Clinical Study Protocol

And

Clinical Study Protocol Administrative Amendment #1

Study Number:	CSL312_3001
Study Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema
Version and Date of Protocol:	FINAL (Original), 04 August 2020 Administrative Amendment #1, 08 December 2020
NCT Number:	NCT04656418
EudraCT Number:	2020-000570-25

Clinical Study Protocol
Administrative Amendment

ADMINISTRATIVE AMENDMENT #1

Study Number:	CSL312_3001
Study Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema
Version and Date of Protocol:	FINAL (Original), 04 August 2020
EudraCT Number:	2020-000570-25
IND Number:	[redacted]
Administrative Amendment Date:	08 December 2020

This amendment is applicable for all study sites. All changes are described herein.

PURPOSE OF AMENDMENT

The purpose of this administrative protocol amendment is to make the following revisions to the CSL312_3001 clinical protocol (Original), dated 04 August 2020:

1. Clarification of the contraception requirement: alignment of the time period with Section 9.6.6 (for 3 months after last dose of investigational product).
   Reason: Subjects should not become pregnant (nor should the partner of a subject become pregnant) for at least 3 months after the last dose of investigational product (Section 9.6.6). It was noted that Section 4.1.2 and Section 7.4 inadvertently state that the contraception requirement is 30 days, which is inconsistent with the half-life of the investigational product and the information provided in Section 9.6.6.
   Applicable sections: Section 4.1.2 (exclusion criterion 12) and Section 7.4.

Appendix 1: Signature of Principal Investigator

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

Protocol Number: CSL312_3001

Version and Date of the Protocol: FINAL (Original), 04 August 2020

Administrative Amendment Number: 1

Administrative Amendment Date: 08 December 2020

Site Number:

To be completed by the study site:

I acknowledge receipt of this administrative amendment. I have read and understood its contents.

_____ _____
(Signature) Date (DD MMM YYYY)

_____
(Printed name)

_____
(Title)

Signature Page

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Signed By	Date (GMT)
PPD	08-Dec-2020 22:27:23
Approved-PPD Approval	
PPD	09-Dec-2020 13:44:15
Approved-PPD Approval	

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CLINICAL STUDY PROTOCOL

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

Study Number:	CSL312_3001
Study Product:	CSL312 (Factor XIIa Inhibitor Monoclonal Antibody)
Development Phase:	Phase 3
Short Title:	Study of the efficacy and safety of CSL312 (garadacimab) in the prevention of hereditary angioedema attacks
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Original
EudraCT Number:	2020-000570-25
IND Number:	139936
Protocol Date:	04 August 2020
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

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, LLC (or delegate) and provided to the study sites as needed.

REVISION HISTORY

Date	Version	Summary of Changes
04 August 2020	Original	Not applicable

Clinical Study Protocol Synopsis

Title	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema
Study Number	CSL312_3001
Sponsor	CSL Behring, LLC
Development Phase	3
Study Product	CSL312 (Factor XIIa Inhibitor Monoclonal Antibody)
Indication	Prophylaxis to prevent hereditary angioedema (HAE) attacks
Study Summary and Overview	This is a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of 200 mg CSL312 (also known as garadacimab) administered subcutaneously (SC) once a month for the prophylaxis to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with C1-esterase inhibitor (C1-INH) HAE. This study will be conducted globally. 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 and none of the exclusion criteria will enter a Run-in Period to confirm the required baseline HAE attack rate of $\geq$ 1 attack per month. 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 if they also meet all other criteria as stated in Section 4.1.3.

	Subjects who do not meet the screening criteria for entering the Run-in Period within 30 days may be able to rescreen with confirmation from the sponsor. Subjects who do not meet the minimum HAE attack rate during the Run-in Period and / or all other criteria for entering the Treatment Period will be considered Run-in failures and will not be allowed to rescreen. Eligible subjects will be randomized 3:2 to either the CSL312 Active Arm (CSL312 SC once a month) or the Placebo Arm. The duration of treatment is 6 months. Randomization will take age ($\leq$ 17 years, > 17 years) and, for adults, baseline attack rate observed during the Run-in Period (1 to < 3 attacks / month, and $\geq$ 3 attacks / month) into account. Following the Treatment Period, subjects will either enter a 2-month Follow-up Period (ie, 3 months after last investigational product administration) or may roll-over into an open-label phase 3b study (CSL312_3002).
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of SC administration of CSL312 as prophylaxis to prevent HAE attacks in subjects with HAE.
Primary Endpoint(s)	The primary endpoint is the time-normalized number of HAE attacks during treatment from Day 1 through Day 182.
Secondary Objective(s)	The secondary objectives of the study are: 1. To characterize the clinical efficacy of SC CSL312 in the prophylactic treatment of HAE. 2. To evaluate the safety of SC CSL312 in the prophylactic treatment of HAE.

Secondary Endpoint(s)	The secondary endpoints of the study are: • The reduction in the attack rate during the Treatment Period compared to the Run-in Period. • The time-normalized number of HAE attacks requiring on-demand treatment. • The time-normalized number of moderate and / or severe HAE attacks. • The time-normalized number of HAE attacks at various time points during the treatment period. • Subject Global Assessment of Response to Treatment (SGART). • Adverse events (AEs). • Adverse events of special interest (AESIs). • Serious adverse events (SAEs). • CSL312 induced anti-CSL312 antibodies. • Clinically significant abnormalities in laboratory assessments (ie, laboratory abnormalities reported as AEs).
Study Duration	The duration of the study for an individual subject is expected to be approximately 7 to 11 months. This estimation is based on: • A Screening Period of up to 1 month. • A Run-in Period of 1 to 2 months (Run-in can occur on the same day as Screening). • A 6-month Treatment Period. • A Follow-up Period of 2 months (ie, 3 months after last investigational product administration). The overall study duration (ie, first subject's Screening Visit to last subject's End of Study Visit) will be approximately 19 months.
Number of Subjects	This study will target to randomize 60 subjects with C1-INH HAE type 1 or type 2 to be included into the Treatment Period. The approximate sample size includes a targeted number of 5 adolescent subjects 12 to 17 (inclusive) years of age.

Study Population and Main Criteria for Eligibility	The main eligibility criteria to enter the study 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 (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria), and b. C1-INH antigen 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.
Study Product Dose, Dosing Regimen and Administration	Subjects randomized to the Active Arm will receive CSL312 SC once monthly for 6 months. The first dose of CSL312 will be a 400 mg loading dose administered SC as 2 separate injections on the same day at the study site (ie, Month 1). Subsequent doses of CSL312 will be 200 mg administered SC once monthly for 5 consecutive months (ie, Months 2 through 6).
Comparator Product, Dose, Dosing Regimen and Administration	Subjects randomized to the Placebo Arm will receive volume-matched placebo. The first dose of placebo in the Placebo Arm will be volume-matched placebo administered SC as 2 separate injections (ie, Month 1). Subjects will then receive volume-matched placebo SC once a month for 5 consecutive months (ie, Months 2 through 6).

Efficacy Assessments	Efficacy will be assessed by the number of HAE attacks (per month and annualized) in subjects treated once monthly with either CSL312 (Active Arm) or placebo (Placebo Arm) during the efficacy evaluation period from Day 1 through Day 182 (6 months). Subjects will record relevant information in an electronic diary (eDiary).
Safety Assessments	Safety will be assessed by treatment-emergent adverse events (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.
Pharmacodynamics	Plasma samples will be collected for assessment of Factor XII (FXII) concentration and activated FXII (FXIIa)-mediated kallikrein activity.
Other Assessments	Quality of life data will be obtained using the Angioedema Quality of Life (AE-QoL) questionnaire, EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire, the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire, the Investigator Global Assessment of Response to Treatment (IGART), and the Subject Global Assessment of Response to Treatment (SGART).

Statistical Analyses

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

It is targeted to randomize approximately 5 adolescents into the treatment period with a randomization ratio of 3:2 (active:placebo). To allow for sufficient safety data, increase the likelihood of adolescents entering the study, and to have at least 40 subjects reaching the end of the study, an additional 20 subjects are planned for randomization.

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

- Population: the target patient population defined by eligibility criteria and who were randomized (intent-to-treat [ITT]).
- Variable: time-normalized number of HAE attacks during treatment from Day 1 through Day 182.
- Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of any of the following intercurrent events:
  - administration of on-demand medication in addition to prophylactic treatment with CSL312
  - non-compliance to treatment
  - early termination
- Population-level summary: median time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182 by treatment.

The primary endpoint will be analyzed using the ITT and Per Protocol (PP) Populations. The ITT population will be used as the primary analysis and the PP will be used as the secondary analysis.

The primary endpoint "time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182" is calculated per subject as:

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

where the length of subject treatment is calculated as:

[the date of Study Visit Day 182 or the date of study discontinuation [whatever is first]– the date of Study Visits Day 1 +1].

To test for a difference in the primary efficacy endpoint between CSL312 and placebo, a comparison of the time-normalized numbers of HAE attacks in the 6 months of the Active Arm and in the 6-month Placebo Arm period will be performed by using a two-sided Wilcoxon Test (alpha = 5%).

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

Schedule of Assessments: Screening and Run-in Period (All Subjects)

Study Period		**Screening**	**Run-in Period** [B]				
Visit Day		**-30 to -1** [A]	**1**	**15**	**30**	**45**	**60** [C]
Visit Window (Days)				**± 4**	**± 4**	**± 4**	**± 4**
Informed consent / IRT registration [D]		X					
Eligibility criteria [E]		X	X				
Study center visit		X					
Telephone contact			X [F]	X	X	X	X
Relevant medical history [G]		X					
Demographics		X					
Pregnancy test (at study site) [H]		X					
Physical examination [I]		X					
Vital signs including height and body weight		X					
Urine collection for urinalysis (central lab)		X					
Blood Draws (central lab)	Hematology / Biochemistry / Coagulation	X					
	C1-INH and C4 [J]	X					
Individual acute action plan [K]		X					
eDiary training		X	X [L]				
Open eDiary access			X				
eDiary completion by subject			←	→	→	→	→
Review eDiary data and assess / document HAE attacks [M]				X	X	X	X
Close eDiary access and collect device [N]							X
Confirm access to on-demand HAE medication [O]			X	X	X	X	X
Prior / concomitant medications and therapies		←	→	→	→	→	→
Adverse events		←	→	→	→	→	→

Abbreviations: C1-INH = C1-esterase inhibitor; C4 = complement C4; CSL = CSL Behring; eDiary = electronic diary; HAE = hereditary angioedema; IRT = interactive response technology

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

A: The first day of the Run-in Period may occur on the same day as the Screening Visit for subjects meeting the eligibility criteria for the Run-in Period.

B: 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.

C: If a subject is unable to enter the Treatment Period after Day 60, then CSL approval is required for the subject to enter the Treatment Period. Day 60 will conclude the study for a subject who has entered the Run-in Period and is subsequently not eligible to be randomized. Eligible subjects will proceed to the Day 1 visit of the Treatment Period.

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

E: Eligibility to be confirmed before any study assessments are performed. The start of the Run-in Period should be recorded in the IRT after reconfirming eligibility.

F: Telephone contact is not applicable when the first day of the Run-in Period occurs on same day as the Screening Visit.

G: Include C1-INH functional activity and antigen, and C4 antigen concentration history, recording of overall health within the 6 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 6 months before Screening, and contraception method (for female subjects of childbearing potential only).

H: A urine test for beta-human chorionic gonadotropin will be performed for sexually active women of childbearing potential (only). A serum pregnancy test will be performed by the site if the urine result is inconclusive.

I: 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.

J: Blood sample for C1-INH functional activity and antigen, 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.

K: 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 and confirmation of subject's access to on-demand HAE medication to treat HAE attacks. The action plan will be reviewed with subjects.

L: Repeat remote training is required if 30 days have elapsed between training at the Screening Visit

M: Refer to Appendix 2 for instructions on HAE attack documentation and assessment.

N: 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.

O: Berinert is the suggested on-demand medication for use during this study. However, 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

Study Period		Treatment Period [A]						End of Treatment Period [B,C]	Follow-up [D] /Final Visit
Month		1	2	3	4	5	6	7	9
Visit Day / Dose Number		1/1	31/2	61/3	91/4	121/5	151/6	182	242
Visit Window (Days)		NA	±4d	±4d	±4d	±4d	±4d	±4d	-14d
Study center visit		X	X	X	X	X	X	X	
Confirm eligibility for Treatment Period [E]		X							
IRT treatment arm assignment		X							
Pregnancy test (at study site) [F,H]		X	X	X	X	X	X	X	
Physical examination [G,H], vital signs, and body weight [H]		X	X	X	X	X	X	X	
12-lead ECG [I]		X						X	
Urine collection for urinalysis (central lab)		X [J]			X			X	
Blood Draws (central lab) [H,P]	Hematology/Biochemistry / Coagulation	X [J]			X			X	
	Retention sample for HAE biomarkers (adults only) [K]	X	X	X	X	X	X	X	X
	PK / PD [L]	X	X	X	X	X	X	X	X
	Immunogenicity [M]	X			X			X	
Concomitant medications and therapies		←	—	—	—	—	—	—	→
Adverse events		←	—	—	—	—	—	—	→
PRO / eCOA tablet training [N]		X							
AE-QoL (subjects ≥ 18 years) and WPAI-GH (subjects ≥ 16 yrs)		X	X	X	X	X	X	X	
EQ-5D-5L		X			X			X	
SGART and IGART [O]					X			X	
Review eDiary data (entered by subject) and assess / document HAE attacks		X	X	X	X	X	X	X	X [P]
eDiary deactivation								X [Q]	X [P]
Confirm access to on-demand HAE medication [R]		X	X	X	X	X	X	X	
IRT investigational product kit assignment		X	X	X	X	X	X		

SC administration of investigational product	X[S]	X[T]	X[T]	X[T]	X[T]	X[T]		
Investigational product accountability	X	X	X	X	X	X		
Offer subject option to enroll in Study CSL312_3002						X[B]		

Abbreviations: AE-QoL = Angioedema Quality of Life; C1-INH = C1-esterase inhibitor; C4 = complement C4; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; EQ-5D-5L = EuroQoL Group 5-Dimension 5-Level; FXII = Factor XII; FXIIa = activated Factor XII; HAE = hereditary angioedema; ICF = informed consent form; IGART = Investigator's Global Assessment of Response to Therapy; IRT = interactive response technology; PK / PD = pharmacokinetic / pharmacodynamics; PRO = patient reported outcomes; SC = subcutaneous; SGART = Subject's Global Assessment of Response to Therapy; WPAI:GH = Work Productivity and Activity Impairment: General Health; yrs = years.

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

A: Treatment Period Visits have ± 4 day window, with a maximum of 33 days between any 2 consecutive doses.

B: The Day 182 End of Treatment Period Visit corresponds to the first day of the open-label phase 3b study for subjects rolling-over into Study CSL312_3002. Subjects will enter Study CSL312_3002 after completing the Day 182 assessments and signing the ICF for Study CSL312_3002. Subjects not entering Study CSL312_3002 will be required to complete the Day 242 study visits after completing the Day 182 assessments.

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

D: Subjects who do not enter Study CSL312_3002 are required to complete the Follow-up Visit. The in-person Follow-up Visit may be waived in place of a telephone contact during which information about adverse events and concomitant therapies / medications will be collected. If the Follow-up Visit is conducted as an in-person visit, then a blood draw for assessment of PK / PD and immunogenicity should occur, as well as collection of information about adverse events, concomitant therapies / medications.

E: Subjects are eligible to exit in the Run-in Period and enter the Treatment Period after completing at least 1 month of the Run-in Period and experiencing at least 2 HAE attacks. C1-INH functional activity and antigen, and C4 antigen concentration levels should be confirmed before randomization into the Treatment Period. Eligibility to be confirmed before randomization and any study assessments are performed.

F: The urine test for beta-human chorionic gonadotropin will be performed for sexually active women of childbearing potential (only). A serum pregnancy test will be performed by the site if urine result is inconclusive.

G: 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.

H: At visits, administration of investigational product will occur after physical examinations, vital signs, body weight, and pregnancy tests have been completed.

I: Standard 12-lead ECGs will be performed.

J: Assessments may be omitted if Screening / Run-in Period assessments occurred within the previous 3 months

K: 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.

L: Blood sample for PK includes CSL312 concentration and blood sample for PD includes FXII concentration and FXIIa-mediated kallikrein activity.

M: Blood sample for binding antibodies (inhibitory and non-inhibitory) specific to FXIIa inhibitor monoclonal antibody (anti-CSL312).

N: The following patient related outcomes will be entered at specified study site visits before any other interaction with the subject about their health status and before review of the electronic diary: AE-QoL, EQ-5D-5L, WPAI:GH, and SGART.

O: Investigator completes IGART in RAVE. Subjects complete SGART.

P: Only applicable for subjects not rolling over to Study CSL312_3002.

Q: The eDiary will be collected and deactivated on Day 182 for subjects rolling over to Study CSL312_3002 and on Day 242 for all other 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.

R: Berinert is the suggested on-demand medication for use during this study. 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.

S: The first dose of investigational product will be a loading dose consisting of either 2 SC injections of 200 mg CSL312 each for a total of 400 mg CSL312 (Active Arm) or 2 SC injections of volume-matched placebo (Placebo Arm) administered by the investigator or delegate at the study site.

T: Investigational product administration consisting of either one 200 mg CSL312 SC injection (Active Arm) or one SC injection of volume-matched placebo (Placebo Arm) may be self-administered by the subject under the supervision of the investigator or delegate at the study site.

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List of Abbreviations

Abbreviation	Term
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
AE-QoL	Angioedema Quality of Life
aPTT	Activated partial thromboplastin time
BK	Bradykinin
CI	Confidence interval
C1-INH	C1-esterase inhibitor
CSL	CSL Behring
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
eDiary	Electronic diary
EQ-5D-5L	EuroQoL-Group 5-Dimension 5-Level
E-R	Exposure-response
FDA	Food and Drug Administration
FXI	Factor XI
FXII	Factor XII
FXIIa	Activated Factor XII
GCP	Good Clinical Practice
GMP	Good Manufacturing 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
IgG4	Human immunoglobulin G subclass 4
IRB	Institutional Review Board
IRT	Interactive response technology

Abbreviation	Term
ISR	Injection site reaction
ITT	Intention-to-Treat
IV	Intravenous
mAb	Monoclonal antibody
nC1-INH	Normal C1-esterase inhibitor
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
SGART	Subject's Global Assessment of Response to Therapy
SOC	System organ class
TEAE	Treatment-emergent adverse events
TEE	Thromboembolic event
TP1	Treatment period 1
TP2	Treatment period 2
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.
- The study arms and periods are defined as follows:
    - **Active Arm**: administration of CSL312 for 6 months.
    - **Placebo Arm**: administration of volume-matched placebo for 6 months.

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 FXII (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]. Bradykinin 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

Hereditary angioedema is a rare genetic disorder classified into 3 disease types [Rosen et al, 1965; Bork et al, 2000], including HAE type 1, HAE type 2, and HAE with normal C1-esterase inhibitor (nC1-INH).

Hereditary angioedema type 1 and type 2 are caused by mutations of the SERPING1 gene, and are characterized by a quantitative decrease in C1-esterase inhibitor (C1-INH) plasma concentrations (type 1) and dysfunctional C1-INH present in normal plasma concentrations (type 2) [Zuraw et al, 2010; Cicardi et al, 2014]. Together, HAE type 1 and type 2 are grouped as HAE with C1-INH deficiency (C1-INH HAE).

A large number of different SERPING1 mutations have been associated with HAE type 1, including missense, nonsense, frameshift, deletion, and insertion mutations [Kalmar et al, 2005]. In general, HAE type 1 is caused by mutations in the C1-INH gene that results in either truncated or misfolded proteins that cannot be secreted [Verpy et al, 1995]. In HAE type 1, an impaired synthesis of normal and functionally active C1-INH occurs, causing a reduction in the availability of functionally active C1-INH levels to between 5% and 30% of normal [Rosen et al, 1965]. Approximately 85% of subjects with C1-INH HAE have HAE type 1 [Longhurst and Bork, 2006].

Most SERPING1 mutations associated with HAE type 2 involve residues at or near the active site on the reactive mobile loop of the C1-INH protein that result in a protein that is secreted but is dysfunctional [Wagenaar-Bos and Hack, 2006]. In HAE type 2, normal levels of a functionally impaired C1-INH molecule are synthesized, but the normal form of C1-INH is considerably reduced in the circulation [Rosen et al, 1965]. Approximately 15% of subjects with C1-INH HAE have HAE type 2 [Longhurst and Bork, 2006].

C1-esterase inhibitor is a serine protease inhibitor that regulates the generation of BK by the plasma contact system, and is the major inhibitor of a number of plasma contact system proteases including FXII and kallikrein [Davis et al, 2010]. Excessive BK formation due to pathological activation of the FXII-driven plasma contact system is a consistent finding in acute episodes of HAE [Björkqvist et al, 2013].

Hereditary angioedema with normal C1-INH is an inherited disorder not associated with C1-INH deficiency, but missense mutations, deletions or insertions of base pairs of the FXII gene [Cicardi et al, 2014], a missense mutation of the plasminogen gene [Bork et al, 2018; Dewald, 2018], or caused by an unknown genetic defect [Cicardi et al, 2014]. A defective mucin-type Thr309-linked glycosylation may lead to increased contact-mediated autoactivation of zymogen FXII, resulting in excessive activation of the BK-forming kallikrein-kinin pathway [Björkqvist et al, 2015]. A Lys311Glu substitution is a disease-causing plasminogen mutation which may cause an irregular cleavage by FXIIa and kallikrein, the serine proteases of the kinin-forming cascade [Dewald, 2018]. For other forms

of HAE with C1-INH, the underlying pathophysiology is poorly understood [Bork et al, 2000].

Clinically, HAE attacks occurring in patients with C1-INH HAE and HAE with nC1-INH are characterized by local swelling of the skin (ie, edema of the extremities, facial edema, and edema of the genitals), abdominal pain, and, occasionally, life-threatening attacks of laryngeal edema [Bork, 2008]. The estimated prevalence of C1-INH HAE is commonly reported as 1:50,000, while the prevalence of nC1-INH HAE is unknown [Cicardi et al, 2010; Nasr et al, 2016].

1.1.4 Background on CSL312 and Rationale for Treatment of Hereditary Angioedema

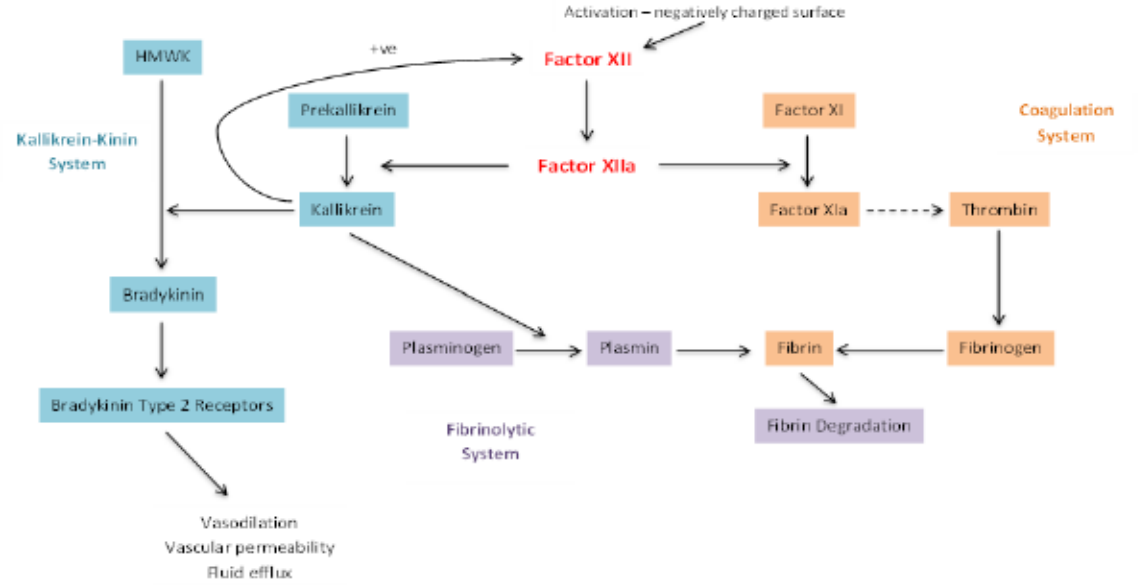
CSL312 (FXIIa inhibitor monoclonal antibody) is a fully human immunoglobulin G subclass 4 (IgG4) / lambda recombinant monoclonal antibody (mAb) which specifically binds to the catalytic domain of FXIIa and potently inhibits its catalytic activity. CSL312 is an affinity-matured variant of the parental antibody 3F7, which was isolated following screening against the 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], a protease cascade involving the proteins FXII, FXI, plasma prekallikrein, and the non-enzymatic cofactor HMWK. As shown in Figure 1, FXII is converted to FXIIa upon contact with a negatively charged surface cleaving both FXI and plasma prekallikrein leading 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; Nussberger et al, 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 bradykinin detected during HAE attacks.

The rationale for evaluating CSL312 for prophylaxis to prevent HAE attacks 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.

Figure 1 **Factor XII and its Role in the Coagulation, Fibrinolytic, and Kallikrein-Kinin Systems**



HMWK = high molecular weight kininogen

1.1.5 Unmet Medical Need

In spite of the growing attention to HAE patients by the medical community and stakeholders, the burden of this disease is very high and quality of life is still negatively impacted. Hereditary angioedema negatively impacts a patient's daily-life, psycho-social health, and productivity both during times of attack and during times of remission [Aygoren-Pursun et al. 2014].

The availability of prophylactic therapies that reduce the frequency and / or severity of attacks has improved, however there are limitations to the treatment armament such as an unfavorable side effect profile (ie, attenuated androgens), a lack of effect (ie, anti-fibrinolytics), or the frequency of administration (intravenous [IV] or subcutaneous [SC] C1-INH). Furthermore, there are currently no therapies specifically developed for treatment or prevention of HAE attacks due to nC1-INH HAE. There remains a medical need for effective and safe therapies that prevent and reduce the disease burden, improve the

quality of life, and offer a convenient dosing regimen for patients with HAE [Valerieva 2018].

CSL312 may have the potential to address current unmet needs as a mAb with a novel mechanism of action targeting FXIIa, which is elevated in the serum during acute HAE attacks compared to normal levels observed during times of remission [Cugno et al. 1996]. CSL312 targets FXIIa to inhibit the kallikrein-kinin pathway, thereby inhibiting excessive production of BK, the mediator of swelling in HAE attacks. In addition, the SC route of administration and once monthly dosing of CSL312 may offer improved patient convenience compared to other products registered for prevention of HAE attacks.

1.2 Information on CSL312

1.2.1 Overview

CSL312 (factor XIIa inhibitor monoclonal antibody) is a fully human IgG4 / lambda recombinant monoclonal antibody which specifically binds to the catalytic domain of FXIIa and potently inhibits its catalytic activity. CSL312 is an affinity-matured variant of the parental antibody 3F7, which was isolated following Screening against the βFXIIa. CSL312 is produced in Chinese hamster ovary cells that have been characterized according to applicable international guidelines.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL312 is provided in the Investigator's Brochure.

CSL312 is not yet approved for any indication in any country.

1.2.2 Nonclinical Evaluation

The non-clinical program conducted to support development of CSL312 included pharmacological, pharmacokinetic (PK), and toxicological studies performed in pharmacologically relevant species that are described in the CSL312investigator's brochure.

1.2.3 Clinical Experience

1.2.3.1 Healthy Subjects

One randomized, double-blind, placebo-controlled, single ascending dose, phase 1 study was conducted in healthy volunteers. During this study (CSL312_1001), the safety and tolerability, and PK of escalating doses of CSL312 were assessed after single IV or 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 all AEs were of mild intensity. Injection site reactions (ISRs) 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 ~19 days. The study results are described in greater detail in the CSL312 investigator's brochure.

1.2.3.2 Subjects with Hereditary Angioedema

One clinical study with CSL312 is ongoing in subjects with HAE.

CSL312_2001 is an ongoing 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 consists 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). In open-label TP2, subjects receive a single SC injection of either 200 mg or 600 mg CSL312 every 4 weeks (for a total of 44 weeks). Currently the study is ongoing and the randomized, double-blinded part of TP1 has been completed.

A total of 32 patients with C1-INH HAE type 1 or type 2 were enrolled in the randomized double-blind treatment arms of TP1 at 20 study sites across 5 countries. Interim results from TP1 demonstrate that CSL312 is safe and well tolerated at all 3 doses and has an overall favorable safety profile. All 3 dose levels of CSL312 SC every 4 weeks achieved clinically meaningful reduction in the HAE attack rate compared to placebo. The most frequent AEs were non-serious ISRs (ie, injection site erythema, pruritus, swelling, and discomfort) that were mild or moderate in severity. No SAEs or AEs of special interest (AESIs, severe hypersensitivity and anaphylaxis, TEEs, bleeding events) were reported.

No difference in the PK of CSL312 was noted between healthy subjects in Study CSL312_1001 and subjects with HAE in Study CSL312_2001.

All eligible subjects who successfully complete Study CSL312_2001 may have the opportunity to enroll in an open-label phase 3b study of CSL312 in subjects with HAE (CSL312_3002).

1.3 Study Overview

CSL312_3001 is a multicenter, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the clinical efficacy and safety of subcutaneously administered CSL312 as prophylaxis to prevent HAE attacks in subjects with C1-INH HAE type 1 or type 2. Section 3.1 presents a detailed overview of the study.

1.4 Potential Risks and Benefits

CSL312 is a fully human mAb that inhibits FXIIa activity. CSL312 is being developed for routine prophylaxis to prevent HAE attacks in subjects with C1-INH HAE type 1 or type 2, as well as to assess the benefit of IV infusion of CSL312 in patients with COVID19. In the current study, CSL312 will be subcutaneously administered once monthly to subjects experiencing recurrent HAE attacks.

Benefits

A potential benefit of this study is the reduction in frequency of attacks and prevention of attacks in subjects with HAE by inhibiting the attack-causing defective pathways. CSL312 targets the initiation of the kallikrein-kinin pathway by acting as an inhibitor to FXIIa, affecting the regulation of BK formation and thus inhibiting excessive BK generation resulting in the prevention of HAE attacks.

Risks

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:

Thromboembolic Events and Bleeding: By blocking FXIIa with CSL312, there may be a potential risk of bleeding or TEEs due to altered hemostasis, unstable clot formation, or impaired clot breakdown. In addition, because of the pharmacological action of CSL312, a prolongation of activated partial thromboplastin time (aPTT) is expected to be observed in a

dose-dependent manner. Clinical experience with CSL312 with healthy volunteers in the phase 1 study CSL312_1001 and subjects with HAE in the on-going phase 2 study CSL312_2001 did not show an effect on either prothrombin time or abnormal bleeding. This is consistent with the observation that patients who have congenital deficiency of FXII do not exhibit a bleeding phenotype, despite having a prolonged aPTT [Lammle et al, 1991; Ratnoff and Colopy, 1955]. In addition, nonclinical studies in mice and rabbits showed no impairment in hemostasis following inhibition of FXIIa [Larsson et al, 2014]. Nevertheless, subjects will be monitored carefully for signs of thrombosis or bleeding during the study.

Severe Hypersensitivity / Anaphylactic-type Reactions: Administration of therapeutic proteins including mAbs such as CSL312 is potentially associated with the risk of severe hypersensitivity and anaphylactic reactions, some of which can be serious and life threatening. Appropriate precautions will be taken when CSL312 is administered at the study site, with vigilant monitoring for potential severe hypersensitivity and anaphylactic reactions. Administration of CSL312, at least the first 2 to 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 anti-drug antibodies. The development of anti-drug antibodies throughout the study will be monitored.

In both the phase 1 study CSL312_1001 and TP1 of the phase 2 study CSL312_2001, no SAEs were reported. Additionally, no AESIs were reported the phase 2 study CSL312_2001. There were no dose dependent safety concerns in either study.

Given the potential benefit of CSL312 for subjects with HAE, as well as the favorable safety data of CSL312 from the phase 1 study (CSL312_1001) and the ongoing phase 2 study (CSL312_2001), the associated benefit-risk assessment is considered acceptable for subjects who participate in study CSL312_3001.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Efficacy Objective

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

2.1.2 Primary Efficacy Endpoint

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

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

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are:

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

2.2.2 Secondary Endpoints

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

Secondary Objective	Endpoint	Summary Measure(s)
1	The time-normalized number of moderate and / or severe HAE attacks	The time-normalized number (per month and annualized) of moderate and / or severe HAE attacks in subjects treated once a month with either CSL312 (Active Arm) or placebo (Placebo Arm) during the period from Day 1 through Day 182 (6 months), as well as for the first 3-month time period and for the second 3-month time period of the Active and Placebo Arms.
1	Time-normalized number of HAE attacks at various time points during the treatment period	The time-normalized number of HAE attacks (per month and annualized) in subjects treated once monthly with either CSL312 (Active Arm) or placebo (Placebo Arm) during the first 3-month time period and the second 3-month time period of CSL312 (Active Arm) and placebo (Placebo Arm). The percentage reduction will be calculated for the time-normalized number of HAE attacks between the Active Arm and the Placebo Arm for the 6-month treatment period, as well as for the first 3 months and the second 3 months of the treatment period.
1	Subject's Global Assessment of Response to Therapy (SGART)	Comparison of the distribution of responses to therapy between CSL312 and placebo at the end of the Treatment Period (Day 182 or Day 91 if discontinuation occurs before Day 182) based on the proportions of subjects with a "excellent, good, fair, poor or none" response to therapy.
Safety Endpoints		
2	• AEs • AESIs • SAEs • CSL312 induced anti-CSL312 antibodies • Clinically significant abnormalities in laboratory assessments (ie, laboratory abnormalities reported as AEs).	The number and percentage of subjects experiencing the specified safety events on treatment with CSL312 or placebo during the entire Treatment Period until Follow-up or Final Visit.

2.3 Exploratory Objective and Endpoints

2.3.1 Exploratory Objective

The exploratory objective of this study is to further evaluate the efficacy, PK / pharmacodynamics (PD), and quality of life (QoL) associated with the use of CSL312 in subjects with HAE.

2.3.2 Exploratory Endpoints

Exploratory endpoints include the following:

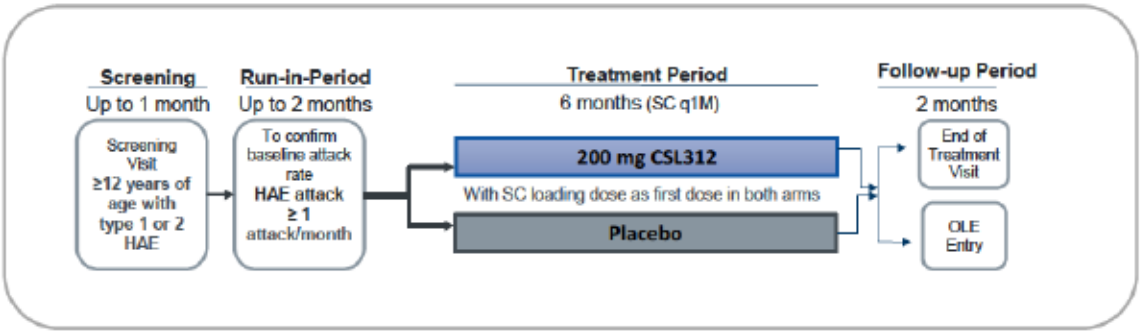
1. The time to first attack after Day 1 and after Day 15.
2. CSL312 concentrations at scheduled time points.
3. FXII concentration and FXIIa-mediated kallikrein activity at scheduled time points.
4. Subject reported outcome measures:
   - Angioedema Quality of Life (AE-QoL)
   - EuroQoL-Group 5-Dimension 5-Level (EQ-5D-5L)
   - Work Productivity and Activity Impairment: General Health (WPAI:GH).
5. Investigator's Global Assessment of Response to Therapy (IGART).

3 Study Design and Oversight

3.1 Overall Design

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

Figure 2 **Study Overview**



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

3.1.1 Screening

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.

3.1.2 Run-In Period

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 for up to an additional month during which time they would be required to experience at least 2 attacks to be eligible to enter the Treatment Period and randomization (Section 4.1.3).

Subjects are not permitted to use 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.

3.1.3 Treatment Period

Subjects meeting the eligibility criteria (Section 4.1.3) will enter the Treatment Period after the Run-in Period. If a subject is unable to enter the Treatment Period by Day 60, then CSL Behring (CSL) approval is required for the subject to enter the Treatment Period.

Eligible subjects will be randomized 3:2 to either the CSL312 Active Arm or the Placebo Arm. The duration of the Treatment Period is 6 months. Randomization will take age ($\leq$ 17 years, > 17 years) and, for adults, baseline attack rate observed during the Run-in Period (1 to < 3 attacks / month, and $\geq$ 3 attacks / month) into account.

3.1.4 Follow-Up Period / Open-label Phase 3b Study Entry

Subjects who successfully complete the current study (CSL312_3001) may have the option to roll over into an open-label phase 3b Study CSL312_3002. Subjects who choose not to participate in Study CSL312_3002 are required to complete the Follow-up Visit (Day 242, which is approximately 3 months after the last dose of investigational product). For subjects who choose to participate in Study CSL312_3002, assessments collected on Day 182 will be used to fulfill applicable assessments for Day 1 of Study CSL312_3002.

Details of open-label phase 3b Study CSL312_3002 are described in a separate protocol.

3.2 Dose and Dosing Regimen

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

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

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

3.3 Scientific Rationale

3.3.1 Study Design Rationale

This phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-arm study will investigate the efficacy and safety of once monthly SC dosing regimen of CSL312 for the prevention of HAE attacks in adolescent (ie, 12 to 17 years of age inclusive) and adult subjects with C1-INH HAE type 1 and type 2.

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, 1 Treatment Period (6 months) for confirmation of the safety and efficacy of the 200 mg CSL312 dose, and a 2-month Follow-up Period (3 months after the last administration of investigational product).

3.3.2 Dose Rationale

The proposed 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 administered once every 28 days (± 3 days) 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 attack 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 at steady-state following 200 mg SC once a month regimen corresponds to the 90% relative attack 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 a month 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 aPTT 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 CLS312 clinical program, the 200 mg of CSL312 SC administered once monthly is expected to achieve clinically meaningful treatment effect and optimal benefit/risk ratio in subjects with C1-INH HAE type 1 and type 2.

3.4 Planned Study Duration

The duration of the study for an individual subject is expected to be approximately 7 to 11 months. This estimation is based on:

- A Screening Period of up to 1 month.
- A Run-in Period of 1 to 2 months (Run-in can occur on the same day as Screening).
- A Treatment Period of 6 months.
- A Follow-up Period of 2 months (ie, 3 months after the last administration of investigational product).

The overall study duration (ie, first subject's Screening Visit to last subject's End of Study Visit) will be approximately 19 months.

3.5 Planned Number of Subjects

This study will randomize approximately 60 subjects with C1-INH HAE type 1 or type 2.

3.6 Definition of Start of the Clinical Study

The start of the clinical study is defined as the date of the first act of recruitment of a 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 either the date of the last visit of the last subject at their Follow-up Visit (ie, Day 242) or the date of the last subject's enrollment into the open-label phase 3b Study CSL312_3002.

3.8 Study Oversight

3.8.1 Independent Data Monitoring Committee

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

3.9 Halting Criteria

3.9.1 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 (i.e., temporarily paused) until an assessment of that subject's safety is completed: Prolonged symptoms of severe hypersensitivity considered by the investigator and/or CSL to be related with CSL312 administration; a confirmed diagnosis of TEE or a clinically significant abnormal bleeding event, irrespective of CSL312 causality; or any event or laboratory abnormality that is considered by the investigator and/or CSL 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 CSL 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 CSL 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 CSL'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. Ad-hoc unblinding procedures may be initiated as per CSL standard operating procedures for further safety assessment, if needed. If the risk assessment concluded that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the CSL 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

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study.

4.1.1 Inclusion Criteria for Entry into the Run-in Period

To be enrolled into the Run-in Period of this study, subjects must meet all of 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 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 (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
    b. C1-INH antigen 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.

4.1.2 Exclusion Criteria for Entry into the Run-in and Treatment Periods

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

1. Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticarial or HAE type 3.
2. Any preplanned major surgeries or procedures during the clinical study.

3. For adult subjects: Use of C1-INH products, androgens, antifibrinolytics or other small molecule medications for routine prophylaxis against HAE attacks within 2 weeks prior to the Run-in Period.
4. For adolescent subjects 12 to 17 years of age, inclusive: Use of long-term prophylactic therapy for HAE before Screening.
5. Use of monoclonal antibodies such as lanadelumab (Takhzyro®) within 3 months prior to the Run-in Period.
6. Use of estrogen-containing medications with systemic absorption (eg, oral contraceptive or hormonal replacement therapy), angiotensin-converting enzyme (ACE) inhibitor within 4 weeks prior to the Run-in Period, or currently receiving a therapy not permitted during the study as defined in Section 7.3.
7. Participation in another interventional clinical study during the 30 days before Screening or within 5 half-lives of the final dose of the investigational product administered during the previous interventional study, whichever is longer.
8. Known or suspected hypersensitivity to monoclonal antibody therapy or hypersensitivity to the investigational product or to any excipients of the investigational product.
9. Subject has any condition that in the judgement of the investigator or CSL, 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.
10. Previously administered CSL312 in another interventional clinical study.
11. Intention to become pregnant or to father a child at any time during the study.
12. Female of childbearing potential or male subjects who are fertile and sexually active either not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 30 days after receipt of the last dose of investigational product. Acceptable methods of contraception are defined in Section 7.4.

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

- Subjects aged > 60 years.

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

13. Pregnant, breastfeeding, or not willing to cease breastfeeding.
14. Involved in the planning and / or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).

4.1.3 Criteria for Entry into the Treatment Period

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 (eg, experienced a total of at least 2 HAE attacks).
3. Does not have laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments.
4. C1-INH functional activity and antigen, and C4 antigen concentration levels have been verified prior to randomization.

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

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 CSL. 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 Failures

Run-in period failures are defined as 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 cannot be rescreened. The primary reason for Run-in failure must be documented for subjects not eligible to enter the Treatment Period.

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 CSL for safety, behavioral, or administrative reasons.

Subjects who discontinue treatment with CSL312 will be encouraged to remain in the study until Day 182 in order to collect study assessments. Refer to Section 4.3.2 for details on handling subject withdrawals.

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 CSL for safety, behavioral, or administrative reasons (eg, because of an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination). If discontinuation occurs before Day 182, subjects who discontinue investigational product will be encouraged to remain in the study until Day 182 in order to collect study assessments and complete the End of Treatment Period Visit. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data and samples collected before withdrawal of consent.

The investigator should record in the electronic case report form (eCRF) 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 Period Visit (Day 182) 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, CSL 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 Products

5.1.1 Description of CSL312

CSL312 will be supplied (1.2 mL per prefilled syringe) as a sterile, preservative-free solution for injection, at pH 6.1. CSL312 is formulated in buffer containing 20 mM L-histidine, 150 mM arginine monohydrochloride, 140 mM L-proline, 0.02% w / v polysorbate 80, and hydrochloric acid. Each vial contains CSL312 at a concentration of 170 mg per 1 mL.

Table 1 Description of CSL312

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 prefilled syringe 200 mg CSL312 at a concentration of 170 mg per 1 mL.

CSL312 will be manufactured by CSL in accordance with ICH Good Manufacturing Practice (GMP) guidelines and local regulatory requirements.

5.1.2 Description of Placebo

Placebo will be supplied (1.2 mL per prefilled syringe) as a sterile, preservative-free solution for injection. Placebo contains the same formulation buffer as CSL312, but does not contain the active substance (ie, Factor XIIa inhibitor mAb).

Table 2 Description of Placebo

Substance number	Not applicable
Substance	Placebo
Trade name	Not applicable
Dosage form	Solution for injection
Mode of administration	Subcutaneous injection

5.1.3 Dosing and Administration

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 3.

Table 3 Investigational Product Dosing Characteristics

	Investigational Product	
Administration parameter	**CSL312**	**Placebo**
Dose	200 mg	Not applicable
Route	Subcutaneous	Subcutaneous
Anatomical Location	Abdomen	Abdomen
Total infusion volume	1.2 mL	1.2 mL

The first dose of CSL312 or placebo will be a SC loading dose consisting of 2 separate injections of 200 mg CSL312 for a total of 400 mg CSL312 or volume-matched placebo. After obtaining the administration training, the first 3 SC administrations will be self-administrated by the subjects or caregivers under the supervision of the investigator or delegate during the study site visits (ie. Day 1, 31, and 61). Subsequent doses can be self-administrated with (if deemed necessary by the investigator) or without supervision of the investigator or delegate.

Detailed information on the preparation and administration of CSL312 or placebo is provided in the Site Investigational Product Manual.

5.1.3.1 Dosing Modification

Dose modifications will not be permitted during this study.

5.1.3.2 Treatment Compliance

The first dose of investigational product and all subsequent injections will be administered by SC injection by the subject at the study site under supervision by the investigator or delegate. The investigator will record the dose and date of investigational product administration in the eCRF. Compliance will be assessed using the administration details entered into the eCRF.

5.1.4 Packaging, Labeling, Supply and Storage

5.1.4.1 Packaging and Labeling

Investigational product will be packaged and labeled according to current ICH GMP and GCP guidelines and national legal requirements. Specific details regarding packaging of CSL312 are provided in the Site Investigational Product Manual.

5.1.4.2 Supply and Storage

Investigational product will be supplied to the study sites by CSL or delegate.

The 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 Investigational Product Manual.

5.2 Accountability and Destruction

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

The investigator or delegate will confirm receipt of all shipments of investigational product in the interactive response technology (IRT) system.

All supplies of investigational product 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 investigational product to CSL / 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 investigational product are provided in the Site Investigational Product 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.

Hereditary angioedema attacks occurring prior to randomization (ie, 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. However, subjects may use other effective on-demand medication of their choice 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.

5.3 Access to Investigational Product After the End of Study

Subjects will not be provided with investigational product by CSL after completion or discontinuation from the study. Eligible subjects will have the option to roll over into the open-label phase 3b Study CSL312_3002 sponsored by CSL.

6 Allocation to Treatment

6.1 Subject Assignment

After providing written informed consent, the subject will be issued a study-level unique subject identification number via an IRT system. The subject identification number will be

used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.2 Randomization Procedures

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

The randomization list will be generated according to the approved randomization specifications, which includes further randomization details. The IRT service provider will keep the randomization code on file.

6.3 Blinding Procedures

Investigational site staff, including the investigators, will be blinded to treatment allocation. Subjects and CSL staff / designates participating in the conduct of the study will also be blinded to treatment allocation (double-blind).

6.3.1 Blinding Method

The investigational product will be packaged and labelled to ensure blinding is maintained and CLS312 PFS is not distinguishable from the placebo. Study unblinding will take place following locking of the study database except in the situations as outlined in Sections 6.3.2, 6.3.3, and 6.3.4.

Adequate procedures are in place to ensure the integrity of the blinded data within CSL. Study data will be provided to the IDMC as blinded data. The IDMC may request the unblinding of an individual's treatment assignment for reasons of safety. These procedures will be outlined in the IDMC Charter.

The investigational product will be packaged and labelled to ensure blinding is maintained.

All blood samples collected for PK / PD analyzed by the central laboratory will remain blinded until database lock. In addition, results from assessment of aPTT will not be available to subjects, study site personnel, or CSL and their delegates who are blinded to treatment assignment

Study unblinding will take place following locking of the study database except in the situations as outlined in Sections 6.3.2, 6.3.3, and 6.3.4.

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

6.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the investigator should use the IRT to identify the treatment allocation for a subject. Whenever possible, the investigator should consult with CSL before unblinding the randomization code. The reason for unblinding the randomization code must be fully recorded in the subject's source documents, and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

6.3.3 Planned Unblinding Procedures

Not applicable.

6.3.4 Ad-hoc Safety Unblinding

CSL Behring's Global Clinical Safety and Pharmacovigilance personnel may, on an ad-hoc basis, unblind the randomization code directly in the IRT at any time during the study, because of a safety concern. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the individual management of a study subject or for the ongoing conduct of the study. The need to unblind a subject or group of subjects may not necessarily arise because of an SAE. The need to unblind on an ad-hoc basis will be determined by CSL's Global Clinical Safety and Phamacovigilance senior leadership.

The IDMC, in consultation with CSL and the Medical Monitor, may request the unblinding of a subject's treatment assignment for reasons of safety.

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).

The following on-demand HAE therapies are PERMITTED at any time during the study for the treatment of HAE attacks if that medication has previously been shown to be effective or if used according to the product label or with deviations from the label as directed by a health care provider:

- Plasma-derived or recombinant C1-INH (eg, Berinert, Cinryze®, Ruconest®).
- Firazyr® (icatibant).
- Kalbitor® (ecallantide).

The use of medications (eg, IV C1-INH) 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, Danazol®, Takhzyro® or future approved medication are PROHIBITED during the entire study.

- ACE inhibitors.
- 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[1] and male subjects[2] must use a highly effective form of contraception during the study duration and for 30 days after the last SC infusion of investigational product. 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 investigational product. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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).
- Bilateral tubal occlusion of female subjects (3 months before providing informed consent).
- Vasectomy of male subjects (3 months before providing informed consent).

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 (All Subjects) and Schedule of Assessments: Treatment Period. 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.

[1] 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 salpingectome, or bilateral tubal ligation.
[2] Male subjects are considered fertile after puberty unless permanently sterile by bilateral orchiectomy, etc.

8.1.1 Demographics and Safety Assessments

Subject demographics and safety assessments to be conducted during this study are provided in Table 4. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments: Screening and Run-in Period (All Subjects) and Schedule of Assessments: Treatment Period. The time windows for each type of assessment are detailed in Section 8.7.1.

Table 4 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
Cardiac function test	12-lead electrocardiogram

Urinalysis [b]	Bilirubin	Occult blood	Erythrocytes
	Glucose	Ketones	Leukocyte esterase
	Nitrite	pH	Protein
	Specific gravity	Urobilinogen	
Hematology [b]	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 [b]	Sodium	Potassium	Chloride
	Bicarbonate	Albumin	ALP
	Direct Bilirubin	Bilirubin, total	AST
	Protein – total	Calcium	ALT
	Creatinine	Phosphate	BUN or urea
	Glucose		
Coagulation [b]	aPTT [d]	D-dimer	
	Prothrombin fragment (pF1+2)	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, and C4 antigen concentration		

Abbreviations: % = percentage; 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 and stored at -70°C 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.

[d] Central laboratory will provide results in a blinded manner until database lock.

Results of safety laboratory tests (hematology, biochemistry, and urinalysis) completed at the central laboratory should be signed and dated 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 at the discretion of the investigator.

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. Body temperature will be measured either sublingually or tympanically, and the method of measurement should be consistent throughout the study for a given subject.

8.1.2 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic and PD assessments to be conducted during the study are provided in Table 5. The time windows for each type of assessment are detailed in Section 8.7.1. Details related to the collection, preparation, and transfer of PK / PD samples will be provided in a Laboratory Manual.

Table 5 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 FXII concentration and FXIIa mediated kallikrein activity.

Abbreviations: FXII = Factor XII; 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 (All Subjects) and Schedule of Assessments: Treatment Period. The time windows for each type of assessment are detailed in Section 8.7.1. Hereditary angioedema attacks that are confirmed by investigator or designee will be used for the efficacy analysis and will be recorded on the eCRF. 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 eCRF. 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 phone contact during the Run-in Period, the investigator or designee will review the subject's electronic diary (eDiary) entries. The investigator will consider all available medical information and may ask clarifying questions to assist in their confirmation of HAE attacks. Subjects will be encouraged to contact the study site within 72 hours of the onset of signs or symptoms of an HAE attack. If the subject is incapacitated and unable to contact the study site, a family member of the individual may contact the study site to provide details of the event. The following information will be documented in the subject 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 additional 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

Quality of life data will be obtained using the SGART, AE-QoL questionnaire, EQ-5D-5L questionnaire, WPAI:GH questionnaire (to be completed by the subject in this order), and IGART. Quality of life data will be captured electronically using a provisioned electronic Clinical Outcome Assessment (eCOA) solution.

The age considerations for these assessments are:

- EQ-5D-5L: all ages
- SGART: all ages
- IGART: all ages
- WPAI: ≥ 16 years
- AE-QoL: ≥ 18 years

8.2.1.1 Angioedema Quality of Life Questionnaire

The AE-QoL questionnaire is an instrument to assess quality of life 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 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The questionnaire, which is designed for self-completion by respondents, is applicable to a wide range of health conditions and treatments [EuroQol Group, 1990].

The EQ-5D-5L consists of 2 parts:

- A descriptive profile, comprising the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Respondents rate each dimension based on 5 levels of severity (ie, no problems, slight problems, moderate problems, severe problems, extreme problems).
- A vertical, visual analog scale, on which the respondent rates their overall health from 'Best imaginable health state' to 'Worst imaginable health state.'

Subjects are to complete the EQ-5D-5L using a provisioned eCOA solution. Additional details will be provided in the SAP.

8.2.1.3 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 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.

8.2.1.4 Subject's Global Assessment of Response to Therapy

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

The SGART will measure the subject's overall treatment response to the investigational product 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.

Further details will be provided in the SAP.

8.2.1.5 Investigator's Global Assessment of Response to Therapy

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

The IGART will measure the subject's overall treatment response to the investigational product 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 eCRF.

Further details will be provided in the SAP.

8.2.2 Electronic Diary and Electronic Clinical Outcome Assessments

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

Patient-reported outcome 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
- AE-QoL
- EQ-5D-5L
- 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 Sample for 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 (Day 182), as well as at the Follow-up Visit. These samples will be stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion 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 eCRF.

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 investigational product during the study, are regarded as concomitant therapies. All concomitant therapies will be recorded in the subject's eCRF.

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 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed (single reading) according to the Schedule of Assessments (Schedule of Assessments: Treatment Period). The date and time of each ECG will be recorded in the source documents and the eCRF. The ECG will be sent to a central vendor for reading and assessment.

8.7 Visit Schedule

8.7.1 Assessment Time Windows

The timing and frequency of the study visits are described in the Schedule of Assessments: Screening and Run-in Period (All Subjects) and Schedule of Assessments: Treatment Period. Time windows for all assessments are detailed in Table 6.

Table 6 Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Screening	Not applicable
Run-in Period: Visit Days 15, 30, 45, and 60	± 4 days
Treatment Period: Visit Days 31, 61, 91, 121, 151, 182	± 4 days
Follow-up: Visit Day 242	- 14 days
Vital signs, physical examination, and pregnancy test	Preinjection on same day

8.7.2 Screening Visit

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. Subjects will be allowed to be rescreened (see Section 4.2).

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 and register the subject via the IRT.
- Review inclusion and exclusion criteria.
- Obtain relevant medical history including overall health for at least the 6 months before the Screening Visit, HAE history before Screening, and contraception method (for females of childbearing potential only).
- Record subject demographics.
- Collect urine for pregnancy test (for sexually active women of childbearing potential).
- Perform physical examination.
- Record vital signs, including height and 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.

- 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 re-consent and may be screened again (for a maximum of 2 Screening Periods per subject) after consultation with CSL. In the event that a potential subject is screened twice, all Screening assessments must be repeated 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 IRT.

8.7.3 Run-in Period

8.7.3.1 Run-in Period: Visit 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 and Screening may occur on the same day. If the Run-in Period begins after Screening, then the first day of the Run-in Period begins with a telephone contact.

The following procedures will be conducted:

- Re-confirm subject eligibility.
- Record start of Run-in Period in IRT.
- Telephone contact for all subjects (not applicable if performed on same day as Screening Visit).

- eDiary training if initial training was conducted 30 days before Run-in Period.
- Open subject access to eDiary and review diary instructions with subject.
- eDiary completion by subject.
- Confirm access to on-demand HAE medication.
- Record prior and concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.

8.7.3.2 Run-in Period: Visit Days 15, 30, and 45 ± 4 days

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

- Telephone contact for all subjects.
- eDiary completion by subject.
- Review of eDiary data.
- Assess / document HAE attacks.
- 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). 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).

8.7.3.3 Run-in Period: Day 60 ± 4 days

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

- Telephone contact for all subjects.
- eDiary completion by subject.

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

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 CSL 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 investigational product 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.

8.7.4 Treatment Period

8.7.4.1 Treatment Period: Visit Day 1

Subjects who complete all screening assessments, fulfill the eligibility criteria (ie, eligible subjects), and meet the Treatment Period entry criteria (Section 4.1.3) will be randomized to investigational product. The following procedures are to be conducted and documented:

- Confirm eligibility for Treatment Period.
- Randomization and assignment of investigational product via IRT.
- Collect urine for pregnancy test (for sexually active women of childbearing potential).
- Perform physical examination.
- Record vital signs and body weight.

- Perform ECG (ECG may be performed during the Run-in Period as an alternative).
- Urine collection for urinalysis*
- Collection of blood to assess:
  - Hematology.*
  - Biochemistry.*
  - Coagulation.*
  - HAE biomarkers (retention sample) (adults only).
  - PK / PD.
  - Immunogenicity.
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.
- PRO / eCOA tablet training.
- Subject to complete:
  - AE-QoL (subjects ≥ 18 years).
  - EQ-5D-5L.
  - WPAI:GH (subjects ≥ 16 years).
- eDiary completion by subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Obtain investigational product kit assignment in IRT.
- Subcutaneous administration of investigational product loading dose by investigator or delegate (after completion of pregnancy test, physical examination, vital signs, and collection of blood samples).
- Accountability of investigational product.

*Assessment may be omitted if Screening / Run-in Period assessments occurred within the previous 3 months.

8.7.4.2 Treatment Period: Visit Days 31, 61, 121, and 151 (± 4 days)

The following procedures will be conducted at the Day 61 and Day 151 (± 4 days) site visits:

- Collect urine for pregnancy test (for women of childbearing potential and sexually active).
- Perform physical examination.
- Record vital signs and body weight.
- Collection of blood to assess:
  - PK / PD.
  - HAE biomarkers (retention sample) (adults only).
- Record concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.
- Subject to complete:
  - AE-QoL (subjects ≥ 18 years).
  - WPAI:GH (subjects ≥ 16 years).
- eDiary completion by subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Obtain investigational product kit assignment in IRT.
- Subcutaneous administration of investigational product by subject under supervision (after completion of pregnancy test, physical examination, vital signs, and blood sample collection).
- Accountability of investigational product.
- Offer subject option to enroll in Study CSL312_3002 (Day 151 only).

8.7.4.3 Treatment Period: Visit Day 91 ± 4 days

The following procedures will be conducted at the Day 91 ± 4 days site visit:

- Collect urine for pregnancy test (for women of childbearing potential and sexually active).
- Perform physical examination.
- Record vital signs and body weight.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / PD.
  - HAE biomarkers (retention sample) (adults).
  - Immunogenicity.
- Document concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.
- Subject to complete:
  - SGART.
  - AE-QoL (subjects ≥ 18 years).
  - EQ-5D-5L.
  - WPAI:GH (subjects ≥ 16 years).
- IGART.
- eDiary completion by subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Obtain investigational product kit assignment in IRT.

- Subcutaneous administration of investigational product by subject under supervision (after completion of pregnancy test, physical examination, vital signs, and blood sample collection).
- Accountability of investigational product.

8.7.4.4 End of Treatment Period: Visit Day 182 ± 4 days

The following procedures will be conducted at the Day 182 ± 4 days site visit:

- Collect urine for pregnancy test (for sexually active women of childbearing potential).
- Perform physical examination.
- Record vital signs and body weight.
- Perform ECG.
- Urine collection for urinalysis.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - HAE biomarkers (retention sample) (adults only).
  - PK / PD.
  - Immunogenicity.
- Document concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.
- Subject to complete:
  - SGART.
  - AE-QoL (subjects ≥ 18 years).
  - EQ-5D-5L.
  - WPAI:GH (subjects ≥ 16 years).
- IGART.
- eDiary completion by subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Device deactivation (eg, eDiary and Tablet) (for subjects entering Study CSL312_3002).

- Confirm access to on-demand HAE medication.

8.7.5 Follow-up Telephone Contact or Final Visit

Follow-up is only applicable to subjects not entering the phase 3b Study CSL312_3002. This visit may be waived in place of a telephone contact. If the visit is to be conducted in person, the following procedures will be performed by the investigator or delegate at Follow-up: Visit Day 242 (- 14) days; 3 months after the last investigational product administration or upon a subject's early termination from the study:

- Collection of blood to assess:
  - HAE biomarkers (retention sample) (adults only).
  - PK / PD.
- Document concomitant medications and therapies (type, dose, route, date, and time).
- Record AEs.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Device deactivation (eg, eDiary and Tablet) (for subjects not entering Study CSL312_3002).

8.7.6 End of Study

The scheduled end of study participation for an individual subject occurs with completion of Day 242 (-14 days) or upon entry into the phase 3b study at Day 182, after which no further study-related procedures will be performed.

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).

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF 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.

Adverse events 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 eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are 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 pre-existing 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

A 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 in-patient hospitalization or prolongation of existing hospitalization** – CSL 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.
  - Any systemic TEE is considered an SAE and should be reported as such. Additionally, any non-systemic TEE (eg, a TEE associated with vascular access) that meets the serious criteria must be reported as an SAE.
  - Any non-serious access-related thrombosis should be entered as an AE on the eCRF and will be part of the regular review of AEs of special interest by the IDMC.
- Bleeding events.
  - All bleeding events that are abnormal and, in the opinion of the investigator, are considered SAEs should be reported as such.
- Severe Hypersensitivity / Anaphylaxis.
  - All events of severe hypersensitivity/anaphylaxis are considered SAEs and should be reported as such.

The reporting requirements for AESIs are detailed in Section 9.6.2.

9.2 Severity of Adverse Events

The severity of each AE (ie, non-serious 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 CSL 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, non-serious AEs that have not resolved or stabilized will be followed until the subject completes the study. Serious adverse events 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 eCRF. 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 pre-existing condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History eCRF.

9.6.2 Adverse Events of Special Interest

Adverse events of special interest should 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 eCRF.

All SAEs that occur during the course of the study, whether or not causally related to investigational product, must be entered into the eCRF 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.

Adverse events 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 eCRF 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 CSL.** Such events are not entered into the eCRF. 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 eCRF 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 eCRF.
- If the subject is no longer participating in the study, report the follow-up information to CSL.

In cases of death, the investigator should supply CSL 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 eCRF 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, injection rate) of overdose of investigational product (defined in Section 9.6.5) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

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.

CSL 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 CSL 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. CSL 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

10.1 Sample Size Estimation

In total, 60 subjects are planned to be randomized.

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

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

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

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

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 and who undergo study screening procedures.

10.2.2 Intent-to-Treat Analysis Set

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

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

10.2.3 Safety Analysis Set

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

10.2.4 Per-protocol Analysis Set

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

10.2.5 Pharmacokinetic Analysis Set

The PK analysis set comprises all subjects in the safety analysis set who receive an injection of investigational product with at least 1 measurable concentration of CSL312.

10.2.6 Pharmacodynamic Analysis Set

The PD analysis set is defined as subjects in the safety analysis set population for whom at least 1 PD measurement was obtained.

10.3 Statistical Analyses and Methods

Continuous variables will be described by using mean values with their respective 95% confidence intervals (CIs); SD; range; 25th, 50th (median), and 75th percentiles; and counts of missing and non-missing values.

The geometric coefficient of variation will be expressed as a percentage for PK and PD data. The geometric mean and its respective 90% CI will be calculated for PK and PD data. The 90% CI for the geometric mean will be calculated by log transforming the data, calculating the lower and upper limits of the 90% CI of the mean of the log-transformed data, and subsequently back transforming the lower and upper limits.

Categorical values will be described using counts and percentages.

All data will be displayed in by-subject listings. The listings will be sorted by treatment arm, study site, subject, time point, and item number (if applicable).

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. Adverse events and early discontinuations caused by COVID-19 will be flagged. Protocol deviations caused by COVID-19 will be documented and listed.

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.

Summary tables by treatment arm and total population will present:

- The number and percentage of subjects who underwent Screening.
- The number and percentage of subjects who entered the Run-in Period.
- The number and percentage of subjects who discontinued from the study during the Run-in Period with reason for discontinuation (percentages based on the number who discontinued).
- The number and percentage of subjects who were not assigned to study treatment.
- The number and percentage of subjects who completed the treatment.
- The number and percentage of subjects who completed the study.
- The number and percentage of subjects who discontinued the study during the Treatment with reason for discontinuation (percentages based on the number who discontinued).
- The number and percentage of subjects who prematurely discontinue treatment.

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 ITT 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:

- 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), number of HAE attacks before Screening for subjects without prophylactic HAE therapy, number and percentage of subjects who took prophylactic HAE therapy, number of HAE attacks before the start of prophylactic therapy.
- Medical history by system organ class (SOC) and preferred term (PT).
- Concomitant diseases by SOC and PT.
- Stratification factors: age (≤17 year, >17), baseline attack rate observed during the Run-in Period (1 to < 3 attacks / month, and ≥ 3 attacks/month).

10.3.2 Efficacy Analyses

10.3.2.1 Primary Estimand

The primary interest is to assess the treatment effect of CSL312 during treatment from Day 1 through Day 182 while subjects are allowed to treat HAE attacks with on-demand medications, administered according to Section 5.2.1.1.

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

- Population: the target patient population defined by eligibility criteria and who were randomized (ITT).
- Variable: time-normalized number of HAE attacks during treatment from Day 1 through Day 182.
- Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of any of the following intercurrent events:
  - administration of on-demand medication in addition to prophylactic treatment with CSL312.

- non-compliance to treatment.
- early discontinuation.

- Population-level summary: median time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182 by treatment.

Subjects will be followed after failure to administer or to continue CSL312 treatment until their completion of the study, ie, Visit Day 182 or Early Termination Visit (whichever occurs first).

10.3.2.2 Supplementary Analysis Primary Estimand

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

Only subjects in the PP analysis set will be included. The interest is to assess the treatment effect of CSL312 during treatment from Day 1 through Day 182 while subjects are allowed to treat HAE attacks with on-demand medications, administered according to Section 5.2.1.1, but excluding subjects who do not comply with the protocol.

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

- Population: the target subject population defined by eligibility criteria, who were randomized, received at least 1 dose of CSL312 and who comply with the protocol (PP).
- Variable: time-normalized number of HAE attacks during treatment from Day 1 through Day 182.
- Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of any of the following intercurrent events:
  - administration of on-demand medication in addition to prophylactic treatment with CSL312.
  - early discontinuation.
- Population-level summary: descriptive statistics of the time-normalized number of HAE attacks during treatment from Day 1 through Day 182 by treatment.

10.3.2.3 Primary Efficacy Analysis

The primary endpoint will be analyzed using the ITT and PP Populations. The ITT population will be used as the primary analysis and the PP will be used as the secondary analysis.

Following the estimand described in Section 10.3.2.1, the primary endpoint "time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182" is calculated per subject as:

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

where the length of subject treatment is calculated as:

> [the date of Study Visit Day 182 or the date of study discontinuation [whatever is first]– the date of Study Visits Day 1 +1].

To test for a difference in the primary efficacy endpoint between CSL312 and placebo, a comparison of the time-normalized numbers of HAE attacks in the 6 months of the Active Arm and in the 6-month Placebo Arm period will be performed by using a two-sided Wilcoxon Test (alpha = 5%).

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

As a sensitivity analysis, the time-normalized number of HAE attacks will be compared for the 6 months of the Active Arm and the 6 months of Placebo Arm using a Poisson Regression model. The time-normalized number of HAE attacks of the Run-in Period and age as covariates and the logarithm of the length of subject treatment as an offset variable will be included. The model will account for overdispersion.

10.3.2.4 Secondary Efficacy Analyses

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)]

for the entire 6-months of the Active Arm and for the 6-month Placebo Arm period and will be tested via a two-sided Wilcoxon Test using the individual percentage reduction between treatment groups.

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

The number and percentage of subjects with a percentage reduction of 100%, ie, who do not experience a HAE attack and so are attack-free, will be presented and summarized with corresponding 95% CI for the 6-month Active Arm period and for the 6-month Placebo Arm period, a Fisher-Test will be performed to asses for differences between treatments.

The percentage reduction in the time-normalized number of HAE attacks for the 6-months of the Active Arm will also be calculated as percentage reduction compared to the 6-month of the Placebo Arm (between subjects) as

> 100 * [1 – (median time-normalized number of HAE attacks per month during 6 months of the Active Arm / median time-normalized number of HAE attacks per month during 6-months Placebo Arm period)]

and will be tested as exploratory via a two-sided Wilcoxon Test using the individual percentage reduction between treatment groups.

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

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

An HAE attack requiring on-demand treatment is defined as an attack for which the date of administration of an on-demand treatment is between the start (including) and end date (including) of a HAE attack. Differences between the 6-months of the Active Arm and the 6-month Placebo Arm period will be tested in an exploratory manner via a two-sided Wilcoxon Test.

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.

The SGART will be presented descriptively. Comparison of the distribution of responses to therapy between CSL312 and placebo at the end of Treatment Period (Day 182) will be done.

To test for a difference in SGART between CSL312 and placebo, a comparison of the distribution of responses at the end of Treatment Period (Day 182) will be performed by using a two-sided Wilcoxon Test (alpha= 5%).

In addition, the secondary endpoints described above (except the SGART) will be summarized for the first 3 months (Day 1 to Day 91), as well as the second 3 months of the Active and Placebo Arms. Further, the following endpoints will be compared between the Active Arm and the Placebo Arm using the first 3 months (Day 1 to Day 91), as well as the second 3 months (Day 92 to Day 182) in an exploratory manner using the same tests as for the respective main analyses:

- Time-normalized number of HAE attacks per month.
- Percentage reduction in the time-normalized number of HAE attacks.
- Percentage of subjects with a percentage reduction of 100%.
- HAE attacks per month requiring on-demand treatment.

10.3.2.5 Multiplicity

Issues related to multiplicity arising from testing the primary endpoint and the secondary endpoints: percentage reduction in the time-normalized number of HAE attacks, percentage of subjects with a percentage reduction of 100%, and the SGART.

The 4 endpoints will be tested in a hierarchical order with an alpha of 5% each.

Four null hypotheses are defined, one for the primary endpoint (H01) and 3 for the 3 secondary endpoints (H02, H03, H04). The null hypothesis associated with each of these endpoints is given below:

- H01: the time-normalized number of HAE attacks in the first 6-month time period of the Active Arm and in the Placebo Arm period are equal.
- H02: the percentage reduction in the time-normalized number of HAE attacks for the 6-months of the Active Arm and the 6-month Placebo Arm period are equal.
- H03: the number of subjects who do not experience a HAE attack in the first 3 months of the Active Arm and the 3-month Placebo Period are equal.

- H04: the SGART at the end of Treatment Period (Day 182) of subjects treated with CSL312 and placebo are equal.

The general process flow of the hypothesis testing is as follows: the null hypothesis associated with the primary endpoint H01 will be tested first. If and only if the resulting 2-sided p-value is < 0.05, testing of H02 will be performed. If and only if H02 can be rejected (2-sided p-value < 0.05), H03 is tested at 2-sided alpha of 5%. If and only if H03 can be rejected (2-sided p-value < 0.05), H04 is tested at 2-sided alpha of 5%. This hierarchical testing procedure does not require adjustment of the alpha level.

All other tests will be performed with 2-sided alpha of 5% in an exploratory manner.

10.3.3 Safety Analyses

Safety data will be summarized using the safety analysis set.

Adverse events with a start date and time occurring after the first administration of the study drug will be considered treatment-emergent AEs (TEAEs). Adverse events with missing or partial start date or time will also be considered TEAEs following the worst-case principle unless the partial data clearly indicates that the AE started before first administration date and time.

Treatment-emergent AEs occurring until the Follow-up Visit will be summarized. Only TEAEs will be included in analysis, although all AEs will be listed.

The following tables will be presented for AEs occurring at any dose:

- Summary of subjects with AEs (number with any AE, with AEs occurring within 24 hours of investigational product injection, with SAE, with related AE, with AEs leading to study discontinuation, with each intensity, and with each outcome).
- Summary of subjects with SAEs (number with any SAE, with SAEs occurring within 24 hours of investigational product injection, with related SAE, with SAEs leading to study discontinuation, with each intensity, and with each outcome).
- Incidence of subjects with AEs by SOC and PT.
- Incidence of subjects with SAEs by SOC and PT.
- Incidence of subjects with AEs by severity and SOC and PT.

- Incidence of subjects with AEs by relationship to investigational product and SOC and PT.
- Incidence of subjects with AEs leading to discontinuation by SOC and PT.
- Incidence of subjects with TEEs by SOC and PT.
- Incidence of subjects with bleeding events by SOC and PT.
- Incidence of subjects with severe hypersensitivity / anaphylaxis by SOC and PT.
- The number of subjects experiencing AEs which occur in at least 1 treatment in at least 1, 2, 3, 4, and 5% of events will also be presented.
- Laboratory findings reported as AEs.

Summaries will include the number and percentage of subjects, the number of AEs, and the number of AEs per injection and per subject year (where applicable).

A summary of non-serious AEs only will be presented by treatment and also by SOC, PT, and treatment.

Summaries of ISRs will be presented by treatment and also by MedDRA SOC and PT, and treatment, with relationship to investigational product and with severity.

A subject with more than 1 occurrence of the same AE will be counted only once in the total of those experiencing that AE. Similarly, a subject with 1 or more AEs in a particular SOC will be counted only once in the total of those experiencing AEs in that particular SOC.

Adverse events, SAEs, AEs leading to study discontinuation and death will be listed.

10.3.4 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. Individual and mean CSL312 plasma concentration versus time will be plotted on linear and semi-logarithmic scales. Plasma CSL312 concentrations will be summarized with descriptive statistics: mean, SD, percent coefficient of variation, median, minimum, maximum, and first and third quartiles for continuous variables, geometric mean and its respective 90% CI.

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

10.3.5 Pharmacodynamic Analyses

Pharmacodynamic data will be summarized using the PD population.

FXIIa-mediated kallikrein activity and FXII concentration will be assessed for the pharmacodynamics of CSL312 as described in Table 5.

FXIIa-mediated kallikrein activity and FXII concentration will be listed by individual subject and summarized by nominal time point and treatment.

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

10.3.6 Pharmacokinetic / Pharmacodynamic Relationships

Population PK and PK / PD modelling will be explored, as feasible, for further time-dependent characterization of PK versus PD endpoints and / or safety / efficacy endpoints and reported separately. Additional information on PK / PD analyses will be provided separately in the Modeling and Simulation Analysis Plan.

10.3.7 Other Analyses

Analyses of exploratory endpoints will be described in the SAP.

10.3.8 Interim Analysis

Not applicable.

11 Quality Assurance

The study may be subject to an audit by CSL, an authorized representative(s) of CSL 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. CSL 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

CSL 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 CSL 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 CSL. 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 contained 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 informed consent form.

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 re-consent 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, phone number and identity in the study) so that regulatory agencies or CSL 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 CSL 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

CSL 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 / CSL 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 CSL ("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 CSL, 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

CSL will provide the relevant clinical study protocol information in public database(s) before or at commencement of the study. CSL 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 CSL 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 CSL 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, these assessments / procedures may be conducted remotely with CSL approval. However, all such assessments / procedures must be promptly reported to CSL and the IRB / IEC. The following options may be implemented "on-demand" in the event of local restrictions and at the discretion of CSL:

- Direct to subject shipment of investigational product 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 phone 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 CSL. 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 CSL 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 eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data).

An eCRF will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless the eCRF 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 CSL's clinical data warehouse at a predefined frequency via a secure data channel for systematic review by the CSL 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 diary 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 eCRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. CSL's study monitor will perform this function.

Following completion of eCRF 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 CSL (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 CSL'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 CSL 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

CSL 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 CSL 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. CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated

coordinating investigator (or delegate). CSL requires that the coordinating investigator will 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 CSL 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

Appendix 1 Signatures

Signature on Behalf of Sponsor

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

Protocol Number: CSL312_3001

I have read the Clinical Study Protocol CSL312_3001 titled "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

(Signature)

PPD

Date (DD MMM YYYY)

PPD

(Printed name)

PPD

(

Signature of Principal Investigator

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

Protocol Number: CSL312_3001 Site Number: <<>>

I have read the Clinical Study Protocol CSL312_3001 titled "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema."

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 Conference on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL 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 CSL312-3001

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 a 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 subjects for 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.

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

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 one 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 eCRF 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 eCRF 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 eCRF (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 needs 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 eCRF. 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 eCRF:

- 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 eCRF.
    - 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 eCRF.

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.

Signature Page

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Signed By	Date (GMT)
PPD	05-Aug-2020 12:58:39
Approved-Clinical Safety Physician Approval	
PPD	05-Aug-2020 13:38:37
Approved-PPD Approval	
PPD	05-Aug-2020 17:26:51
Approved-PPD Approval	

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