from the injection site, preventing post-injection needle stick injuries.

5.1.5 Packaging, Labeling, Supply and Storage

5.1.5.1 Packaging and Labeling

CSL312 will be packaged and labeled according to current ICH Good Manufacturing Practice (GMP) and GCP guidelines and national legal requirements. Specific details regarding packaging of CSL312 are provided in the Site Pharmacy Manual.

5.1.5.2 Supply and Storage

CSL312 will be supplied to the study sites by the Sponsor or delegate.

At the study site, investigational product must be stored under temperature-controlled and monitored conditions from +2°C to +8°C in a secure storage area as specified in the Site Pharmacy Manual.

In cases where investigational product is stored at a subject's home, detailed storage instructions will be provided in a separate manual.

5.1.6 Access to Investigational Product After the End of Study

Subjects will not be provided with investigational product by the Sponsor after completion or discontinuation from the study.

5.2 Accountability and Destruction

CSL312 must be used only as directed in the clinical study protocol.

The investigator or delegate will confirm receipt of all shipments of CSL312 in the interactive response technology (IRT) system. All supplies of CSL312 must be accounted for throughout the study.

Records for the delivery of investigational product to the study site, the inventory at the study site, the use by each subject, and the destruction or return of CSL312 to the Sponsor / designee must be maintained by the investigator or delegate using the IRT system. The investigator or delegate must provide reasons for any discrepancies in drug accountability in the IRT.

For Japan sites only, drug inventory and accountability logs / reports must be dated and signed by the head of the medical institute or the study drug storage manager (if assigned by the head of the medical institute).

Further details regarding accountability and destruction of CSL312 are provided in the Site Pharmacy Manual.

5.2.1 Concomitant Study-related Therapies

5.2.1.1 On-demand Medication

Subjects must be assessed by the investigator to be capable of managing their HAE attacks during participation in the study. An individual action plan will be reviewed with the subject.

HAE attacks occurring during the Screening and Run-in Periods or during the study should be managed in accordance with the investigator's usual standard of care of their patients, including use of on-demand attack therapies that the investigator deems medically appropriate. Berinert® will be supplied by CSL in countries where Berinert is licensed or where it meets the local regulation as a noninvestigational product to those subjects who elect to use C1-INH for on-demand treatment of HAE attacks. Berinert will not be supplied to

study sites in Japan as a study medication. Subjects may use other effective on-demand medication of their choice (in accordance with the standard of care in the region) to treat HAE attacks experienced during the study as described in Section 7.2. Use of IV C1-INH will be permitted as an on-demand attack therapy, short-term prophylaxis use prior to medically indicated procedures, but not as a long-term prophylaxis.

6 Allocation to Treatment

6.1 Subject Assignment

All subjects who meet the criteria to enter the study will be assigned to 1 dose, 200 mg, to be given SC once monthly. For CSL312-naïve subjects, a loading dose of 400 mg (200 mg doses) will be administered SC on the first month, then 200 mg once monthly in subsequent months.

6.2 Randomization Procedures

Not applicable.

6.3 Blinding Procedures

This is an open-label study; thus, blinding procedures are not applicable.

7 Contraindications, Permitted Therapies, and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

There are no contraindications or precautions associated with CSL312 administration.

7.2 Permitted Therapies

The following medications and therapies are PERMITTED at any time during the study:

- Prescribed medication(s) required for the management of acute or chronic medical conditions.
- Therapies to treat any AEs the subject experiences during the study, including nonprophylactic aspirin (eg, to treat a headache).

All on-demand HAE therapies are permitted at any time during the study for the treatment of HAE attacks used according to the product label.

The use of approved medication for the prevention of HAE attacks prior to any surgical procedure is PERMITTED at any time during the study.

7.3 Prohibited Therapies

Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products, androgens, antifibrinolytics, approved or future approved medication are PROHIBITED during the entire study (not including the Follow-up Period).

- Use of Estrogen-containing contraceptive regimens or replacement therapy with systemic absorption (eg, oral contraceptive or hormonal replacement therapy).

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrollment.

7.4 Lifestyle Restrictions

Female subjects considered to be women of childbearing potential[2] and male subjects[3] must use a medically reliable form of contraception during the study duration and for 3 months after the last SC infusion of CSL312. Acceptable methods of contraception are:

- Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the CSL312. Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable definitions of abstinence.
- Acceptable hormonal methods include: progestin-only oral contraceptives, contraceptive medication patch, contraceptive medication injection, vaginal ring, or contraceptive medication implant.
- Use of intrauterine device (placed more than 3 months before providing informed consent).

[2] Female subjects considered to be women of childbearing potential are those who have not experienced menopause (ie, natural amenorrhea for > 12 months), or are without a history of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation.
[3] Male subjects are considered fertile after puberty unless permanently sterile by bilateral orchiectomy, etc.

- Bilateral tubal occlusion of female subjects (3 months before providing informed consent).
- Vasectomy of male subjects (3 months before providing informed consent).[4]

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the Schedule of Assessments: Screening and Run-in Period (CSL312-naïve Subjects Only), Schedule of Assessments: Treatment Period (All CSL312_3001 Subjects and CSL312-naïve Subjects), Schedule of Assessments: Treatment Period (CSL312_2001 Subjects), and Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1. More frequent assessments may be performed, if clinically indicated, at the discretion of the investigator. Refer to the provided study manuals for detailed instructions on how the assessments should be performed.

8.1.1 Demographics and Safety Assessments

The clinical procedures to be conducted during this study related to the evaluation of safety are provided below. Some laboratory assessments may also be used as screening assessments. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Section 8.6.1.

[4] For Czech Republic sites only (per Administrative Amendment 1 dated 13 May 2021): According to CTFG "Recommendations related to contraception and pregnancy testing in clinical trials," vasectomy is also a highly effective contraceptive method for male partners of female subjects of childbearing potential, provided that the partner is the sole sexual partner of the female study subject and the vasectomized partner has received medical assessment of the surgical success.

Table 2 Study Procedures: Demographics and Safety Assessments

Assessment	Description
Demographics	Year of birth / age Sex Race and ethnicity

Medical history	Relevant medical history within the 6 months before Screening with respect to the overall health of the subject
	• Medical history of HAE:
	  o type 1 or type 2
	  o age of diagnosis
	  o any history of laryngeal attacks
	  o family history of HAE
	• Lab values C1-INH functional activity and antigen / C4 antigen concentration medical records to support diagnosis
	• HAE attacks in the last 3 months
	  o If on prophylactic therapy 3 months prior to screening, collect history of number of HAE attacks 3 months prior to the start of prophylactic therapy
	• Prior prophylaxis therapy and on-demand treatment medication 3 months prior to screening
	• Contraception method
	• Prior (within 6 months before Screening) / concomitant medications and therapies

Pregnancy test[a]	Urine test for Choriogonadotropin Beta (beta-human chorionic gonadotropin), for women of childbearing potential.
Physical examination	As per the investigator's standard procedure, including assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis
Adverse events	Evaluation of all adverse events (eg, causality / relatedness, severity, seriousness) Adverse events of special interest: • Abnormal bleeding events • Thromboembolic events • Severe hypersensitivity including anaphylaxis
Vital signs	Blood pressure (systolic and diastolic) Respiratory rate Pulse rate Temperature Height and body weight
Urinalysis	Bilirubin Occult blood Leukocyte esterase Glucose Ketones Protein Nitrite pH Specific gravity Urobilinogen
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 Platelet count

Biochemistry	Sodium	Potassium	Chloride
	Bicarbonate	Albumin	ALP
	Direct Bilirubin	Bilirubin, total	AST
	Protein – total	Calcium	ALT
	Creatinine	Phosphate	BUN
	Glucose		
Coagulation [b]	aPTT		D-dimer
			Prothrombin time
			INR
HAE biomarkers [c]	A blood sample will be retained for potential assessment of HAE biomarker assessment (retention sample)		
Immunogenicity [b]	Binding antibodies (inhibitory and non-inhibitory) specific to FXIIa inhibitor monoclonal antibody (anti-CSL312).		
Other	C1-INH functional activity and antigen concentration, and C4 antigen concentration		

aPTT = activated partial thromboplastin time; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = Aspartate aminotransferase; BUN = blood urea nitrogen; C1-INH = C1-esterase inhibitor; FXIIa = activated Factor XII; HAE = hereditary angioedema; INR = international normalized ratio.

Footnotes:

[a] Urine pregnancy test will be conducted at the study site. If the urine pregnancy test is inconclusive, a serum pregnancy test will be performed and analyzed at a local laboratory.

[b] Analysis will be conducted at a central laboratory. Additional details will be provided in the Laboratory Manual.

[c] HAE biomarker samples will be shipped to a central laboratory for potential testing of HAE markers or used for research and will be destroyed within 5 years after completion of the study. For adults only.

Reports of laboratory tests completed at the central laboratory (hematology, biochemistry, and urinalysis) should be signed after review and retained at the study site as source data. The investigator should make an evaluation of the available safety assessment results with regard to clinically relevant abnormalities. Refer to Section 9 for information on how AEs based on laboratory tests should be assessed and reported.

Laboratory Parameters

Details related to the collection, preparation, and transfer of blood and urine samples for laboratory assessments will be provided in the Laboratory Manual.

Refer to Section 9.1.1 for assessment of abnormal laboratory values. Tests resulting in abnormal laboratory values during the study period that have been classified by the investigator as clinically significant should be followed up after receiving the laboratory report and may include an unscheduled repeat safety sampling under the investigator's discretion.

Vital Signs

Blood pressure and heart rate will be measured with the subject in a supine or seated position after resting for at least 5 minutes.

8.1.2 Pharmacokinetic and Pharmacodynamic Assessments

PK and PD assessments to be conducted during the study are provided in Table 3. The time windows for each type of assessment are detailed in Section 8.6.1. PK / PD assessments are to be assessed based on 3 different categories:

- PK / PD in all subjects at scheduled time points
- Additional PK / PD samples in all adolescents at steady-state
- PK subgroup analysis in adult CSL312-naïve subjects to characterize the PK after the SC loading dose

PK and PD assessments are to be performed at time points as detailed in the Schedule of Assessments: Treatment Period (CSL312_3001 Subjects and CSL312-naïve Subjects), Schedule of Assessments: Treatment Period (CSL312_2001), Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1, Schedule of Additional Assessments for Pharmacokinetic Subgroup Analysis in a Subset of CSL312-naive Adult Subjects, and Schedule of Assessments for Pharmacokinetic Sampling in All Adolescents. Details related to the collection, preparation, and transfer of PK / PD samples will be provided in a Laboratory Manual.

Table 3 Clinical Procedures: Pharmacokinetic and Pharmacodynamic Assessments

Procedure	Description
Pharmacokinetics evaluations (central laboratory)	Plasma samples will be collected for assessment of CSL312 concentration.
Pharmacodynamics evaluations (central laboratory)	Plasma samples will be collected for assessment of FXIIa mediated kallikrein activity.

FXIIa = activated Factor XII.

8.1.3 Efficacy Assessments

Efficacy assessments are to be performed at time points as detailed in the Schedule of Assessments: Screening and Run-in Period (CSL312-naïve Subjects Only), Schedule of Assessments: Treatment Period (All CSL312_3001 Subjects and CSL312-naïve Subjects), Schedule of Assessments: Treatment Period (CSL312_2001 Subjects), and Schedule of Assessments: Treatment Period for All Subjects Under Amendment 1. The time windows for each type of assessment are detailed in Section 8.6.1. HAE attacks that are confirmed by investigator or designee will be used for the efficacy analysis and will be recorded on the CRF. All HAE symptoms reported by the subject will be displayed in a by-subject listing. The investigator will review the symptom(s) reported by the subjects. The investigator should confirm if the symptom(s) represent an HAE attack and, if not an HAE attack, then document the symptom(s) as an AE in the CRF. A prodromal symptom by itself or use of on-demand medication alone should not be considered as an attack. Appendix 2 contains assessment criteria for investigator confirmation of HAE attacks.

At each study visit and telephone contact during the Run-in Period, the investigator or designee will review the subject's eDiary entries. The investigator will consider all available medical information and may ask clarifying questions to assist in their confirmation of HAE attacks. The following information will be documented in the subject's eDiary:

- Date and time of HAE symptom onset.
- Date and time of HAE symptom resolution (ie, subject no longer experiencing symptoms of the attack).
- Location of HAE symptom(s).
- Confirmation of interference of symptom(s) with the subject's daily activities.
- If on-demand medication was used to treat HAE symptoms:
    - Name of medication.
    - Date and time of administration.
- Confirmation of medical assistance received for the HAE symptoms.

The investigator will confirm the following details with the subject related to the symptoms:

- Location of HAE symptom(s).

- Start / end date / time of symptom(s).
- Dose(s) of on-demand medication(s) used.
- Route(s) of Administration of on-demand medication(s) used.
- Self-administered on-demand medication(s)? (yes / no).
- Administration of on-demand medication(s) at a study site, home or emergency room.
- Type of medical assistance or intervention provided by a healthcare professional during HAE symptoms, including hospitalization or emergency department visits.
- Severity of the attack (based on degree of interference in daily activities, and whether or not the use of on-demand medication and / or medical assistance was needed).

8.2 Other Assessments

8.2.1 Outcome Research Assessments

QoL data will be obtained using the AE-QoL questionnaire, the WPAI:GH questionnaire, Subject's Global Assessment of Response to Treatment (SGART), IGART, and TSQM II. QoL data will be obtained electronically using a provisioned electronic Clinical Outcome Assessment (eCOA) solution for the following questionnaires: AE-QoL, the WPAI:GH, SGART, and TSQM II. The IGART QoL will be captured in Rave.

The age considerations for these assessments are:

- IGART: all ages
- SGART: all ages
- TSQM II: ≥ 18 years
- AE-QoL: ≥ 18 years
- WPAI:GH: ≥ 16 years

8.2.1.1 Angioedema Quality of Life Questionnaire

The AE-QoL questionnaire is an instrument to assess QoL impairment in subjects with recurrent angioedema attacks [Weller et al, 2012].

The AE-QoL is a questionnaire that covers 4 dimensions (functioning, fatigue / mood, fear / shame, and nutrition), and consists of 17 questions with 5 levels of response (never, rarely, occasionally, often, and very often). A linear transformation of raw scores results in a range of possible total scores from 0 (minimum) to 100 (maximum).

The AE-QoL will be completed using a provisioned eCOA solution.

Further details will be provided in the statistical analysis plan (SAP).

8.2.1.2 Work Productivity and Activity Impairment Questionnaire: General Health

The WPAI:GH questionnaire is an instrument to measure impairments in both paid and unpaid work [Reilly et al, 1993].

The WPAI:GH measures absenteeism, presenteeism, as well as impairments in unpaid activity because of health problems during the 7 days before administration of the questionnaire. It has been validated to quantify work impairments for numerous diseases. The WPAI:GH has been used to compare work impairments between treatment groups in clinical studies or trials or between subjects with different disease severity levels.

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

The WPAI:GH will be completed using a provisioned eCOA solution.

Further details will be provided in the SAP.

8.2.1.3 Subject's Global Assessment of Response to Therapy

The overall response to treatment with the CSL312 will be self-assessed by the subject using the SGART.

The SGART will measure the subject's overall treatment response to CSL312 using the following ratings:

- (0) none – worse or no response at all, not acceptable.
- (1) poor – very little response, not acceptable.
- (2) fair – some response, acceptable but could be better.
- (3) good – good response, acceptable.
- (4) excellent – excellent response, as good as can be imagined.

The SGART will require subjects to rate themselves using the following direction (or an appropriate translation, as applicable): "Considering all of the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this Treatment Period".

The SGART will be completed using a provisioned eCOA solution with a laminated card that defines each of the categories listed above.

Further details will be provided in the SAP.

8.2.1.4 Investigator's Global Assessment of Response to Therapy

The overall response to treatment with the CSL312 will be assessed by the investigator using the IGART.

The IGART will measure the subject's overall treatment response to the CSL312 using the following ratings:

- (0) none – worse or no response at all, not acceptable;
- (1) poor – very little response, not acceptable;
- (2) fair – some response, acceptable but could be better;
- (3) good – good response, acceptable;

- (4) excellent – excellent response, as good as can be imagined.

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

The IGART will be completed in the CRF.

Additional details will be provided in the SAP.

8.2.1.5 Treatment Satisfaction for Medication Questionnaire

The validated TSQM II questionnaire assesses subjects' satisfaction with medication, providing scores on 3 scales: effectiveness, side effects, convenience, and global satisfaction [Atkinson et al, 2005].

The TSQM II will be completed using a provisioned eCOA solution.

Additional details will be provided in the SAP.

8.2.2 Electronic Diary and Electronic Clinical Outcome Assessments

The study will employ a 3rd-party provisioned eCOA solution to capture both patient reported outcome (PRO) measures and eDiary information.

PRO assessments will be completed by subjects using the eCOA solution via a provisioned electronic device (eg, tablet) provided at the study site. eDiary entries will also be completed via a provisioned electronic device (eg, handheld) and are to be entered by the subject while at home. Subjects will be fully trained by the site staff in the use of the eDiary and tablet. Refer to Section 8.1.3 for eDiary content.

The following assessments will be completed by the subject using the eCOA solution at the study site:

- SGART
- TSQM II

- AE-QoL
- WPAI:GH

A web portal will provide site staff with on-demand, role-based access to all PRO data and eDiary data.

8.3 Blood Samples

During the study, blood will be taken from each subject for laboratory safety assessments and PK / PD evaluations. Detailed information on the volume of blood to be sampled for each assessment will be available in the laboratory manual. Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Information on the volume of blood to be collected for each visit will be available in the informed consent form (ICF).

Refer to the laboratory manual for details about the volume, collection, storage, handling and processing of blood samples.

8.4 Retention of Samples

Refer to the laboratory manual for further details about the storage and destruction of retention samples.

8.4.1 Retention Samples for Pharmacokinetic / Pharmacodynamic Evaluations and HAE Biomarkers

Blood samples for potential future assessment of HAE biomarkers will be obtained during the Treatment Period at all visits, including the End of Treatment Visit. These samples will be stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion of the study. Per Amendment 1, blood samples for potential future assessment of HAE biomarkers will be obtained for the last time at the visit that the subject consents to Amendment 1 (ie, Month 12, Month 18, Month 24, or Month 30). If consent into Amendment 1 and switching to CSL312 200 mg AI is performed at an unscheduled visit after the Month 12 Visit, the last collection of HAE biomarkers will be from the last visit prior to the unscheduled visit (under the original protocol). These samples will be stored for potential future assessment of HAE biomarkers and will be destroyed within 5 years after completion of the study. These samples will not be collected in adolescents.

PK / PD samples may be retained for other analyses such as FXII concentration if deemed to be required throughout the course of the study.

8.5 Prior and Concomitant Therapies

All medications and therapies that have been administered to a subject within 6 months before signing informed consent are regarded as prior medications and therapies and must be documented as such in the CRF.

All drugs and / or procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to CSL312 during the study, are regarded as concomitant therapies. All concomitant therapies will be recorded in the subject's CRF.

Both pharmacological (eg, prescription and over-the-counter medications, and herbal and vitamin supplements) and nonpharmacological (eg, any surgical or diagnostic procedures) will be reported.

8.6 Visit Schedule

8.6.1 Assessment Time Windows

The timing and frequency of the study visits are described in the Schedule of Assessments. Time windows for all assessments are detailed in Table 4.

Table 4 Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Screening	Not applicable
Run-in Period: All visits	± 4 days
Treatment Period: All visits	± 4 days
Follow-up Visit	± 7 days (per original protocol); - 14 days (per Amendment 1)
Vital signs	Pre-injection on same day

8.6.2 Screening and Run-in Period (CSL312-naïve Subjects Only)

8.6.2.1 Screening (Days -30 to 1)

All subjects (or the subject's authorized representative) must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

A screening examination should be performed within 30 days before the start of the Run-in Period.

The following procedures will be conducted and documented at the Screening Visit:

- Obtain written informed consent.
- Review inclusion and exclusion criteria.
- Record subject demographics.
- Obtain relevant medical history including C1-INH functional activity and antigen, and C4 antigen concentration history, recording of overall health within the 3 months before Screening; HAE history including type, age of diagnosis, medical records to support diagnosis (ie, attack frequency, history of laryngeal attacks, prior prophylaxis therapy and on-demand treatment medication) within the 3 months before Screening, and contraception method (for female subjects of childbearing potential only).
- Perform physical examination, include assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

- Record vital signs including body weight.
- Collect urine for urinalysis.
- Collect blood for:
  - Hematology
  - Biochemistry
  - Coagulation
  - C1-INH functional activity and antigen, and C4 antigen concentration for confirmation of historical laboratory values contained in the subject's medical record.
- Collect urine for pregnancy test (for women of childbearing potential).
- Develop an individual acute action plan, including assessment of subject's ability to manage HAE attacks and confirmation of subject's access to on-demand HAE medication to treat HAE attacks.
- Perform eDiary training.
- Record prior and concomitant medications and therapies (type, dose, route, date, and time) in the last 6 months.
- Begin to monitor AEs.

Re-screening: If a potential subject is not eligible for entry into the Run-in Period within 30 days after providing informed consent, then the subjects may reconsent and may be screened again (for a maximum of 2 Screening Periods per subject) after consultation with the Sponsor. In the event that a potential subject is screened twice, all Screening assessments must be repeated, based on Sponsor recommendation, during the second Screening Period. If the subject is not eligible for the study (ie, the subject is a Screen Failure), all eligibility criteria that are not met must be recorded in the IRT.

8.6.2.2 Run-in Period

8.6.2.2.1 Run-in Period Day 1

Subjects who complete all Screening assessments and who fulfill the eligibility criteria (ie, eligible subjects) will be enrolled into the study. The first day of the Run-in Period may

occur on the same day as the Screening Visit if the subject meets the criteria for entering the Run-in Period.

The following procedures / assessments will be conducted:

- Open subject access to eDiary and review diary instructions with subject.
- Confirm access to on-demand HAE medication.
- Record prior and concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.2.2.2 Run-in Period Days 15, 30, and 45 ± 4 days

The following procedures / assessments will be conducted at Visit Days 15, 30, and 45 during the Run-in Period:

- Telephone contacts for all subjects
- Review of eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.2.2.3 Run-in Period Day 60 ± 4 days

The following procedures will be conducted at Visit Day 60 during the Run-in Period:

- Telephone contacts for all subjects
- Review of eDiary data and assess / document HAE attacks.
- Close eDiary access (only applicable subjects not eligible to enter the Treatment Period on Day 60).
- Confirm access to on-demand HAE medication.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

Subjects must participate in the Run-in Period for at least 1 month. Subjects may exit the Run-in Period and enter the Treatment Period when they have met the criteria specified in protocol Section 4.1.1.2. Specifically, subjects must have experienced an average of 1 HAE attack per month during the 2-month Run-in Period (ie, for a minimum of 2 HAE attacks if the subject enters the Treatment Period with 2 months from Day 1 of Run-in).

Subjects should enter the Treatment Period no later than 15 days after the Day 60 telephone contact. If a subject is unable to enter the Treatment Period within the 15 days after the Day 60 telephone contact, then the Sponsor approval is required for the subject to enter the Treatment Period. The Day 60 telephone contact will conclude the Run-in Period for a subject who has entered the Run-in Period and is subsequently not eligible to be assigned to treatment with CSL312 in the Treatment Period.

Subjects who enter the Run-in Period but are not eligible to enter the Treatment Period will be considered Run-in failures. If a subject is not eligible to enter the Treatment Period, the primary reason for Run-in failure must be documented. These subjects may not be rescreened.

8.6.3 Treatment Period (All CSL312_3001 Subjects and CSL312-naïve Subjects) for Original Protocol

8.6.3.1 Treatment Period Visit Day 1

CSL312-naïve subjects must complete all screening assessments, fulfill the eligibility criteria (ie, eligible subjects), and meet the Treatment Period entry criteria (Section 4.1.1.2).

For subjects who completed Study CSL312_3001 and choose to participate in Study CSL312_3002 (CSL312_3001 rollover subjects), assessments from Day 182 of Study CSL312_3001 will be used to fulfill assessments for Day 1 of Study CSL312_3002

(ie, the last study visit of CSL312_3001 and the first study visit of Treatment Period in CSL312_3002 occur on the same day).

If a subject did not participate in a Screening Visit (CSL312_3001 subjects), then a written informed consent / assent must be obtained before any study-specific assessments or procedures are performed at the first visit in the Treatment Period.

The following procedures / assessments will be conducted and documented:

- Written informed consent for subjects rolling over from Study CSL312_3001.
- Confirm eligibility for Treatment Period
- Perform physical examination.
- Record vital signs, including body weight and height.
- TSQM II (subjects ≥ 18 years).
- AE-QoL (subjects ≥ 18 years).
- WPAI:GH (subjects ≥ 16 years).

  Note: Subjects rolling over from Study CSL312_3001 who have completed the AE-QoL and WPAI:GH as part of the last visit of Study CSL312_3001 will only need to complete the TSQM II at Day 1.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity.
- Collect urine for pregnancy test (for women of childbearing potential).
- PRO / eCOA tablet training

- Review eDiary instructions with subject
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- Accountability of CSL312
- Subcutaneous administration of CSL312 dose by investigator or delegate (after completion of physical examination and vital signs). For CSL312 naïve subjects, the first dose of CSL312 will be a loading dose consisting of 2 SC injections of 200 mg CSL312 each for a total dose of 400 mg CSL312. Subjects rolling over from Studies CSL312_3001 and CSL312_2001 will not receive a loading dose. Subjects will complete the Medication Dosing Diary on the eDiary after dosing at the site is complete.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.2 Treatment Period: Months 1 and 2 ± 4 days

The following procedures / assessments will be conducted at the Months 1 and 2 site visits:

- Perform physical examination.
- Record vital signs, including body weight.
- Collection of blood to assess:
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability.

- Subcutaneous administration of CSL312 dose by investigator or delegate or by the subject under the supervision of the investigator or delegate (after completion of physical examination and vital signs). Subjects will complete the Medication Dosing Diary on the eDiary after dosing at the site is complete.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.3 Treatment Period: Months 3, 18, and 30 ± 4 days

The following procedures / assessments will be conducted at the Months 3, 18, and 30 site visits:

- Perform physical examination.
- Record vital signs, including body weight.
- TSQM II (subjects ≥ 18 years) (at Months 3 and 18 only).
- AE-QoL (subjects ≥ 18 years) (at Months 3 and 18 only).
- WPAI:GH (subjects ≥ 16 years) (at Months 3 and 18 only).
- Urine collection for urinalysis (at Months 18 and 30 only).
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability.

- At Month 3 only, subcutaneous administration of CSL312 dose by investigator or delegate or by subject under the supervision of the investigator or delegate (after completion of physical examination and vital signs). Subjects will complete the Medication Dosing Diary on the eDiary after dosing at the site is complete.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.4 Treatment Period: Months 6, 12, and 24 ± 4 days

The following procedures / assessments will be conducted at the Months 6, 12, and 24 site visits:

- Perform physical examination.
- Record vital signs, including body weight.
- SGART / IGART (all ages) (at Months 12 and 24 only).
- TSQM II (subjects ≥ 18 years).
- AE-QoL (subjects ≥ 18 years).
- WPAI:GH (subjects ≥ 16 years).
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.

- IRT CSL312 kit assignment.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.5 Treatment Period: Month 9 ± 4 days

The following procedures / assessments will be conducted at the Month 9 site visit:

- Perform physical examination.
- Record vital signs, including body weight.
- TSQM II (subjects ≥ 18 years).
- AE-QoL (subjects ≥ 18 years).
- WPAI:GH (subjects ≥ 16 years).
- Collection of blood to assess:
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.6 End of Treatment

The following procedures / assessments will be conducted at the End of Treatment site visit:

- Perform physical examination.

- Record vital signs, including body weight.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.3.7 Follow-up Telephone Contact or Final Visit

The following procedures / assessments will be conducted at the Final Visit, which occurs 2 months after the End of Treatment Visit:

- Review eDiary data and assess / document HAE attacks.
- eDiary deactivation.

8.6.4 Treatment Period (CSL312_2001 Subjects Only) for Original Protocol

8.6.4.1 Treatment Period: Day 1

For subjects who completed Study CSL312_2001 and choose to participate in Study CSL312_3002 (CSL312_2001 rollover subjects), assessments from Week 57 (Day 399) of Study CSL312_2001 will be used to fulfill assessments for Day 1 of Study

CSL312_3002 (ie, the last study visit of CSL312_2001 and the first study visit of Treatment Period in CSL312_3002 occur on the same day).

Written informed consent / assent must be obtained before any study-specific assessments or procedures are performed at the first visit in Treatment Period.

The following procedures / assessments will be conducted:

- Written informed consent.
- Confirm eligibility for Treatment Period.
- Perform physical examination.
- Record vital signs, including body weight and height.
- TSQM II (subjects ≥ 18 years).
- AE-QoL (subjects ≥ 18 years).
- WPAI:GH (subjects ≥ 16 years).

  Note: Subjects rolling over from Study CSL312_2001 who have completed the AE-QoL and WPAI:GH as part of the last visit of Study CSL312_2001 will only need to complete the TSQM II at Day 1.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity
- Collect urine for pregnancy test (for women of childbearing potential).
- PRO / eCOA tablet training.
- Review eDiary instructions with subject.

- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability
- Subcutaneous administration of CSL312 dose by investigator or delegate or by the subject under the supervision of the investigator or delegate (after completion of physical examination and vital signs). Subjects will complete the Medication Dosing Diary on the eDiary after dosing at the site is complete.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.4.2 Treatment Period: Month 3 ± 4 Days

The following procedures / assessments will be conducted at Month 3:

- Perform physical examination.
- Record vital signs, including body weight.
- Collection of blood to assess:
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.4.3 Treatment Period: Months 6, 18, and 30 ± 4 Days

The following procedures / assessments will be conducted at Months 6, 18, and 30:

- Perform physical examination.
- Record vital signs, including body weight.
- TSQM II (subjects ≥ 18 years) (at Months 6 and 18 only).
- AE-QoL (subjects ≥ 18 years) (at Months 6 and 18 only).
- WPAI:GH (subjects ≥ 16 years) (at Months 6 and 18 only).
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity (at Month 6 only).
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.4.4 Treatment Period: Months 12 and 24 ± 4 Days

The following procedures / assessments will be conducted at Months 12 and 24:

- Perform physical examination.
- Record vital signs, including body weight.
- IGART / SGART (all ages).
- TSQM II (subjects ≥ 18 years).
- AE-QoL (subjects ≥ 18 years).
- WPAI:GH (subjects ≥ 16 years).
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- IRT CSL312 kit assignment.
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.4.5 End of Treatment Period

The following procedures will be conducted at the End of Treatment Visit:

- Perform physical examination.
- Record vital signs, including body weight.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention sample for HAE biomarkers (adults only).
  - PK / PD.
  - Immunogenicity.
- Collect urine for pregnancy test (for women of childbearing potential).
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- CSL312 accountability.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.6.4.6 Follow-up Telephone Contact or Final Visit ± 7 Days

The following procedures / assessments will be conducted at the Final Visit (2 months after the End of Treatment Visit):

- Review eDiary data and assess / document HAE attacks.
- Deactivate eDiary.

8.6.5 End of Study for Original Protocol

The study will continue until each of the subjects receives a minimum of 12 months of treatment; the treatment period for each subject will be variable. The Sponsor reserves the right to stop the study at any time.

8.6.6 Amendment 1 Visit Schedule

8.6.6.1 Treatment Period (All Subjects Under Amendment 1)

The specific site visit to consent into Amendment 1 and to switch to CSL312 200 mg AI may vary per individual subject. Consent into Amendment 1 and switching to CSL312 200 mg AI may occur starting at the Month 12 Visit. An unscheduled visit to accommodate consent into Amendment 1 and switching to CSL312 200 mg AI (with no other assessments performed at this visit) may be scheduled as needed at dates planned for home doses; this unscheduled visit should be performed according to the dosing schedule. The first administration with CSL312 200 mg AI will always occur at the site.

8.6.6.1.1 Treatment Period: Month 12 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 12 study site visit:

- Written informed consent for Amendment 1 and switch to CSL312 200 mg AI
- Perform physical examination
- Record vital signs, including body weight
- SGART / IGART (all ages)
- TSQM II (subjects ≥ 18 years)
- AE-QoL (subjects ≥ 18 years)
- WPAI:GH (subjects ≥ 16 years)
- Urine collection for urinalysis
- Collection of blood to assess:
    - Hematology
    - Biochemistry

- Coagulation
- Retention sample for HAE biomarkers (adults only)
- PK / PD
- Immunogenicity

- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.1.2 Treatment Period: Month 18 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 18 study site visit:

- Written informed consent for Amendment 1 and switch to CSL312 200 mg AI (only for subjects who consent to Amendment 1 at the Month 18 Visit)
- Perform physical examination
- Record vital signs, including body weight
- TSQM II (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 18 Visit)
- AE-QoL (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 18 Visit)
- WPAI:GH (subjects ≥ 16 years) (only for subjects who consent to Amendment 1 at the Month 18 Visit)
- Urine collection for urinalysis (only for subjects who consent to Amendment 1 at the Month 18 Visit)

- Collection of blood to assess:
  - Retention sample for HAE biomarkers (adults only) (only for subjects who consent to Amendment 1 at the Month 18 Visit)
  - PK / PD
- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.1.3 Treatment Period: Month 24 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 24 study site visit:

- Written informed consent for Amendment 1 and switch to CSL312 200 mg AI (only for subjects who consent to Amendment 1 at the Month 24 Visit)
- Perform physical examination
- Record vital signs, including body weight
- SGART / IGART (all ages)
- TSQM II (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 24 Visit)
- AE-QoL (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 24 Visit)
- WPAI:GH (subjects ≥ 16 years) (only for subjects who consent to Amendment 1 at the Month 24 Visit)

- Urine collection for urinalysis (only for subjects who consent to Amendment 1 at the Month 24 Visit)
- Collection of blood to assess:
  - Hematology
  - Biochemistry
  - Coagulation
  - Retention sample for HAE biomarkers (adults only) (only for subjects who consent to Amendment 1 at the Month 24 Visit)
  - PK / PD
  - Immunogenicity
- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.1.4 Treatment Period: Month 30 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 30 study site visit:

- Written informed consent for Amendment 1 and switch to CSL312 200 mg AI (only for subjects who consent to Amendment 1 at the Month 30 Visit)
- Perform physical examination
- Record vital signs, including body weight

- TSQM II (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 30 Visit)
- AE-QoL (subjects ≥ 18 years) (only for subjects who consent to Amendment 1 at the Month 30 Visit)
- WPAI:GH (subjects ≥ 16 years) (only for subjects who consent to Amendment 1 at the Month 30 Visit)
- Urine collection for urinalysis (only for subjects who consent to Amendment 1 at the Month 30 Visit)
- Collection of blood to assess:
  - Retention sample for HAE biomarkers (adults only) (only for subjects who consent to Amendment 1 at the Month 30 Visit)
  - PK / PD
- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.1.5 Treatment Period: Month 36 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 36 study site visit:

- Perform physical examination
- Record vital signs, including body weight
- SGART / IGART (all ages)
- Collection of blood to assess:

- Hematology
- Biochemistry
- Coagulation
- PK / PD
- Immunogenicity

- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.1.6 Treatment Period: Month 42 for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Month 42 study site visit (any visit beyond Month 36 requires approval from the Sponsor):

- Perform physical examination
- Record vital signs, including body weight
- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Confirm plan for managing potential attack
- IRT CSL312 kit assignment (AI)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)

- Record AEs

8.6.6.2 End of Treatment Period for All Subjects Under Amendment 1

The following procedures will be conducted at the End of Treatment Visit (1 month after the last dose of CSL312):

- Perform physical examination
- Record vital signs, including body weight
- Collection of blood to assess:
  - Hematology
  - Biochemistry
  - Coagulation
  - PK / PD
  - Immunogenicity
- Collect urine for pregnancy test (for women of childbearing potential)
- Review eDiary data, including investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- eDiary deactivation (including eDiary collection)
- CSL312 accountability
- Record concomitant medications and therapies (type, dose, route, date, and time)
- Record AEs

8.6.6.3 Follow-up Telephone Contact for All Subjects Under Amendment 1

The following procedures / assessments will be conducted at the Follow-up Telephone Contact (2 months after the End of Treatment Visit):

- Investigator assessment of subject-reported symptoms and documentation as HAE attacks or as AEs
- Record concomitant medications and therapies (type, dose, route, date, and time)

- Record AEs

8.6.6.4 End of Study for All Subjects Under Amendment 1

The treatment period for each subject will be variable. The Sponsor reserves the right to stop the study at any time.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time the subject gives informed consent until the end of study (see Section 9.4 for further details).

AEs may include:

- Exacerbation (ie, an increase in the frequency or severity) of a preexisting condition. Illness present before study entry should be recorded in the medical history section of the CRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before investigational product administration.
- Intercurrent illnesses with an onset after administration of investigational product.

AEs do not include:

- Events identified at screening that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure is the AE).
- Situations where an untoward medical occurrence has not taken place. For example:

- Planned hospitalizations due to pre-existing conditions, which have not worsened.
- Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
- Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).
- Overdose of investigational product or any concomitant therapy that does not result in any adverse signs or symptoms.

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 CRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the CRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at screening, unless a further increase / decrease can be considered an exacerbation of a preexisting condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

9.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.

- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** – the Sponsor considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

9.1.3 Adverse Event of Special Interest

There are several AEs that will be monitored as AESIs to enable an adequate risk-benefit evaluation of CSL312.

The following events will be considered AESIs:

- Thromboembolic events
  - Non-systemic thrombosis (eg, localized thrombosis associated with vascular access) is not considered an AESI
- Bleeding events that are abnormal in the opinion of the investigator
- Severe hypersensitivity, including anaphylaxis

The reporting requirements for AESIs are detailed in Section 9.6.2

9.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Source: CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

9.3 Causality of Adverse Events

The causal relationship of an AE to investigational product, the medical device (constituent), or the combination of device and investigational product, **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to investigational product, the medical device (constituent), or the combination of device and investigational product. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to investigational product, the medical device (constituent), or the combination of device and investigational product.

The degree of certainty with which an AE is attributed to investigational product or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of investigational product.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).

- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with investigational product, drug withdrawal or reproduced on rechallenge).

9.4 Observation Period for Adverse Events

The observation period for the reporting of AEs (and SAEs) for an individual subject will start at the time of giving written informed consent for participation in the current study and finish upon the subject's final visit.

If the investigator becomes aware of an SAE that has started after the observation period has finished, and there is at least a possible causal relationship with the investigational product or medical device constituent, the event must be reported to the Sponsor following the same timelines and procedures described for SAEs occurring during the study (see Section 9.6.3).

9.5 Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, nonserious AEs that have not resolved or stabilized will be followed until the subject completes the study. SAEs will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

9.6 Adverse Event Reporting

9.6.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. All AEs are to be recorded in the CRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and / or symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the end of study visit, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

If, during the study period, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History CRF.

9.6.2 Adverse Events of Special Interest

AESIs must be reported as AEs in the subject's CRF. Additional data might be requested in the CRF for these events. Serious and non-serious AESIs must be reported following expedited reporting procedures, as described for SAEs (Section 9.6.3). See Section 9.1.3 for a list of AESIs.

9.6.3 Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the CRF.

All SAEs that occur during the course of the study, whether or not causally related to investigational product, **must be entered into the CRF immediately (within 24 hours of the investigator becoming aware of the event). For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirement and ICH GCP.**

AEs occurring in the period between the time the subject gave written informed consent and the first exposure to investigational product, and that meet 1 or more of the seriousness criteria, must be entered into the CRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the End of Study Visit that is considered to be causally related to investigational product must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to the Sponsor.** Such events are not entered into the CRF. For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number.
- Suspected medicinal product and / or procedure.

- Event term.
- Reporting source identification.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board (IRB) / IEC within the timeframe specified by the IRB / IEC.
- If the subject is an active participant in the study:
  - Enter follow-up information in the CRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
  - Ensure that the causality assessment for all SAEs is entered in the CRF.
- If the subject is no longer participating in the study, report the follow-up information to the Sponsor.

In cases of death, the investigator should supply the Sponsor and the IEC / IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

9.6.4 Other Significant Events

Not applicable.

9.6.5 Overdose

Overdose is defined as the infusion or ingestion of any dose (single or cumulative) of a product that is considered excessive. The effects of any potential overdose with CSL312 have not been studied. In case of overdose, the subject should be closely monitored, and supportive treatment should be administered, as needed.

Any overdose that occurs in association with an adverse sign or symptom must be entered into the CRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.3).

Details (ie, volume, location of injection) of overdose of investigational product must be recorded in the study treatment administration CRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication CRF.

9.6.6 Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 3 months after the last dose of investigational product, must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue treatment with investigational product, but may continue other study procedures at the discretion of the investigator.

The Sponsor must be notified within 5 days of the investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to investigational product should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to the Sponsor using a Pregnancy Reporting / Outcome Form.

9.7 IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's (for Japan sites only: the head of the medical institution's) responsibility to comply with the requirements for IRB / IEC notification. The Sponsor will provide investigators (for Japan sites only: the head of the medical institution's) with all details of all SAEs reported to health authorities.

10 Statistics

This section provides a description of the key statistical analyses for this study. Further details and analyses are described in the SAP.

10.1 Sample Size Estimation

A minimum of 100 subjects are planned to receive treatment for a minimum of 12 months. This is a single arm study without a control arm. The sample size for this single arm, open-label study is not based on a formal statistical sample size calculation but on the guideline E1A issued by the International Conference on Harmonisation, March 1995. The sample size of 100 subjects allows observation of ≥ 1 AE with a probability of 3% at 95% confidence.

10.2 Description of Study Analysis Sets

10.2.1 Screened Analysis Set

The screened analysis set comprises all subjects who provide written informed consent.

10.2.2 All Treated Subjects Analysis Set

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

10.2.3 Safety Analysis Set

The Safety analysis set comprises all subjects in the ATS analysis set who receive at least 1 dose of investigational product, and will be analyzed using the actual treatment received.

10.2.4 Per-protocol Analysis Set

The Per-protocol (PP) analysis set comprises all subjects in the ATS analysis who receive at least 1 dose of investigational product (IP) and who comply with the protocol. Decisions regarding exclusion from the PP analysis will be made and documented before Database Lock.

10.2.5 Pharmacokinetic Analysis Set

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

10.2.6 Pharmacodynamic Analysis Set

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

10.3 Statistical Analyses and Methods

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

Continuous variables will be described by the number of observations, mean values with their 95% confidence intervals (CIs), 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 PD 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 PD 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.

No hypothesis testing is planned for this study.

As it is expected that the coronavirus disease 2019 (COVID-19) pandemic is still ongoing during the conduct of the study, it will be assessed for subjects who are affected by COVID-19 during their participation in the study if they will be excluded from some analyses. Reasons for an exclusion will be documented. The impact of COVID-19 will be summarized. Listings of COVID-19-associated AEs will be provided for any AEs. Treatment-emergent adverse events (TEAEs) occurring or not occurring within 7 days of a COVID-19 vaccination will be summarized. Concomitant medications used to treat COVID-19-associated AEs will be flagged. COVID-19 vaccinations will be assessed. COVID-19-related protocol deviations will be summarized, and all COVID-19-related protocol deviations will appear in the listing of protocol deviations and will be flagged. All protocol deviations will be reviewed during the Data Review Meeting.

A complete description of the statistical analyses and methods will be available in an SAP, which will be finalized before the database is locked.

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

Subject disposition will be summarized using all subjects.

In general, summary tables will be presented by CSL312 200 mg AI, CSL312 200 mg NSD (if applicable), and overall:

- The number and percentage of subjects who provided informed consent.
- The number and percentage of subjects who entered the Run-in Period.
- The number and percentage of subjects who discontinued from the study during the Run-in Period with reason for discontinuation (percentages based on the number who discontinued).
- The number and percentage of subjects who were not assigned to study treatment.
- The number and percentages of subjects who received 200 mg CSL312 once monthly, and who used CSL312 200 mg AI or CSL312 200 mg NSD.
- The number and percentage of subjects who completed the treatment (ie, received the last dose according to the Schedule of Assessments).
- The number and percentage of subjects who discontinued the treatment with reason for discontinuation (percentages based on the number who discontinued under the current device).
- The number and percentage of subjects who completed the study (ie, completed the Follow-up Visit as detailed in the Schedule of Assessments).
- The number and percentage of subjects who discontinued the study during the Treatment Period with reason for discontinuation (percentages based on the number who discontinued under the current device).

Cases of study discontinuation due to COVID-19 will be included in the summary of subject disposition.

Reasons for discontinuing the investigational product and withdrawing a subject from the study will be listed by subject.

10.3.1.2 Subject Characteristics

Demographic and subject characteristics will be summarized using the ATS and PP sets.

At minimum, subject characteristics will be presented in summary tables. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject.

The following summaries will be provided for all subjects in the ATS and PP sets:

- Demographic characteristics: sex, race, ethnicity, age, height, and body weight at Screening, and body mass index.
- HAE history: HAE type (C1-INH type 1, C1-INH type 2, nC1-INH), number of HAE attacks before Screening for subjects with / without prophylactic HAE therapy, number and percentage of subjects who took prophylactic HAE therapy, number of HAE attacks before the start of prophylactic therapy, number of HAE attacks before Screening for subjects without prophylactic HAE therapy or before start of prophylactic therapy.
- Medical history by system organ class (SOC) and preferred term (PT).
- Concomitant diseases by SOC and PT.
- Demographic and subject characteristics will also be summarized for subjects who used CSL312 200 mg AI.

10.3.2 Analyses of the Primary Endpoint

The TEAEs for all C1-INH HAE subjects receiving CSL312 once monthly, independent of the use of CSL312 200 mg AI or CSL312 200 mg NSD, will be summarized using the Safety Analysis Set. TEAEs are AEs that start on or after the date and time of the first administration of study treatment. TEAEs occurring until the Follow-up Visit will be summarized. TEAEs 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.

TEAEs will be summarized by the number of subjects and percentage of subjects experiencing at least 1 TEAE, the number of events, as well as the event rates per injection and per subject year. TEAEs will be presented for the following:

- All subjects in the Safety Analysis Set (ie, subjects on 200 mg CSL312 once monthly)
- Subjects on 200 mg CSL312 monthly and using CSL312 200 mg AI
- Subjects on 200 mg CSL312 monthly and using CSL312 200 mg NSD

TEAE rates per injection will be calculated as follows:

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

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

TEAE rates per subject years will be calculated as follows:

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

where subject years will be the sum of the time in years that subjects were exposed to study treatment during the respective safety evaluation period.

An overview summary of TEAEs will be provided including:

- TEAE
- SAEs
- Deaths
- TEAEs occurring within 24 hours of investigational product administration
- Related TEAEs
- TEAEs leading to study discontinuation
- TEAEs in each severity category
- TEAEs in each outcome category
- AESIs

A summary table by SOC and PT and an overview summary table of COVID-19 associated TEAEs and a listing showing all COVID-19 associated AEs will be provided.

TEAEs which can be clearly identified to be related to an HAE therapy medication other than CSL312 during the Follow-up Period will be flagged in listings and will be summarized separately.

The overview summary and the summary table by SOC and PT will also be provided for TEAEs occurring while using CSL312 200 mg AI and occurring while using CSL312 200 mg NSD.

10.3.2.1 Analyses of the Secondary Endpoints

10.3.2.1.1 Safety Secondary Endpoints

Safety data for C1-INH HAE subjects and nC1-INH subjects will be summarized using the Safety Analysis Set.

TEAEs are AEs that start on or after the date and time of the first administration of study treatment.

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 nontreatment-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 nontreatment-emergent.

AEs will be coded using the 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.

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

TEAEs which can be clearly identified to be related to an HAE therapy medication other than CSL312 during the Follow-up Period will be included in TEAE tables. They will be flagged in listings.

The following summary tables will be provided for all subjects in the Safety Analysis Set:

- Overview table of TEAEs
- Overview table of SAEs (same as above, restricted to SAEs)
- SAE by SOC and PT
- TEAEs by severity, SOC, and PT
- Related TEAEs by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- AESIs by SOC and PT
- Nonserious TEAEs by SOC and PT
- Laboratory Findings reported as TEAEs by PT
- Anti-CSL312 antibodies
- TEAEs occurring within 7 days of COVID-19 vaccine administration by PT
- TEAEs excluding those occurring within 7 days of COVID-19 vaccine administration by PT

The number of subjects and percentage of subjects experiencing at least 1 TEAE, the number of events, as well as the event rates per injection and per subject year will be displayed.

For nC1-INH subjects only, an overview table for TEAEs and a summary table for TEAEs by SOC and PT will be generated.

Subjects with multiple occurrences of the same TEAE will be counted once in the total of those experiencing this PT. Similarly, a subject with 1 or more PT in a SOC will be counted

once in the total of those experiencing PTs in that SOC. Percentages for subject incidence rates will be based on the Safety Analysis Set.

Tables will be presented for the following:

- All subjects in the Safety Analysis Set (ie, subject on 200 mg CSL312 once monthly)
- Subjects on 200 mg CSL312 once monthly and using CSL312 200 mg AI
- Subjects on 200 mg CSL312 once monthly and using CSL312 200 mg NSD

Non-TEAEs, TEAEs, SAEs, AESIs, TEAEs leading to study discontinuation, COVID-19 associated AEs, and deaths will be listed.

10.3.2.1.2 Efficacy Secondary Endpoints

The secondary efficacy endpoints will be analyzed using the ATS Analysis Set. The endpoint **"**Time-normalized number of HAE attacks" will also be analyzed using the PP Analysis Set.

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

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

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

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

where the length of subject treatment is calculated as:

[the date of End of Treatment Visit – the date of Study Visit Day 1 + 1]

The time-normalized number of HAE attacks per month will be summarized descriptively by 200 mg CSL312 once monthly overall, including median (primary) and mean (secondary)

with corresponding 95% CIs. The time-normalized number of HAE attacks will also be calculated for the Run-in Period. For non-naïve subjects, the Run-in Period of their previous CSL312 study will be used.

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

> 100 * [1 – (time-normalized number of HAE attacks per month during treatment / time-normalized number of HAE attacks per month during Run-in)]

and will be summarized descriptively by 200 mg CSL312 once monthly overall. For non-naïve subjects, the Run-in Period of their previous CSL312 study will be used.

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

Furthermore, the number and percentage of attack-free subject will be presented and summarized with corresponding 95% CI.

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

> [number of HAE attacks requiring on-demand treatment during treatment / length of subject treatment in days] * 30.4375

and will be summarized descriptively by 200 mg CSL312 once monthly overall.

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

For the analysis of the time-normalized number of moderate and / or severe HAE attacks, an analogue calculation will be done using all HAE attacks classified as moderate or severe.

To transform the time-normalized numbers described above to years, the length of subject treatment in days is divided by 365.25.

In addition, all above described secondary efficacy endpoints will also be assessed over time for 3-month (ie, 91 days) time windows starting on Visit Day 1.

As supportive analyses, the number of HAE attacks experienced by each subject as well as the timing of (recurrent) HAE attacks will be assessed. Different time-to-event analyses will be performed (eg, time to second HAE attack and maximum attack-free time).

For the SGART, the number and percentage of subjects in CSL312_3002 with a good or excellent response to therapy will be presented.

Further details and description to the analyses will be provided in the SAP.

10.3.3 Pharmacokinetics Analyses

The PK analysis will be performed using the PK population.

Plasma concentrations of CSL312 will be listed by individual subjects and will be summarized by nominal time points. Plasma CSL312 concentrations will be summarized with descriptive statistics: mean, SD, percent coefficient of variation (CV%), median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean and its respective 90% CI.

From the PK subgroup analysis in CSL312-naïve adult subjects, PK parameters will be derived using non-compartmental PK analyses and will be summarized descriptively. PK parameters will include C_{max}, T_{max}, and $AUC_{0\text{-}30days}$. The following descriptive statistics will be presented for all PK parameters, except for T_{max}: n, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum, and maximum. For T_{max}, n, median, minimum, and maximum will be summarized.

Additional information on PK analyses will be provided in the SAP.

10.3.4 Pharmacodynamic Analyses

PD data will be summarized using the PD population.

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

FXIIa-mediated kallikrein activity will be listed by individual subjects and will be summarized by nominal time points. The PD data will be summarized with descriptive statistics: mean, SD, %CV, median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean, and its respective 90% CI.

Additional information for PD analyses will be provided in the SAP.

10.3.5 Interim Analysis

Interim analyses will be conducted in order to support regulatory activities. The results of the interim analyses are not intended to be used to stop or adapt the study. No sample size adjustment is planned. Details of the analyses for the first and the second interim analyses will be described in the SAP.

11 Quality Assurance

The study may be subject to an audit by the Sponsor, an authorized representative(s) of the Sponsor and / or inspections by an authorized health authority (eg, US Food and Drug Administration [FDA]). Health authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. The Sponsor will notify the investigator of any upcoming audit / inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

The Sponsor or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under an FDA Biological License Application and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board / Independent Ethics Committee

The investigator must submit the clinical study protocol and ICFs for review by an authorized and properly constituted (according to local guidelines) IRB / IEC. Written approval must be received from the IRB / IEC before commencement of the study.

For Japan sites only, the head of the study site should submit a written report to the IRB providing the details of all safety-related information reported by the Sponsor. In addition, the clinical study protocol is to be reapproved by the IRB annually.

12.3 Subject Information and Informed Consent

Informed consent of study subjects according to the standards of GCP and the principles in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form and should be deemed appropriate by the IRB / IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

The subject (or if necessary, legally acceptable representatives) must be provided with a copy of the signed ICF.

Should there be any amendments to the clinical study protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF indicating that they reconsent to participate in the study.

12.4 Subject Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, telephone number, and identity in the study) so that regulatory agencies or the Sponsor may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected / audited at any time by the Sponsor employees or their duly authorized representatives, a health authority or the IRB / IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections / audits.

12.5 Indemnity and Compensation

The Sponsor has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator / the Sponsor are provided in the Clinical Trial Research Agreement for the study (see Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Research Agreement between the Sponsor (“Sponsor”) and the institution(s) representing the investigational study site(s) (“Authority”). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Research Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and the Sponsor, and will form the contractual basis under which the clinical study will be conducted. Clinical Trial Agreements may be executed by electronic signature (current provider DocuSign) in compliance with 21 CFR Part 11 and simple or advanced electronic signature according to EU Regulation No 910/2014 – eIDAS.

13.2 Clinical Study Registration and Results Disclosure

The Sponsor will provide the relevant clinical study protocol information in public database(s) before or at commencement of the study. The Sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original clinical study protocol registration record.

13.3 Implementation of the Clinical Study Protocol and Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed clinical study protocol will be permitted without documented approval of the Sponsor Medical Monitor or designee and the IRB / IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor Medical Monitor and the IRB / IEC.

Modifications to the clinical study protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB / IEC.

Administrative changes to the clinical study protocol, defined as minor corrections and / or clarifications that have no effect on the way the study is to be conducted, will not require IRB / IEC approval, but will be submitted to the IRB / IEC for their information.

In the event of a state of emergency or public health threat resulting in travel restrictions that prevent a subject from returning to the study site for required study assessments or procedures, or if the subject is unable to attend site visits due to extenuating circumstances, these assessments / procedures may be conducted remotely with the Sponsor approval.

However, all such assessments / procedures must be promptly reported to the Sponsor and the IRB / IEC. The following options may be implemented “on-demand” in the event of local restrictions or extenuating circumstances and at the discretion of the Sponsor:

- Direct-to-subject shipment of IP for subject self-administration.
- Assessments and / or collection of blood (eg, safety, PK / PD) may be performed remotely from the site via home health visits or via local lab.
- Remote study visits via telephone or video to:
    - assess subject health status (AEs, side effects).
    - confirm supply of on-demand medication.

- check on concomitant medications.
- review eDiary entries to assess HAE attacks.
- remote completion of questionnaires.
- supervise investigational product administration if needed.

13.4 Protocol Deviations

All instances where the requirements of the clinical study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and / or the Sponsor. Clinical study protocol deviations arise when either subjects who have been entered in the study and / or the study sites deviate from the IEC / IRB-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data) occurs, the investigator must notify the Sponsor and the appropriate IRB / IEC as soon as possible or as per local requirements.

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of investigational product or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the CRF is the site of the original recordings (ie, there is no other written or electronic record of the data).

An CRF will be provided by the Sponsor (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the CRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the CRF must be backed up by source data unless the CRF is considered source data. All source data will be kept according to all applicable regulatory

requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

An eCOA solution will be used by the subjects for entry and / or sites for review.

The eCOA solution is provided as a means to capture electronic source data in a controlled and consistent way, and to provide access for investigators to these source data. The system also allows the subject's health status to be remotely monitored during the study. The data residing in the eCOA system provider's database are considered the source, and are under the control of the investigator at all times.

The investigator (or delegate) will have access to all eCOA data entered at site and / or all data reported within the subject eDiary via a secure, role-based web portal provided by an external eCOA system provider. The eCOA system provider will transfer a copy of the source data across to the Sponsor's clinical data warehouse at a predefined frequency via a secure data channel for systematic review by the Sponsor clinical team.

The eCOA vendor engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is not in any way intended as a substitute for normal medical care of the subject. The vendor provides the service of hosting of the eCOA data on behalf of the study investigators, until such a time as the investigator is in receipt of a certified archive copy of all eDiary data relating to subjects at that site and has confirmed it is readable.

13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the CRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. The Sponsor's study monitor will perform this function.

Following completion of CRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

13.5.3 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. An investigator study file prepared by the Sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by the Sponsor's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from the Sponsor or a competent health authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

13.6 Study and Site Closure

The Sponsor reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the Sponsor Study Monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators (for Japan sites only: the heads of the medical institutes) in writing. If the study is suspended or terminated for safety reasons, all investigators (for Japan sites only: the heads of the medical institutes) and the relevant regulatory agencies will be immediately notified of the action as well as the reason for the suspension / termination. The investigator (for Japan sites only: the heads of the medical institutes) at each study site will advise their IRB / IEC overseeing the study of the suspension / termination.

13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. The Sponsor or its agent will write the report in consultation with the investigator or, if applicable, a nominated

coordinating investigator (or delegate). The Sponsor requires that the coordinating investigator sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

13.8 Use of Data and Publications

The rights and obligations of investigators and the Sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

14 References

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15 Appendices

Signature of Principal Investigator

Protocol Number: CSL312_3002 Site Number:

I have read the Clinical Study Protocol CSL312_3002 Amendment 1 titled "An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema."

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

Appendix 2 Hereditary Angioedema Attack Assessment and Reporting Instructions for Study CSL312-3002

Version: Version 3.0

Version Date: 28 Jul 2020

1 Purpose

The purpose of this document is to provide instructions on the reporting of HAE symptoms by the subject and the assessment of HAE attacks and subsequent follow up by the investigator. This document will also present a definition of an HAE attack and a set of standardized requirements to aid the investigator in determining and recording an HAE attack based on the subject's reported symptoms.

2 Hereditary Angioedema Symptom Reporting and HAE Attack Assessment

All symptoms potentially related to an HAE attack and information on the use of on-demand medication to treat those symptoms during the Run-in, Treatment and Follow-Up periods, will be entered by the subject in an eDiary. The investigator or delegate will review the data in the eDiary and collect additional information that may be missing from the eDiary and other relevant information needed for the assessment of the subject reported symptoms.

2.1 Subject Training

During screening, eligible CSL312-naïve subjects entering the run-in period will be trained by the site's personnel on identifying symptoms of a potential HAE attack, the use of the eDiary to report a symptom(s) and the information they will need to report about their symptoms. The subject (with parent/legal guardian if applicable for minors) will confirm his / her understanding of what is required to report symptoms potentially related to an attack. Sites will assess the subject's compliance with the reporting requirements during the study and may retrain the subject if necessary.

This training will occur on Day 1 for subjects rolling over from Studies CSL312_2001 and CSL312_3001.

2.2 Subject-reported symptoms

At the onset of a symptom(s) of a potential HAE attack, subjects will be instructed to enter information about the symptom(s) in the eDiary. Subjects (with parent / or legal guardian if applicable for minors) will also be encouraged to notify and report details to the study site within 72 hours of the start of the first symptom(s) of a potential HAE attack. When a subject initiates the reporting of symptoms of a potential HAE attack in the eDiary, he / she will be

reminded to contact the site within 72 hours of the onset of symptoms. In tandem, the site will receive an email alert from the eDiary portal indicating that a subject is experiencing symptoms of a potential HAE attack.

If on-demand medication is needed, subjects do not have to hold off / delay the start of the medication to treat the symptoms of the potential HAE attack till after contacting the site. Note: if additional symptoms are experienced within 24hrs, the symptoms should be entered in the eDiary as "updates." In order to report onset (start) of a new symptom(s), the new symptom(s) must occur at least 24 hours after resolution of the previously reported symptom(s). Hereditary angioedema symptom resolution is defined as the subject no longer having symptoms of the potential attack.

The following information needs to be reported in the eDiary:

- Date and time of onset of first symptom of potential HAE attack
- Date and time of HAE symptom(s) resolution (defined as the subject no longer having symptoms of an attack)
- Location (s) of HAE symptom(s)
- Confirmation of degree of interference of HAE symptom(s) with the subject's daily activities
- If on-demand HAE medication (s) was used to treat HAE symptoms:
    - Name of medication
    - Date and time of administration

The investigator will confirm additional details with the subject related to the HAE symptoms:

- Location of HAE symptom(s).
- Start / End date / time of symptom(s).
- Dose(s) of on-demand medication(s) used.
- Route(s) of Administration of on-demand medication(s) used.
- Self-administered on-demand medication(s)? (yes / no).

- Administration of on-demand medication(s) at a study site, home or emergency room.
- Type of medical assistance or intervention provided by a healthcare professional during HAE symptoms, including hospitalization or emergency department visits.
- Severity of the attack (based on degree of interference in daily activities, and whether or not the use of on-demand medication and / or medical assistance was needed)

Note: All on-demand medications used between the onset and resolution of HAE symptoms need to be recorded.

2.3 Hereditary Angioedema Symptoms Indicative of an HAE Attack

An HAE attack must be associated with at least 1 symptom/location or any of combined multiple symptoms / locations, as listed on Table 1 below. These symptoms may develop concurrently or consecutively, typically within 24 hours. The list of symptoms below is not exhaustive and it is meant to assist the investigator / delegate in identifying HAE attack-related symptoms and their indicative locations.

Table 1. HAE Symptom / Location Associated with an HAE attack

	Peripheral Attack Symptoms (cutaneous)	**Abdominal Attack Symptoms**	**Laryngeal Attack Symptoms**
Locations	• head • face (external): lips, nose, cheeks or eyes • neck • arms/hands • chest, shoulder or back • external abdominal area • external genitourinary areas (buttocks) • legs/Feet • Others	• internal abdomen (including, but not limited to, the intestine, the bladder, and / or testicles or uterus) • internal genitourinary (including, but not limited to, the penis and / or scrotum, or the labia and / or vulva)	• face internal or upper airway / throat • tongue / palate/inside mouth • nasal cavity • throat / voice box • uvula • larynx
Symptoms	• pain / discomfort • skin swelling • itching / irritation • tight skin • burning • redness / rash	• pain / cramping / discomfort • vomiting/nausea • abdominal swelling / bloating / tightness / hard stomach • diarrhea • gassy • low blood pressure • pass out / feel dizzy	• difficult breathing (dyspnea), speaking, or swallowing • voice change • stridor / wheezing • throat tightening • turning blue

HAE = hereditary angioedema.

2.4 Attack Assessment / Confirmation by the Investigator

The Investigator or delegate at each site will review the HAE symptoms reported by the subject in the eDiary, and confirm an HAE attack(s) if applicable. It is recommended that the sites limit the number of experienced individuals responsible for assessing subject reported symptoms to 1 or 2 individuals, where one of them should be the investigator. The assessors must be experienced with HAE and familiar with the study subject's disease history.

Each time the investigator / delegate contacts the subject or at a site visit, he/she will review the subject's eDiary entries. Additionally, the subject will be reminded to have his / her eDiary entries up-to-date and to check that symptoms indicative of an HAE attack are documented as instructed. The investigator / delegate may ask additional probing questions about the HAE symptoms experienced by the subject to assist his / her assessment of the symptoms and rule out if there are any possible alternative etiologies of the symptoms. For example, whether only prodromal symptoms were experienced and / or if anything is different from previous experiences.

Each individual HAE attack must be associated with at least 1 symptom or location, but may be associated with multiple symptoms. These symptoms may develop concurrently or consecutively within 24 hours. If the investigator confirms an HAE attack, this should be reported in the CRF as a single HAE attack including the symptom(s) associated with the attack. If there has been a completely symptom-free 24-hour minimum separation between the resolution of the prior attack and the onset of next attack, this new set of symptoms would constitute a new event and should be reported as a separate single attack if the investigator confirms the HAE attack.

The investigator will determine if the symptoms reported by the subject did not represent an HAE attack. For example, if the symptoms are not typical of an attack or if there is a more likely alternative cause for the symptoms, or if the symptoms did not resolve following the administration of the on-demand medication. Examples are throat irritation due to an upper respiratory illness or abdominal discomfort due to gastrointestinal upset.

In an effort to maintain consistency across data collection and analysis within this HAE prophylaxis development program, the following recommendations should be followed:

- The presence of prodromal symptoms by themselves are not considered as HAE attacks.

- Subject reported use of on-demand medication to treat the prodromal symptoms by itself will not be confirmation that an HAE attack occurred.
- Any use of on-demand medication associated with prodromal symptoms only, will be reported as concomitant medication in the CRF and not as an HAE on-demand medication.

HAE symptoms that are confirmed as HAE attacks by the Investigator or delegate will be recorded in the CRF (See Section 2.4.1) as such and will be used for the primary efficacy analysis. All HAE symptoms reported by the subject will be displayed in a by-subject listing. Note: that the assessment and outcome need to also be recorded in the subject's medical records.

Symptoms reported as AEs

The investigator or designee will evaluate the symptom data entered in the eDiary by the subject using the standardized set of requirements to determine if the symptoms reported constitute an HAE attack or not. If the investigator confirms the symptoms as an HAE attack, then the HAE attack will be reported in the CRF. If the assessment of the symptoms are not confirmed as an HAE attack, then the etiology of the symptoms must be reported and recorded as an AE.

2.4.1 Documenting Investigator-Confirmed Attacks

Accurate and complete documenting Investigator-confirmed HAE attacks is important for the study, as it will be used for the study primary endpoint analysis. All HAE attack information should be substantiated by supporting documentation and medical records.

The site should record the following information on each attack in the CRF:

- Start date and time of an attack.
- End date and time of an attack.
- Location(s) of HAE symptoms.
- HAE symptom description.
- HAE attack severity evaluation (refer to Section 2.4.1.3).

- Use of on-demand treatment (If yes, enter the following information in HAE treatment form):
  - Name of on-demand medication.
  - Dose(s) of on-demand medication(s) used.
  - Route(s) of administration of on-demand medication(s) used.
  - Start date and time of administration(s) of on-demand medication(s) used.
  - Select the identification number of the HAE attack the on-demand treatment was given for (to be selected from a list) in the CRF.
  - Administration of on-demand medication(s) at a study site, home, emergency room.

2.4.1.1 Attack Duration

The duration of an HAE attack will be reported by the investigator / delegate considering all available medical information including the onset of first symptom and resolution of last of symptom of each attack entered in the eDiary. Unless there has been a completely symptom-free 24-hour minimum separation between the onset and resolution of all symptoms, a single HAE attack will be documented on the basis of the earliest start and the latest end date of symptoms in the anatomic locations listed.

2.4.1.2 Attack Location

Hereditary angioedema attacks can occur in any anatomical location or multiple locations of the body and these locations are highly variable. An HAE attack may manifest itself in multiple anatomic locations. For example, swelling of the hand and abdomen may occur as symptoms of a single attack if they are temporally associated (ie, occurring at the same time or occurring within overlapping periods within 24 hours). Unless there has been a completely symptom-free 24-hour minimum separation between the onset of new symptom and resolution of prior symptoms in any / all location(s), a single HAE attack will be documented with all relevant locations listed in the CRF.

2.4.1.3 Attack Severity

The severity of each HAE attack (ie, mild, moderate, or severe) will be assessed by the investigator or designee based on the subject's description of the attack. The severity over the

time that the attack develops, progresses, and resolves can range from mild to severe. The overall attack severity will reflect the maximum intensity of the attack, as assessed by the investigator.

All attacks regardless of the severity should be associated with perceivable swelling and / or discomfort. Further qualifiers for attack severity are described below. Note that these may vary between subjects and attacks.

- **Mild**
  - The HAE attack has little to no effect on daily activities.
  - The use of HAE on-demand medication to treat the attack may not be necessary.
  - Other concomitant medication (eg, analgesics) may be used to treat attack symptoms.
- **Moderate**
  - The HAE attack causes daily activities to be difficult.
  - Some assistance may be needed to complete daily activities.
  - The use of HAE on-demand medication to treat the attack is probable.
- **Severe**
  - The HAE attack causes marked limitation of daily activities.
  - Medical assistance and intervention may be required, including at clinic emergency room visit or hospitalization.
  - HAE on-demand medication is used to treat the attack.