CLINICAL STUDY PROTOCOL

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

Study Number:	CSL312_2001
Study Product:	CSL312 (Factor XIIa Antagonist Monoclonal Antibody)
Development Phase:	Phase 2
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Amendment 2
EudraCT Number:	2018-000605-24
Protocol Date:	20 March 2020
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on 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 (or delegate) and provided to the study sites as needed.

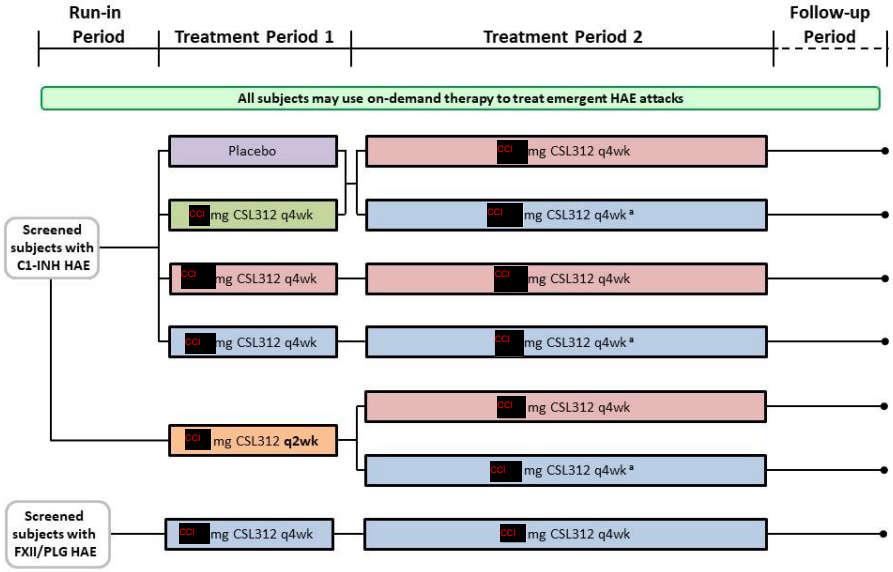
Revision History

Date	Version	Summary of Changes
30 May 2018	Original	Not applicable
18 December 2018	Amendment 1	• Frequency of pregnancy testing was increased in Treatment Period 2. • Urine testing for pregnancy was added as an alternative to serum testing. • Acceptable methods of contraception were updated. • The requirement that pregnancy test results obtained outside of the study site will be documented and tracked was added. • The duration of the Follow-up Period was extended to 95 days. • Activities related to the accessibility and accountability of CSL312 were clarified, in the case that Treatment Period 2 is extended. • Acceptable use of routine (long-term) HAE prophylaxis during the study was clarified. • Clarification to the laboratory values that are to be documented in the medical history page of the eCRF. • Clarifications to statistical methods.
20 March 2020	Amendment 2	• For hereditary angioedema subjects with C1-esterase inhibitor deficiency (C1-INH HAE) receiving the CCI mg dose in Treatment Period 2, the dose will be decreased to CCI mg. • Edits were made to the Statistical Analysis and Methods section. • Administrative clarifications for accuracy, grammar, formatting, and consistency.

Protocol Synopsis

Title	A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with hereditary angioedema
Study Number	CSL312_2001
Sponsor	CSL Behring LLC (CSL)
Development Phase	Phase 2
Study Product	CSL312 (Factor XIIa Antagonist Monoclonal Antibody)
Indication	Hereditary angioedema
Study Summary and Overview	This is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study to investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 as prophylaxis to prevent hereditary angioedema (HAE). The study consists of a Screening Period, a Run-in Period, 2 treatment periods, and a Follow-up Period.

An overview of the study design is presented in the following schematic:



Abbreviations presented in the study schematic: C1-INH HAE = HAE with C1-esterase inhibitor deficiency; FXII/PLG HAE = HAE with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE = hereditary angioedema; q2wk = administered every 2 weeks; q4wk = administered every 4 weeks.

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

Run-in Period

After Screening, eligible subjects will enter into an initial Run-in Period lasting at least 4 and up to 8 weeks to confirm their underlying disease status and to assess their eligibility for participation in Treatment Period 1. The first day of the Run-in Period may occur on the same day as Screening. Subjects may stop participation in the Run-in Period and begin Treatment Period 1when they have met pre-specified criteria, including:

1. For subjects with hereditary angioedema with C1-esterase inhibitor deficiency (C1-INH HAE), subjects must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.
2. For subjects with FXII/PLG HAE, subjects must have experienced ≥ 1 HAE attack during the Run-in Period.

Treatment Period 1

Investigators will assess and document the occurrence of HAE attacks based on data reported by subjects in an eDiary. Safety and pharmacokinetic (PK) / [redacted] parameters, and use of on-demand HAE medication will also be assessed.

The first 32 subjects with C1-INH HAE who are eligible to participate in Treatment Period 1 will be randomly assigned to receive treatment with investigational product in a 1:1:1:1 ratio ([redacted] mg CSL312 administered every 4 weeks [q4wk] subcutaneously [SC]; [redacted] mg CSL312 q4wk SC; [redacted] mg CSL312 q4wk SC; placebo q4wk SC) during Treatment Period 1. Treatment in each of these arms will begin with an intravenous (IV) loading dose of CSL312 or placebo. For these C1-INH HAE subjects, Treatment Period 1 will be conducted in a blinded manner.

After the first 32 subjects with C1-INH HAE are randomly assigned to treatment, up to an additional 8 subjects will be assigned to receive [redacted] mg CSL312 administered every 2 weeks (q2wk) SC. [redacted]. For these C1-INH HAE subjects, Treatment Period 1 will be conducted in an open-label manner.

Up to 10 eligible subjects with FXII/PLG HAE will be assigned to receive [redacted] mg CSL312 q4wk SC. Treatment in this arm will begin with an IV loading dose of CSL312. For these FXII/PLG HAE subjects, Treatment Period 1 will be conducted in an open-label manner.

Treatment Period 2

C1-INH HAE subjects who continue to participate in Treatment Period 2 will be receiving CSL312 [redacted] mg or [redacted] mg q4wk SC at the beginning of Treatment Period 2. Effective with Amendment 2, all C1-INH HAE subjects receiving the [redacted] mg dose will have their dose reduced to [redacted] mg q4wk SC at their next scheduled study visit. FXII/PLG HAE subjects will be maintained on the [redacted] mg q4wk SC dose. Investigators will continue to assess and document the occurrence of HAE attacks based on data reported by subjects in an eDiary. Safety and PK / [redacted] parameters, and use of on-demand HAE medication will also continue to be assessed. Treatment Period 2 will be conducted in an open-label manner for all subjects.

	Post-treatment Follow-up All subjects, including those who discontinue participation, will attend a Follow-up Visit ~14 weeks after each subject's final visit in Treatment Period 1 or Treatment Period 2.
Primary Objective	The primary objective of this study is to evaluate the efficacy of CSL312 in the prevention of HAE attacks in subjects with C1-INH HAE.
Primary Endpoint	The primary endpoint is the time-normalized number of HAE attacks.
Secondary Objective(s)	The secondary objectives of the study are: 1. To further evaluate the efficacy of CSL312 in subjects with C1-INH HAE. 2. To evaluate the PK of CSL312 in subjects with C1-INH HAE. 3. To evaluate the safety and tolerability of CSL312 in subjects with C1-INH HAE.
Secondary Endpoint(s)	The secondary endpoints of the study are: 1. Responder subjects. 2. HAE attack-free subjects. 3. HAE attacks. 4. HAE attacks treated with on-demand HAE medication. 5. CSL312 PK in plasma: • Maximum concentration (C_{max}). • Area under the concentration-time curve in 1 dosing interval ($AUC_{0\text{-}tau}$). • Time of maximum concentration (T_{max}). • Terminal elimination half-life ($T_{1/2}$). • Total systemic clearance (CL_{tot}). • Volume of distribution during the elimination phase (V_z). 6. Subjects experiencing the following safety events: • Adverse events. • Serious adverse events. • Adverse events of special interest (ie, anaphylaxis, thromboembolic events, and bleeding events). • Injection site reactions.

	• Inhibitory antibodies to CSL312. • Clinically significant abnormalities in laboratory assessment that are reported as adverse events.
Number of Subjects	Up to 50 subjects are planned to be assigned to treatment with investigational product in Treatment Period 1, including: • 8 subjects with C1-INH HAE who will be assigned to receive placebo q4wk. • 8 subjects with C1-INH HAE who will be assigned to receive [redacted] mg CSL312 q4wk. • 8 subjects with C1-INH HAE who will be assigned to receive [redacted] mg CSL312 q4wk. • 8 subjects with C1-INH HAE who will be assigned to receive [redacted] mg CSL312 q4wk. • Up to 8 subjects with C1-INH HAE who will be assigned to receive [redacted] mg CSL312 q2wk. • Up to 10 subjects with FXII/PLG HAE who will be assigned to receive [redacted] mg CSL312 q4wk.
Study Duration	The duration of the study for an individual subject who participates in Treatment Period 1and Treatment Period 2 is up to approximately 83 weeks if the duration of Treatment Period 2 is not extended. This estimation is based on: • A Screening Period of up to 4 weeks. • A Run-in Period of up to 8 weeks. • A treatment period of ~13 weeks (Treatment Period 1). • A treatment period of ~44 weeks (Treatment Period 2). • A Follow-up Period of ~14 weeks. Treatment Period 2 will extend until another CSL312 study is opened for subjects to join, or until the current study is discontinued.
Study Population and Main Criteria for Eligibility	**To enter the Run-in Period, subjects must meet all of the following inclusion criteria:** 1. Male or female. 2. Aged ≥ 18 to ≤ 65 years at the time of providing written informed consent.

3. A diagnosis of C1-INH HAE or FXII/PLG HAE:
   - For C1-INH HAE (type 1): Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria); CCI [redacted] < 50% of the lower limit of the reference range, as documented in the subject's medical record; CCI [redacted] below the lower limit of the reference range, as documented in the subject's medical record.
   - For C1-INH HAE (type 2): Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria); CCI [redacted] < 50% of the lower limit of the reference range, as documented in the subject's medical record; CCI [redacted] below the lower limit of the reference range, as documented in the subject's medical record.
   - For FXII/PLG HAE: Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria); an HAE-associated FXII gene mutation [eg, FXII point mutation Thr328Lys or Thr328Arg, or deletion of 72 base pairs (c.971_1018 + 24del72), or duplication of 18 base pairs (c.892-909dup)], as documented in the subject's medical record, **OR** an HAE-associated PLG gene mutation (eg, PLG point mutation Lys330Glu), as documented in the subject's medical record; CCI [redacted] 70 -120 % of the normal level, as documented in the subject's medical record.
4. For subjects with C1-INH HAE: ≥ 4 HAE attacks over a consecutive 2-month period 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, ≥ 4 HAE attacks may be documented over any consecutive 2-month period during the 3 months before commencing the prophylactic therapy.
5. For subjects with FXII/PLG HAE: ≥ 1 HAE attack 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, 1 HAE attack may

be documented during the 3 months before commencing the prophylactic therapy.

6. Willing to cease the use of any medications for routine prophylaxis against HAE attacks (eg, C1-INH, androgens, antifibrinolytics) on the first day of the Run-in Period, after being assessed by the investigator to be able to adequately manage on-demand treatments of HAE attacks without assistance.

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

1. History of clinically significant arterial or venous thrombosis, or current clinically significant prothrombotic risk, including presence of a central venous access device.
2. History of an uncontrolled, abnormal bleeding event due to a coagulopathy, or a current clinically significant coagulopathy or clinically significant risks for bleeding events.
3. Any pre-planned surgeries during the trial that have an inherent clinically significant risk for thrombotic events or bleeding.
4. Any previous treatment with any monoclonal antibody, recombinant protein bearing an Fc domain, ribonucleic acid (RNA) silencing, or gene transfer technologies.
5. Pregnant or nursing mother.
6. Known or suspected hypersensitivity to the investigational product or to any excipients of the investigational product.

Subjects will be eligible to exit the Run-in Period and begin Treatment Period 1 if they meet the following criteria:

1. Subject participated in the Run-in Period for at least 4 weeks (28 days).
2. A diagnosis of C1-INH HAE, confirmation of diagnosis by central laboratory testing:
   a. For subjects with C1-INH HAE (type 1): CCI [redacted] < 50% of the lower limit of the reference range; CCI [redacted] below the lower limit of the reference range
   b. For subjects with C1-INH HAE (type 2): CCI [redacted] < 50% of the lower limit of the reference range; CCI [redacted] below the lower limit of the reference range.

	3. For subjects with C1-INH HAE: the occurrence of ≥ 2 HAE attacks within any consecutive 4-week period during the Run-in Period. 4. For subjects with FXII/PLG HAE: the occurrence of ≥ 1 HAE attack during the Run-in Period. 5. Do not have any clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments performed during Screening.
Investigational Product Dose, Dosing Regimen, and Administration	**Treatment Period 1** The first 32 subjects with C1-INH HAE who are eligible to participate in Treatment Period 1 will be randomly assigned to receive 1 of the following treatment regimens in a blinded manner: • A single loading dose of [redacted] mg CSL312 IV followed ~1 week later by [redacted] mg CSL312 q4wk SC; • A single loading dose of [redacted] mg CSL312 IV followed ~1 week later by [redacted] mg CSL312 q4wk SC; • A single loading dose of [redacted] mg CSL312 IV followed ~1 week later by [redacted] mg CSL312 q4wk SC; • A single loading dose of placebo IV followed ~1 week later by placebo q4wk SC. After the first 32 subjects with C1-INH HAE are randomly assigned to treatment (as above), up to an additional 8 subjects will be assigned in an open-label manner to receive [redacted] mg CSL312 q2wk SC. [redacted]. Up to 10 eligible subjects with FXII/PLG HAE will be assigned in an open-label manner to receive a loading dose of [redacted] mg CSL312 IV followed ~1 week later by [redacted] mg CSL312 q4wk SC. All IV loading doses of investigational product (ie, CSL312 or placebo) will be administered by the investigator or delegate at the study site. All SC doses of investigational product will be self-administered under supervision of the investigator or delegate at the study site. **Treatment Period 2** C1-INH HAE subjects who continue to participate in Treatment Period 2 will be receiving CSL312 [redacted] mg or [redacted] mg q4wk SC at the beginning of Treatment Period 2. Effective with Amendment 2, all C1-INH HAE subjects receiving the [redacted] mg dose will have their dose reduced to [redacted] mg q4wk SC at their next scheduled study visit.

	FXII/PLG HAE subjects will be maintained on the [redacted] mg q4wk SC dose. The first dose of CSL312 in Treatment Period 2 will be administered at the Week 13 (Day 91) Visit and at the Week 13 (Day 85) Visit for subjects who administer investigational product q4wk and q2wk in Treatment Period 1, respectively. Administration of CSL312 at the Week 13 (Day 85 / 91) Visit, the Week 17 (Day 119) Visit, and the Week 21 (Day 147) Visit will be self-administered under supervision of the investigator or delegate at the study site. After administration of CSL312 at the Week 21 (Day 147) Visit, all subsequent doses of CSL312 will be self-administered SC every 28 days (± 2 days) by the subject at home or at the study site.
Efficacy Assessments	Investigators will assess and document the occurrence of HAE attacks based on subject eDiary data. The following information will be documented in the subject eDiary: • Date and time of HAE symptom onset and resolution. • Location of HAE symptom(s). • Interference of symptom(s) with the subject's daily activities. • On-demand medication used to treat HAE symptoms. • Assistance by a healthcare professional during HAE symptoms.

Safety Assessments	The safety and tolerability of CSL312 will be assessed based on:
	• Adverse events.
	• Vital signs.
	• Physical examinations.
	• Clinical laboratory assessments:
	  • Urinalysis.
	  • Hematology.
	  • Biochemistry.
	  • Coagulation.
	  • Immunogenicity.
	In addition, a blood sample will be retained for potential assessment of viral serology.

Pharmacokinetics	Blood samples will be collected for assessment of CSL312 PK in plasma.

CCI	CCI

Statistical Analyses

Sample Size

Overall, up to 50 subjects will be assigned to treatment in Treatment Period 1.

- Seven subjects assigned to placebo, and CCI mg and CCI mg CSL312 q4wk are needed to reach power of ~82% for the comparisons of CCI mg CSL312 q4wk versus placebo q4wk and CCI mg CSL312 q4wk versus placebo q4wk in Treatment Period 1. An additional subject will be added to each of these treatment arms to account for drop outs during Treatment Period 1, resulting in 8 subjects in each of these treatment arms (ie, 24 subjects total).
- Seven subjects will be assigned to receive CCI mg CSL312 q4wk. The sample size for this arm is not driven by an efficacy comparison, but instead, by consistency with other treatment arms and for maintenance of blinding of the study. No testing for efficacy of CCI mg CSL312 against placebo will be performed and no power calculation has been done. An additional subject will be added to the treatment arm to account for drop outs during Treatment Period 1, resulting in 8 subjects in the treatment arm.
- Up to 7 subjects with C1-INH HAE will be assigned to receive CCI mg CSL312 q2wk. This arm is included for informational purposes, and therefore no testing against placebo is planned and no power calculation has been done. An additional subject may be added to the treatment arm to account for drop outs during Treatment Period 1, resulting in up to 8 subjects in the treatment arm.
- Up to 10 subjects with FXII/PLG HAE will take part in the study.

Data Analysis

The data from Treatment Period 1 and Treatment Period 2 will be analyzed separately. In addition, Treatment Period 1 and Treatment Period 2 will be analyzed together for subjects who are being continuously administered the same dose of CSL312 during both treatment periods, unless otherwise specified.

Subjects with C1-INH HAE who are treated with placebo or [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk will be analyzed separately from subjects with C1-INH HAE who are treated with [redacted] mg CSL312 q2wk. Subjects with FXII/PLG HAE will be analyzed separately from subjects with C1-INH HAE.

Continuous variables will be described by using mean values with their respective 95% confidence intervals; standard deviation; 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 [redacted] data. The geometric mean and its respective 90% confidence interval will be calculated for PK and [redacted] data. 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, study site, subject, time point, and item number (if applicable).

Primary Endpoint Analysis

For subjects with C1-INH HAE who were treated with placebo, or [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk during Treatment Period 1: To test for a difference in the primary efficacy endpoint between [redacted] mg CSL312 q4wk or [redacted] mg CSL312 q4wk and placebo, pairwise comparisons will be performed by testing the hypotheses using a two-sided Mann-Whitney Test. To account for multiple testing, the alpha level of 5% will be evenly split between the hypotheses tested. Therefore, the [redacted] mg CSL312 q4wk or [redacted] mg CSL312 q4wk CSL312 doses (in subjects with C1-INH HAE) will each be evaluated against placebo at alpha = 0.025 for each test. The time-normalized number of HAE attacks will be summarized descriptively by treatment. There will be no testing of the [redacted] mg CSL312 q4wk dose against placebo. The time-normalized number of HAE attacks will be presented descriptively (only).

For all other subjects: There will be no testing of the of [redacted] mg CSL312 q2wk dose against placebo for subjects with C1-INH HAE or the [redacted] mg CSL312 q4wk dose against placebo for subjects with FXII/PLG HAE.

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

Study Period	Screening	Run-in Period [a]				
Week	-4 to -1	1	3	5	7	9 [b]
Day	-28 to -1	1	15	29	43	57
Window (Days)			± 3	± 3	± 3	± 3
Study center visit	X [c]					
Telephone contact		X	X	X	X	X
Written informed consent [d]	X					
Medical history / demographics	X					
Inclusion / exclusion criteria	X					
Physical examination [e]	X					
Vital signs including height and body weight	X					
Urine collection for urinalysis	X					
Blood Draws Hematology / Biochemistry / Coagulation	X					
CCI						
Pregnancy [g]	X					
Confirmation of FXII or PLG mutation [h]	X					
Individual acute action plan [i]	X					
eDiary training	X					
Open eDiary access / review eDiary instructions with subject		X				
Review eDiary data and assess / document HAE attacks			X	X	X	X
Confirm access to on-demand HAE medication [j]		X	X	X	X	X
Close eDiary access						X [k]
Prior / concomitant medications and therapies	←	—	—	—	—	→
Adverse events	←	—	—	—	—	→

Abbreviations: CCI; C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; C4 = complement C4; eDiary = electronic diary; FXII = factor XII; FXII/PLG HAE = Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE = hereditary angioedema; CCI; PLG = plasminogen.

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

[a] Subjects must participate in the Run-in Period for at least 4 weeks (see Section 8.5.1.2.2). Subjects may stop participation in the Run-in Period and begin Treatment Period 1 when they have met the criteria specified in Section 4.1.3, including:

- For subjects with **C1-INH HAE**, subjects must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.
- For subjects with **FXII/PLG HAE**, subjects must have experienced ≥ 1 HAE attacks during the Run-in Period.

[b] Subjects should enter Treatment Period 1 no later than 14 days after the Week 9 (Day 57) Telephone Contact. If a subject is unable to enter Treatment Period 1 within the 14 days after the Week 9 (Day 57) Telephone Contact, then CSL approval is required for the subject to enter into Treatment Period 1. The Week 9 (Day 57) 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 Treatment Period 1.

[c] Screening may occur on the same day as the first day of the Run-in Period.

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

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

CCI

[g] The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive.

[h] Confirmation of the FXII or PLG gene mutation will be based on the subject's medical record.

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

[j] 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 (see Section 7.2).

[k] Access to the eDiary should be closed within 14 days after the Week 9 Telephone Contact for subjects who will not participate in Treatment Period 1.

Schedule of Assessments: Treatment Period 1 [C1-INH HAE and FXII/PLG HAE Subjects Receiving Investigational Product Every 4 Weeks]

Study Period		Treatment Period 1												Follow-up [b]
Visit Week		1				5	9		10	11	12	13 [a]		26 [b]
Visit Day		1			6	35	63	66	70	77	84	91 [a]		186 [b]
Visit Window (Days)					± 2	± 2	± 2	± 1	± 2	± 2	± 2	± 2		± 3
Time (Hours)		Pre-dose	0.5	4.0 [c]	8.0 [c]									
Time window (Minutes)			± 15	± 60	± 120									
Study center visit		X				X	X	X [d]	X [d]	X [d]	X	X	X	X [l]
Confirm eligibility for Treatment Period 1 [e]		X												
Assignment to treatment via IRT		X												
Physical examination [f, g]		X				X	X	X					X	
Vital signs including body weight [g]		X				X	X	X					X	
CCI														
CCI														
Urine collection for urinalysis [g]		X					X	X					X	
Blood Draws [g]	Hematology / Biochemistry / Coagulation	X					X	X					X	
	Retention sample for viral serology	X											X	
	Pharmacokinetics / CCI	X	X	X [c]	X [c]	X	X	X [d]	X [d]	X [d]	X	X	X	X [l]
	Immunogenicity	X											X	
Pregnancy [h]		X					X	X					X	
Review of eDiary instructions with subject		X												
Review eDiary data and assess / document HAE attacks		X				X	X	X					X	X
Close eDiary access														X
Confirm access to on-demand HAE medication [i]		X				X	X	X						
Dispense and administer investigational product [j]		X				X	X	X [k]						
Accountability of investigational product		X				X	X	X						
Concomitant medications and therapies		←												→
Adverse events		←												→

Abbreviations: CCI; CCI; C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; C4 = complement C4; eDiary = electronic diary; FXII = factor XII; FXII/PLG HAE = Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE = hereditary angioedema; CCI; IRT = interactive responses technology; IV = intravenous; CCI; PK = pharmacokinetic; PLG = plasminogen; SC = subcutaneous; CCI; CCI.

Footnotes to the Schedule of Assessments: Treatment Period 1 [C1-INH HAE and FXII/PLG HAE Subjects Receiving Investigational Product Every 4 Weeks]

[a] For subjects who are taking part in Treatment Period 2, the Week 13 (Day 91) Visit is the first study visit in Treatment Period 2; refer to the Schedule of Events: Treatment Period 2 [All Subjects]. If a subject is discontinued from the study before completing Treatment Period 1, the subject will undergo the assessments scheduled for the Week 13 (Day 91) Visit and then attend the Treatment Period 1 Follow-up Visit ~14 weeks later.

[b] If a subject participates in Treatment Period 2, then the subject will not attend the Treatment Period 1 Follow-up Visit. Refer to the Schedule of Events: Treatment Period 2 [All Subjects] for the visit schedule for subjects who participate in Treatment Period 2.

[c] The PK / CCI blood draws at 4.0 hours (± 60 minutes) post-dose and 8.0 hours (± 120 minutes) post-dose at the Week 1 (Day 1) Visit should occur ≥ 120 minutes apart.

[d] The Week 9 (Day 63) and Week 9 (Day 66) Visits and corresponding PK / CCI blood draws should each occur at least 24 hours apart. The Week 9 (Day 66) and Week 10 (Day 70) Visits and corresponding PK / CCI blood draws should each occur at least 72 hours apart.

[e] Subjects may stop participation in the Run-in Period and begin Treatment Period 1 when they have met the criteria specified in Section 4.1.3, including:

- For subjects with **C1-INH HAE**, subjects must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.
- For subjects with **FXII/PLG HAE**, subjects must have experienced ≥ 1 HAE attacks during the Run-in Period.

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

[g] At visits where physical examinations, vital signs, urine collection, and blood draws are scheduled to occur on the same day as administration of the investigational product, administration of investigational product will occur after these assessments have been completed.

[h] The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive.

[i] 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 (see Section 7.2).

[j] Investigational product will be administered IV by the investigator or delegate at the study site during the Week 1 (Day 1) Visit, and will be self-administered SC by the subject under supervision of the investigator or delegate at the study site during the Week 1 (Day 6) Visit, the Week 5 (Day 35) Visit, and the Week 9 (Day 63) Visit.

[k] For subjects who do not participate in Treatment Period 2, the final dose of investigational product will be administered at the Week 9 (Day 63) Visit.

[l] The Treatment Period 1 Follow-up Visit may be waived in place of a telephone contact. If the Treatment Period 1 Follow-up is conducted as a visit, then a blood draw for assessment of PK / CCI should occur.

Schedule of Assessments: Treatment Period 1 [C1-INH HAE Subjects Receiving Investigational Product Every 2 Weeks]

Study Period		**Treatment Period 1**									**Follow-up [b]**
Visit Week		**1**	**3**	**5**	**7**	**9**	**10**	**11**	**12**	**13 [a]**	**25 [b]**
Visit Day		**1**	**15**	**29**	**43**	**57**	**64**	**71**	**77**	**85 [a]**	**180 [b]**
Visit Window (Days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
Study center visit		X	X	X	X	X	X [c]	X	X [d]	X	X [l]
Confirm eligibility for Treatment Period 1 [e]		X									
Assignment to treatment via IRT		X									
Physical examination [f, g]		X		X		X				X	
Vital signs including body weight [g]		X		X		X				X	
CCI											
CCI											
Urine collection for urinalysis [g]		X		X		X				X	
Blood Draws [g]	Hematology / Biochemistry / Coagulation	X		X		X				X	
	Retention sample for viral serology	X								X	
	Pharmacokinetics / CCI	X	X	X	X	X	X [c]	X	X [d]	X	X [l]
	Immunogenicity	X								X	
Pregnancy [h]		X		X		X				X	
Review of eDiary instructions with subject		X									
Review eDiary data and assess / document HAE attacks		X	X	X	X	X		X		X	X
Close eDiary access											X
Confirm access to on-demand HAE medication [i]		X	X	X	X	X		X		X	
Dispense and administer investigational product [j]		X	X	X	X	X		X [k]			
Accountability of investigational product		X	X	X	X	X		X			
Concomitant medications and therapies		←	―	―	―	―	―	―	―	―	→
Adverse events		←	―	―	―	―	―	―	―	―	→

Abbreviations: CCI; CCI; C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; C4 = complement C4; eDiary = electronic diary; HAE = hereditary angioedema; CCI; IRT = interactive responses technology; CCI; PK = pharmacokinetic; SC = subcutaneous; CCI; CCI.

Footnotes to the Schedule of Assessments: Treatment Period 1 [C1-INH HAE Subjects Receiving Investigational Product Every 2 Weeks]

[a] For subjects who are taking part in Treatment Period 2, the Week 13 (Day 85) Visit is the first study visit in Treatment Period 2; refer to the Schedule of Events: Treatment Period 2 [All Subjects]. If a subject is discontinued from the study before completing Treatment Period 1, the subject will undergo the assessments scheduled for the Week 13 (Day 85) Visit and then attend the Treatment Period 1 Follow-up Visit ~14 weeks later.

[b] If a subject participates in Treatment Period 2, then the subject will not attend the Treatment Period 1 Follow-up Visit. Refer to the Schedule of Events: Treatment Period 2 [All Subjects] for the visit schedule for subjects who participate in Treatment Period 2.

[c] The Week 10 (Day 64) Visit is optional, and blood for assessment of PK / CCI may be collected off-site.

[d] Blood for assessment of PK / CCI may be collected off-site. If blood is collected off-site, then a study visit is not required.

[e] Subjects may stop participation in the Run-in Period and begin Treatment Period 1 when they have met the criteria specified in Section 4.1.3, including:

- For subjects with **C1-INH HAE**, subjects must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.

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

[g] At visits where physical examinations, vital signs, urine collection, and blood draws are scheduled to occur on the same day as administration of the investigational product, administration of investigational product will occur after these assessments have been completed.

[h] The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum test will be performed by the site if result from urine test is inconclusive.

[i] 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 (see Section 7.2).

[j] Investigational product will be self-administered SC by the subject under the supervision of the investigator or delegate at designated study visits.

[k] For subjects who do not participate in Treatment Period 2, the final dose of investigational product will be administered at the Week 11 (Day 71) Visit.

[l] The Treatment Period 1 Follow-up Visit may be waived in place of a telephone contact. If the Treatment Period 1 Follow-up is conducted as a visit, then a blood draw for assessment of PK / CCI should occur.

Schedule of Assessments: Treatment Period 2 [All Subjects]

Study Period		Treatment Period 2											Follow-up
Visit Week		13	17	21	25	29	33	37	41	45	49	53	57 [b]	70
Visit Day		85 / 91 [a]	119	147	175	203	231	259	287	315	343	371	399 [b]	494
Visit Window (Days)		± 2	± 2	± 2	± 10	± 10	± 2	± 10	± 10	± 2	± 10	± 10	± 2	± 3
Study center visit		X	X	X	X [c]	X [c]	X	X [c]	X [c]	X	X [c]	X [c]	X	X [i]
Assignment to treatment via IRT		X												
Physical examination [d, e]		X	X	X			X			X			X	
Vital signs including body weight [e]		X	X	X			X			X			X	
CCI														
CCI														
Urine collection for urinalysis [e]		X	X	X			X			X			X	
Blood Draws [e]	Hematology / Biochemistry / Coagulation	X	X	X			X			X			X	
	Retention sample for viral serology	X											X	
	Pharmacokinetics / CCI	X	X	X			X			X			X	X [i]
	Immunogenicity	X											X	
Pregnancy [f]		X	X	X	X [c]	X [c]	X	X [c]	X [c]	X	X [c]	X [c]	X	
Review eDiary data and assess / document HAE attacks		X	X	X			X			X			X	X
Close eDiary access														X
Confirm access to on-demand HAE medication [g]		X	X	X			X			X			X	
Administer investigational product [h]		X	X	X	←	—	—	—	—	—	—	—	→	
Dispense investigational product		X	X	X			X			X			X [j]	
Accountability of investigational product		X	X	X			X			X			X [j]	
Concomitant medications and therapies		←	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events		←	—	—	—	—	—	—	—	—	—	—	—	→

Abbreviations: CCI; CCI; C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; C4 = complement C4; FXII = factor XII; FXII/PLG HAE = Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; eDiary = electronic diary; HAE = hereditary angioedema; CCI; IRT = interactive responses technology; PK = pharmacokinetics; CCI; PLG = plasminogen; q2wk = administered every 2 weeks; q4wk = administered every 4 weeks; SC = subcutaneous; CCI; CCI.

Note: Treatment Period 2 will extend until another CSL312 study is opened for enrollment, or until the current study is discontinued. If Treatment Period 2 is extended, procedures from the Week 45 (Day 315) Visit will be repeated approximately every 12 weeks starting 12 weeks after all listed assessments are completed at the Week 57 (Day 399) Visit. If Treatment Period 2 is extended, then all assessments scheduled for the Week 57 (Day 399) Visit will be repeated at each subject's final Treatment Period 2 visit. A Follow-up Visit will occur ~14 weeks after each subject's final Treatment Period 2 visit.

Footnotes to the Schedule of Assessments: Treatment Period 2 [All Subjects]

[a] The Week 13 (Day 91) Visit will be the first visit in Treatment Period 2 for C1-INH HAE subjects receiving placebo, CCI mg, CCI mg, or CCI mg CSL312 q4wk, and FXII/PLG HAE subjects receiving CCI mg CSL312 q4wk in Treatment Period 1. The Week 13 (Day 85) Visit will be the first visit in Treatment Period 2 for C1-INH HAE subjects receiving CCI mg CSL312 q2wk in Treatment Period 1.

[b] If a subject is discontinued from the study before completing Treatment Period 2, the subject will undergo the assessments scheduled for the Week 57 (Day 399) Visit in Treatment Period 2, and will then attend the Treatment Period 2 Follow-up Visit ~14 weeks later.

[c] Pregnancy testing is mandatory. However, site visits for pregnancy tests are optional. Documentation and tracking of pregnancy testing must be conducted by the site.

[d] 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.

[e] At visits where physical examinations, vital signs, urine collection, and blood draws are scheduled to occur on the same day as administration of CSL312, administration of CSL312 will occur after these assessments have been completed.

[f] The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive.

[g] 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 (see Section 7.2).

[h] The first administration of investigational product in Treatment Period 2 will occur at the Week 13 (Day 85 / 91) Visit. Investigational product will be self-administered by the subject under the supervision of the investigator or delegate at the Week 13 (Day 85 / 91) Visit, the Week 17 (Day 119) Visit, and the Week 21 (Day 147) Visit. After administration of the investigational product at the Week 21 (Day 147) Visit, all subsequent doses of investigational product will be self-administered SC every 28 days (± 2 days) by the subject at home or at the study site.

[i] The Treatment Period 2 Follow-up Visit may be waived in place of a telephone contact. If the Treatment Period 2 Follow-up is conducted as a visit, then a blood draw for assessment of PK / CCI should occur.

[j] Investigational product will be dispensed and accountability will be conducted only if Treatment Period 2 is extended beyond the subject's Week 57 (Day 399) Visit (see Section 8.5.4.14).

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
CCI [redacted]	CCI [redacted]
ALT	Alanine aminotransferase
CCI [redacted]	CCI [redacted]
AST	Aspartate aminotransferase
$AUC_{0\text{-}tau}$	Area under the concentration curve in 1 dosing interval
BK	Bradykinin
C1-INH	C1-esterase inhibitor
C1-INH HAE	Hereditary angioedema with C1-esterase inhibitor deficiency
C4	Complement C4
CI	Confidence interval
CL/F	Apparent clearance
CL_{tot}	Total systemic clearance
C_{max}	Maximum concentration
CSL312	Factor XIIa antagonist monoclonal antibody
CSL	CSL Behring LLC
CVAD	Central venous access device
eCRF	Electronic case report form
eDiary	Electronic diary
FXII	Factor XII
FXII/PLG HAE	Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation
FXIIa	Activated factor XII
GCP	Good Clinical Practice
HAE	Hereditary angioedema
CCI [redacted]	CCI [redacted]
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
CCI [redacted]	CCI [redacted]
IEC	Independent ethics committee
IRB	Institutional review board
IRT	Interactive response technology

Abbreviation	Term
ISR	Injection site reaction
ITT	Intent-to-Treat
IV	Intravenous(ly)
nC1-INH	Normal C1-esterase inhibitor
CCI	CCI
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin time
q2wk	Administered every 2 weeks
q4wk	Administered every 4 weeks
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
CCI	CCI
SOC	System Organ Class
Study 1001	Study CSL312_1001
TEE	Thromboembolic event
$T_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach the maximum concentration in plasma
Vd/F	Apparent volume of distribution
Vz	Volume of distribution during the elimination phase
CCI	CCI

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).

- The abbreviation "FXII/PLG HAE" is used in this clinical study protocol to include hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation.

- In some sections of the protocol, dosing regimens are identified without reference to the initial intravenously administered loading dose that some subjects are required to receive. This approach has been taken to streamline presentation of protocol text and is not intended to indicate that the loading dose is optional. Full details for dosing and administration are presented in Section 3.2, with supportive information presented in Section 5.5 and Section 6.2.

- For subjects who administer investigational product subcutaneously every 4 weeks in Treatment Period 1, the first dose of CSL312 in Treatment Period 2 will be administered at the Week 13 (Day 91) Visit. For subjects who administer investigational product subcutaneously every 2 weeks in Treatment Period 1, the first dose of CSL312 in Treatment Period 2 will be administered at the Week 13 (Day 85) Visit. Within the body of the protocol, these visits are presented together as "the Week 13 (Day 85 / 91) Visit".

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 CCI (CCI). 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 CCI to release the potent inflammatory mediator BK. The binding of BK to BK type 2 (B2) 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 Hereditary Angioedema

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).

HAE 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, 2010; Cicardi, 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 as low as 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 et al, 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 factor XII (FXII)-driven plasma contact system is a consistent finding in acute episodes of HAE [Björkqvist, 2013].

HAE with normal C1-INH (nC1-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, 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, 2015]. A Lys311Glu substitution is a disease-causing plasminogen mutation which may cause an irregular cleavage by activated factor XII and kallikrein, the serine

proteases of the kinin-forming cascade [Dewald, 2018]. For other forms of HAE with nC1-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, 2010b; Nasr et al, 2016].

1.1.4 Treatment of Hereditary Angioedema

Current treatment options for HAE can be subdivided into the acute treatment of attacks and prophylaxis. The treatment of choice in the event of an acute HAE attack is the rapid intravenous (IV) administration of C1-INH concentrate [Bork 2008; Gompels et al, 2005; Longhurst 2005]. Recently, compounds including a kallikrein inhibitor and a BK receptor antagonist have been added to the spectrum of medications available to treat acute HAE attacks [Cicardi et al, 2010a; Cicardi et al, 2010b].

Despite a number of treatment options for acute HAE attacks, the prophylactic treatment of HAE remains an area of unmet medical need. Limitations of current prophylactic therapies are an unfavorable side effect profile (androgens), a lack of effect (antifibrinolytics), or the frequency of administration (IV or subcutaneous [SC] C1-INH). Although emerging therapies are providing improved prophylactic clinical outcomes, there is a need for further modalities in the prophylactic management of HAE, especially those targeting novel pharmacological pathways.

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 during remission [Csuka et al, 2015; Cugno et al, 1996]. Given the importance of FXIIa in the initiation of the plasma contact system it is a novel target for the inhibition of the kallikrein-kinin pathway and the excessive production of BK detected during HAE attacks.

1.2 Background Information on CSL312

1.2.1 Overview

CSL312 (factor XIIa antagonist 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 active catalytic fragment of FXII (βFXIIa). CSL312 is produced in Chinese hamster ovary cells that have been characterized according to applicable international guidelines.

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 CSL312 investigator's brochure.

1.2.3 Clinical Experience

1.2.3.1 Healthy Subjects

Previous clinical experience with CSL312 is limited to a single, randomized, double-blind, placebo-controlled, single ascending dose, phase 1 study. During this study, 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 behavior 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

No clinical studies with CSL312 have been conducted in subjects with HAE.

1.3 Study Overview

This is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study to investigate the clinical efficacy, PK, and safety of CSL312 as prophylaxis to prevent HAE attacks in subjects with C1-INH HAE or FXII/PLG HAE. Section 3.1 presents a detailed overview of the study.

1.4 Potential Risks and Benefits

CSL312 is a fully human monoclonal antibody that inhibits factor XIIa activity. CSL312 is being developed for routine prophylaxis to prevent angioedema attacks in patients with C1-INH HAE or FXII/PLG HAE. In the current study, CSL312 will be administered to subjects experiencing recurrent HAE attacks for the first time.

CSL312 is currently only administered in the clinical trial setting in accordance with the study protocol. The maximum dose and the predicted corresponding maximum concentration (C_{max}) in this study is lower than the highest administered dose and its corresponding C_{max} observed in the phase 1 study CSL312_1001 (Study 1001). Each subject who participated in Study 1001 received a single dose of CSL312 as a part of Study 1001; however, each subject who participates in the current study will receive multiple doses of CSL312 to produce target trough levels for up to 12 weeks or longer.

Benefits

A potential benefit of this study is the prevention of attacks in subjects with HAE type 1 and 2 or normal C1-INH with known mutation in the FXII or Plasminogen gene by inhibiting the attack-causing defective pathways. CSL312 acts as an antagonist to FXIIa, affecting the regulation of BK formation via the kallikrein-kinin pathway. In Study 1001, a dose-dependent inhibition of CCI was observed after single-dose IV or SC administration of CSL312 with near complete inhibition at the 3 and 10 mg / kg IV and SC Cohorts. Because FXIIa is an inherent part in the kallikrein-kinin cascade, its inhibition is expected to prevent the excessive BK generation, and with that, the occurrence of HAE attacks. This is supported by preclinical data in disease related models and the understanding that the major inhibitor of FXIIa is C1-INH.

The lack of sufficient functional C1-INH leads to recurring HAE attacks in HAE type 1 and 2 patients, and the administration of C1-INH prevents HAE attacks almost completely. In contrast, patients with normal C1-INH but mutations in the FXII or plasminogen gene are symptomatic despite the presence of sufficient C1-INH protein. Mutated FXII may be

susceptible to an increased activation of FXII, whereas the plasminogen mutation may lead to a dysregulation between the plasminogen / plasmin system and the kinin pathway, both resulting in an over activated kallikrein-kinin pathway. There is currently no licensed treatment available for HAE subjects with a known mutation in the FXII or Plasminogen gene.

Risks

The following risks were not observed in the phase 1 Study 1001, but are potential risks based on the drug class and mechanism of action of CSL312:

- **Hypersensitivity / Anaphylactic-type Reactions:** Administration of therapeutic proteins including monoclonal antibodies such as CSL312 is associated with the risk of 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 anaphylactic reactions. The initial administrations of CSL312 will be performed under medical supervision with immediate access to emergency equipment and medication for treatment of adverse reactions. Subjects who self-administer CSL312 outside of the study site will be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of CSL312 if hypersensitivity reactions occur and to seek immediate medical assistance.
- **Thromboembolic Events and Bleeding:** By blocking FXIIa with CSL312, there may be a potential risk of bleeding or TEEs due to altered haemostasis, unstable clot formation, or impaired clot breakdown. Subjects will be monitored carefully for signs of thrombosis or bleeding during the study. Also, because of the pharmacological action of CSL312, a prolonged of CCI [redacted] is expected to be observed in a concentration-dependent manner. However, no effect on prothrombin time (PT) was seen in the phase 1 Study 1001. This is consistent with the observation that patients who have congenital deficiency of FXII do not exhibit a bleeding phenotype, despite having a prolonged CCI [redacted] [Lammle et al, 1991; Ratnoff and Colopy, 1955]. In addition, nonclinical studies in mice and rabbits showed no impairment in haemostasis following inhibition of FXIIa [Larsson et al, 2014]. Coagulation parameters, including CCI [redacted] and PT will be monitored throughout the study.
- **Immunogenicity (Anti-drug Antibodies):** All protein therapeutics are potentially immunogenic. Because CSL312 is a protein it has the potential to cause the development

of neutralizing and non-neutralizing anti-drug antibodies. Subjects will be monitored for the development of anti-drug antibodies throughout the study.

During Study 1001, CSL312 was administered as a single IV or SC dose up to 10 mg / kg to healthy male subjects, it was safe and well tolerated. No dose dependent trends were seen in treatment emergent AE frequency or severity. No deaths, SAEs, or AEs leading to discontinuation were reported. The majority of all treatment emergent AEs were mild. There were no TEEs, bleeding, or anaphylaxis events. No clinically relevant changes in laboratory parameters, vital signs, or electrocardiograms were observed. No anti-CSL312 antibodies were detected in any subject at baseline or at any time point during the study.

Subjects randomized to placebo, and not participating in an optional open-label extension period, will have no benefits.

Given the potential benefit of CSL312 for HAE patients, the acceptable safety data for CSL312 from Study 1001, and the implementation of study procedures in the current study (Study 2001) that will closely monitor the safety of study subjects, the associated benefit-risk assessment is considered acceptable for subjects who participate in the study. Additional information on CSL312 can be found in the CSL312 investigator's brochure.

2 Study Objectives and Endpoints

Primary, secondary, and some CCI will be analyzed for subjects with C1-INH HAE, as indicated.

Other CCI will be analyzed for subjects with FXII/PLG HAE, as indicated.

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of CSL312 in the prevention of HAE attacks in subjects with C1-INH HAE.

2.1.2 Primary Endpoints

Table 1 Primary Endpoint

Primary Endpoint	Summary Measure
Time-normalized number of HAE attacks.	The time-normalized number (per month) of HAE attacks in subjects with C1-INH HAE on treatment with CSL312 (CCI mg, or CCI mg administered every 4 weeks [q4wk]) compared to placebo q4wk during Treatment Period 1.

Abbreviations: HAE = hereditary angioedema; C1-INH HAE = Hereditary angioedema with C1-esterase inhibitor deficiency; q4wk = administered every 4 weeks.

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are:

1. To further evaluate the efficacy of CSL312 in subjects with C1-INH HAE.
2. To evaluate the PK of CSL312 in subjects with C1-INH HAE.
3. To evaluate the safety and tolerability of CSL312 in subjects with C1-INH HAE.

2.2.2 Secondary Endpoints

Table 2 Secondary Endpoints

Secondary Objective	Secondary Endpoints	Summary Measure(s)
1	Responder subjects.	The number and percentage of subjects with C1-INH HAE who respond to treatment with CSL312 or placebo during Treatment Period 1, where "response" is defined as a ≥ 50% relative reduction in the time-normalized number of HAE attacks (per month) compared to each subject's time-normalized

Secondary Objective	Secondary Endpoints	Summary Measure(s)
		number of HAE attacks (per month) during the Run-in Period.
1	HAE attack-free subjects.	The number and percentage of subjects with C1-INH HAE who do not experience an HAE attack on treatment with CSL312 or placebo during Treatment Period 1.
1	HAE attacks.	The number, time-normalized number (per month), and percentage of mild, moderate, or severe HAE attacks in subjects with C1-INH HAE on treatment with CSL312 or placebo during Treatment Period 1.
1	HAE attacks treated with on-demand HAE medication.	The number, time-normalized number (per month), and percentage of mild, moderate, or severe HAE attacks in subjects with C1-INH HAE treated with on-demand HAE medication on treatment with CSL312 or placebo during Treatment Period 1.
2	CSL312 PK in plasma: • Maximum concentration (C_{max}). • Area under the concentration-time curve in 1 dosing interval ($AUC_{0\text{-}tau}$). • Time of maximum concentration (T_{max}). • Terminal elimination half-life ($T_{1/2}$). • Total systemic clearance (CL_{tot}).	CSL312 concentration in plasma in subjects with C1-INH HAE during treatment with CSL312 or placebo at specified time points during Treatment Period 1.

Secondary Objective	Secondary Endpoints	Summary Measure(s)
	• Volume of distribution during the elimination phase (V_z).	
3	Subjects experiencing: • AEs. • SAEs. • AEs of special interest (ie, anaphylaxis, TEEs, and bleeding events). • ISRs. • Inhibitory antibodies to CSL312. • Clinically significant abnormalities in laboratory assessment that are reported as AEs.	The number and percentage of subjects with C1-INH HAE experiencing the specified safety events on treatment with CSL312 or placebo during Treatment Period 1.

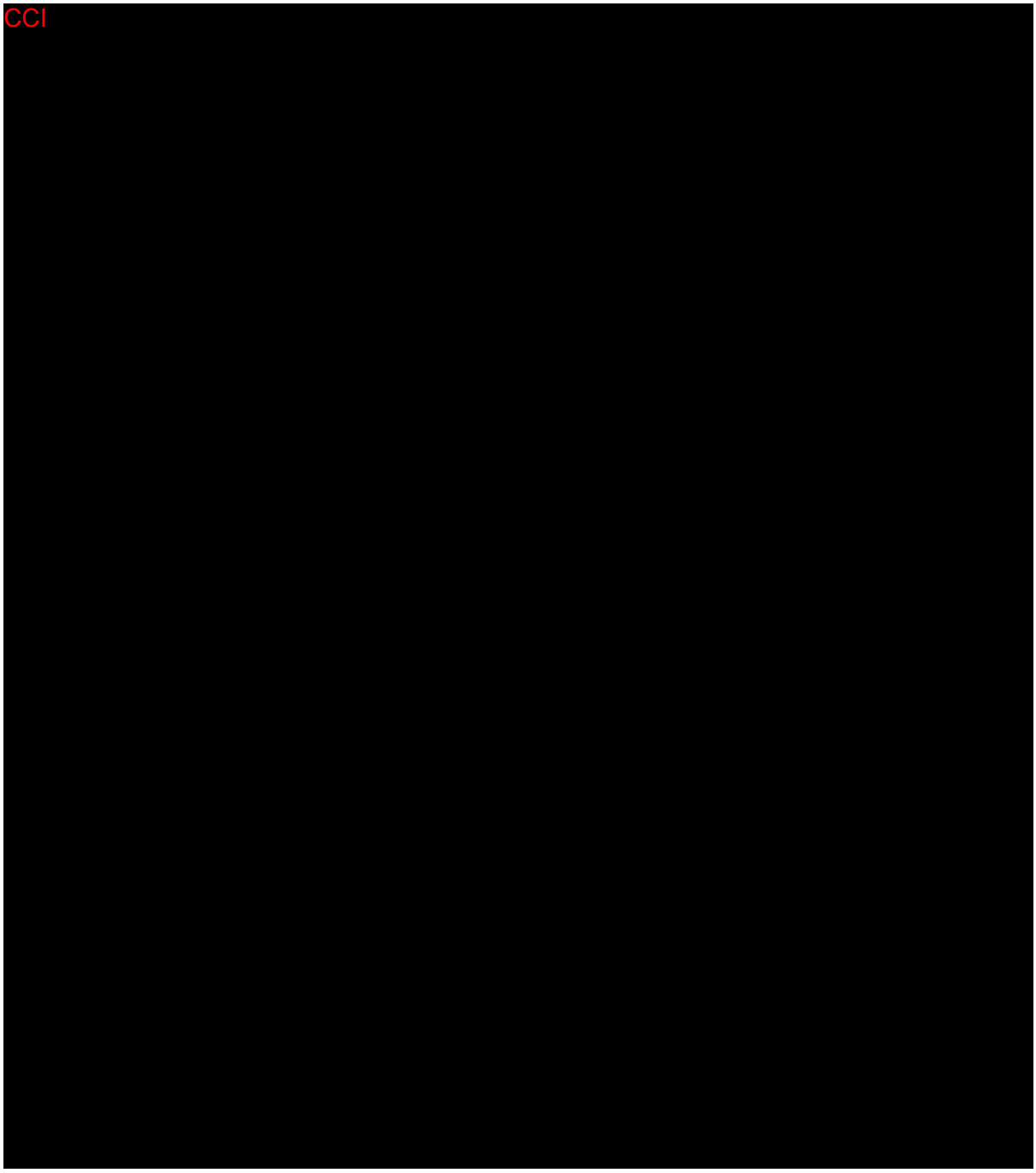
Abbreviations: AEs = adverse events; HAE = hereditary angioedema; C1-INH HAE = Hereditary angioedema with C1-esterase inhibitor deficiency; ISRs = injection site reactions; SAEs = serious adverse events; TEEs = thromboembolic events.

2.3 CCI

2.3.1 CCI

CCI

2.3.2 CCI

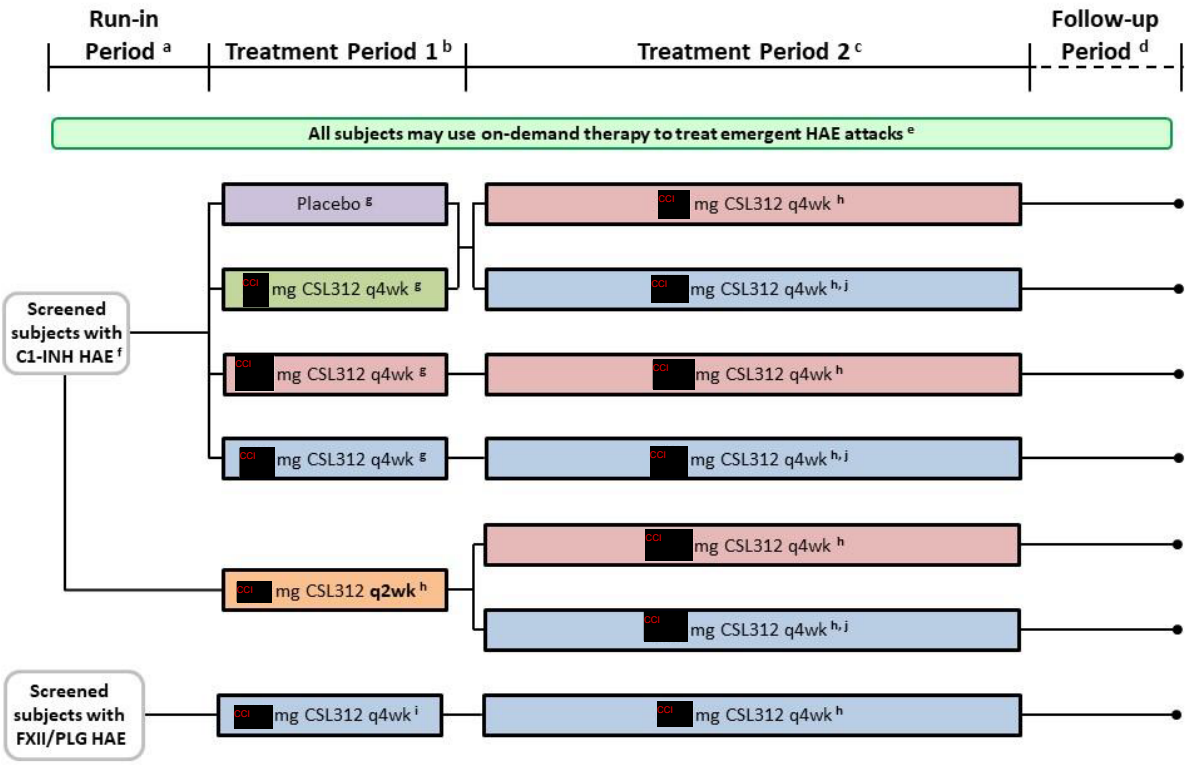


3 Study Overview

3.1 Study Design

This is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study to investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 as prophylaxis to prevent HAE attacks in subjects with C1-INH HAE or FXII/PLG HAE. As presented in Figure 1, the study consists of a Screening Period, a Run-in Period, 2 treatment periods, and a Follow-up Period.

Figure 1 Study Overview



Abbreviations: C1-INH HAE = HAE with C1-esterase inhibitor deficiency; FXII/PLG HAE = HAE with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE = hereditary angioedema; q2wk = administered every 2 weeks; q4wk = administered every 4 weeks.

Footnotes:

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

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

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

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

[e] Subjects may use the medication of their choice to treat HAE attacks experienced during the study if that medication has previously been shown to be effective (Section 7.2). Investigators should ensure that participating subjects are capable of managing their HAE attacks.

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

[g] Subjects will receive treatment with investigational product in a blinded manner (Section 6.1.3). These subjects will receive an initial IV loading dose of investigational product in Treatment Period 1 before receiving investigational product q4wk (Section 3.2).

[h] Subjects will receive treatment with CSL312 in an open-label manner (Section 6.1.3).

[i] Subjects will receive treatment with CSL312 in an open-label manner (Section 6.1.3). These subjects will receive an initial IV loading dose of investigational product in Treatment Period 1 before receiving investigational product q4wk (Section 3.2).

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

3.1.1 Screening

Subjects who provide written informed consent will be screened for their eligibility to enter the Run-in Period. Screening will be completed within 28 days before the first day of the Run-in Period.

3.1.2 Run-in Period

After Screening, eligible subjects will enter into an initial Run-in Period lasting at least 4 and up to 8 weeks to confirm their underlying disease status and to assess their eligibility for participation in Treatment Period 1. The first day of the Run-in Period may occur on the same day as Screening.

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 emerging HAE attacks if that medication has previously been shown to be effective (Section 7.2).

Subjects may stop participation in the Run-in Period and begin Treatment Period 1 when they have met the criteria specified in Section 4.1.3, including:

- For subjects with **C1-INH HAE**, subjects must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.

- For subjects with **FXII/PLG HAE**, subjects must have experienced ≥ 1 HAE attack during the Run-in Period.

3.1.3 Treatment Period 1

Subjects should enter Treatment Period 1 no later than 14 days after the Week 9 (Day 57) Telephone Contact of the Run-in Period. If a subject is unable to enter Treatment Period 1 within the 14 days after the Week 9 (Day 57) Telephone Contact, then CSL approval is required for the subject to enter into Treatment Period 1.

Treatment Period 1 will last for ~ 13 weeks, during which time investigators will assess and document the occurrence of HAE attacks based on data reported by subjects in an electronic diary (eDiary).

Subjects with C1-INH HAE

The first 32 subjects with C1-INH HAE who are eligible to participate in Treatment Period 1 will be randomly assigned to receive treatment with investigational product in a 1:1:1:1 ratio (a loading dose of CCI mg CSL312 IV followed by CCI mg CSL312 q4wk SC; a loading dose of CCI mg CSL312 IV followed by CCI mg CSL312 q4wk SC; a loading dose of CCI mg CSL312 IV followed by CCI mg CSL312 q4wk SC; a loading dose of placebo IV followed by placebo q4wk SC) during Treatment Period 1 (see Section 3.2.1). For these C1-INH HAE subjects, Treatment Period 1 will be conducted in a blinded manner. In order to maintain the blind, investigational product will be volume-normalized (Section 6.1.3.1).

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

Subjects with FXII/PLG HAE

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

3.1.4 Treatment Period 2

All subjects who participated in Treatment Period 1 may participate in Treatment Period 2. Treatment Period 2 will last for at least 44 weeks, or until another CSL312 study is opened for subjects to join, or until the current study is discontinued. During Treatment Period 2 investigators will continue to assess and document the occurrence of HAE attacks based on data reported by subjects in an eDiary. Treatment Period 2 will be conducted in an open-label manner for all subjects.

- Subjects with C1-INH HAE who received placebo or [redacted] mg CSL312 q4wk in Treatment Period 1 will be randomly assigned to receive either [redacted] mg or [redacted] mg CSL312 q4wk SC in a 1:1 ratio in Treatment Period 2.
- Subjects with C1-INH HAE who received [redacted] mg CSL312 q4wk in Treatment Period 1 will continue to receive [redacted] mg CSL312 q4wk SC in Treatment Period 2.
- Subjects with C1-INH HAE who received [redacted] mg CSL312 q4wk in Treatment Period 1 will continue to receive [redacted] mg CSL312 q4wk SC in Treatment Period 2.
- Subjects with C1-INH HAE who received [redacted] mg CSL312 q2wk in Treatment Period 1 will be randomly assigned to receive either [redacted] mg or [redacted] mg CSL312 q4wk SC in a 1:1 ratio in Treatment Period 2.
- Subjects with FXII/PLG HAE will continue to receive [redacted] mg CSL312 q4w SC in Treatment Period 2.

Dose modification details for Treatment Period 2 are presented in Section 5.5. All C1-INH HAE subjects receiving the [redacted] mg dose will have their dose reduced to [redacted] mg q4wk SC at their next scheduled study visit, effective with Amendment 2.

3.1.5 Post-Treatment Follow-up Period

Subjects will attend a Follow-up Visit ~14 weeks after each subject's final treatment period visit; however, the Follow-up Visit may be waived in place of a telephone contact, at the discretion of the investigator.

3.2 Dose and Dosing Regimen

3.2.1 Treatment Period 1

The first 32 subjects with C1-INH HAE who are eligible to participate in Treatment Period 1 will be randomly assigned to receive 1 of the following treatment regimens in a blinded manner:

- A single loading dose of CCI mg CSL312 IV followed ~1 week later by CCI mg CSL312 q4wk SC.
- A single loading dose of CCI mg CSL312 IV followed ~1 week later by CCI mg CSL312 q4wk SC.
- A single loading dose of CCI mg CSL312 IV followed ~1 week later by CCI mg CSL312 q4wk SC.
- A single loading dose of placebo IV followed ~1 week later by placebo q4wk SC.

After the first 32 subjects with C1-INH HAE are randomly assigned to treatment (as above), up to an additional 8 subjects will be assigned in an open-label manner to receive CCI mg CSL312 q2wk SC. CCI [redacted].

Up to 10 eligible subjects with FXII/PLG HAE will be assigned in an open-label manner to receive a loading dose of CCI mg CSL312 IV followed ~1 week later by CCI mg CSL312 q4wk SC.

All IV loading doses of investigational product (ie, CSL312 or placebo) will be administered by the investigator or delegate at the study site. All SC doses of investigational product will be self-administered under supervision of the investigator or delegate at the study site.

Subjects should remain on site for at least 30 minutes after the investigational product is administered.

Dose modification is NOT permitted in Treatment Period 1, and additional details are presented in Section 5.5.

Additional information related to dosing and administration of investigational product is presented in Section 6.2.

3.2.2 Treatment Period 2

C1-INH HAE subjects who continue to participate in Treatment Period 2 will be receiving CSL312 CCI mg or CCI mg q4wk SC at the beginning of Treatment Period 2. Effective with Amendment 2, all C1-INH HAE subjects receiving the CCI mg dose will have their dose reduced to CCI mg q4wk SC at their next scheduled study visit. FXII/PLG HAE subjects will be maintained on the CCI mg q4wk SC dose. The first dose of CSL312 in Treatment Period 2 will be administered at the Week 13 (Day 91) Visit and at the Week 13 (Day 85) Visit for subjects who administer investigational product q4wk and q2wk in Treatment Period 1, respectively. Administration of CSL312 at the Week 13 (Day 85 / 91) Visit, the Week 17 (Day 119) Visit, and the Week 21 (Day 147) Visit will be self-administered under supervision of the investigator or delegate at the study site. After administration of the CSL312 at the Week 21 (Day 147) Visit, all subsequent doses of CSL312 will be self-administered SC every 28 days (± 2 days) by the subject at home or at the study site.

Subjects should remain at the study site for at least 30 minutes after any CSL312 administration that occurs at the study site.

Dose modification details for Treatment Period◦2 are presented in Section 5.5.

Additional information related to dosing and administration of investigational product is presented in Section 6.2.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

The present phase 2 study will evaluate the efficacy, safety, tolerability, and PK profile of multiple subcutaneous administrations of CSL312 across a range of doses in subjects with C1-INH HAE or FXII/PLG HAE. The study consists of a Screening Period to assess subject eligibility, a Run-in Period to assess underlying disease activity, and 2 treatment periods to assess initial and long-term (respectively) safety, tolerability, and efficacy. The data from this study will be used to select dose(s) for a potential phase 3 study.

3.3.2 Dose Rationale

Dose selection was based on the safety, PK and CCI data obtained in the phase 1 single ascending dose study (Study 1001) after administration of single IV and SC doses ranging from 0.1 to 10 mg / kg (7.75 to 1015 mg) in healthy volunteers. The key CCI endpoint used

for dose selection was CCI [redacted] It is hypothesized that inhibiting CCI [redacted] consistently to a particular % target inhibition is expected to provide protection from HAE attacks. The exact % target CCI [redacted] to prevent HAE attacks is unknown and will be evaluated in this study in HAE patients.

A PK / CCI [redacted] model was developed to quantify the relationship between CSL312 plasma concentrations and CCI [redacted] from the IV and SC cohorts in Study 1001. The modeled relationship showed an increase in inhibition of CCI [redacted] with increasing concentrations of CSL312. The IC50 was estimated to be 14.9 µg / mL.

Based on the relationship between CSL312 plasma concentration and CCI [redacted] the % target inhibition levels that were chosen included ≥ 30, ≥ 50, and ≥ 90% (corresponding to doses that would result in inhibition below the IC50, at the inflection point and at the maximum effect of the curve), which would provide information along the entire spectrum of the curve allowing for a robust assessment of doses in this study. Simulations using the final PK / CCI [redacted] model determined that fixed doses of CCI [redacted] mg, CCI [redacted] mg, and CCI [redacted] mg administered every 4 weeks would result in at least 75% of the patients reaching a % target inhibition of CCI [redacted] of ≥ 30, ≥ 50, and ≥ 90%, respectively.

The dosing interval of every 4 weeks was selected based on the calculated half-life of CSL312 of ~19 days in the phase 1 single ascending dose study (Study 1001). The interval between the IV loading dose and the SC maintenance doses was chosen such that the CSL312 plasma trough concentration after the IV loading dose would be within 20% of the trough concentration at steady-state after SC doses given every 4 weeks. The IV route of administration was selected for the loading dose as CSL312 plasma concentrations higher than the trough concentrations observed at steady state after SC doses given every 4 weeks are expected to be achieved instantaneously. The IV loading doses selected for this study are expected to result in exposures that are similar to the exposures after SC doses given the ~50% bioavailability of CSL312 when administered SC based on the results from phase 1 single ascending dose study (Study 1001).

A dose of CCI [redacted] mg q2wk for subjects with C1-INH HAE in the open-label arm of the study was selected to explore a dosing interval of 2 weeks. This dosing regimen was chosen to target a % inhibition of ≥ 90% of the CCI [redacted]

A dose of CCI mg q4wk was selected for subjects with FXII/PLG HAE to provide the maximum potential benefit of treatment with a target of ≥ 90% inhibition of their CCI .

The maximum dose (IV or SC) and the predicted corresponding C_{max} in this study is lower than the highest administered dose (IV or SC) and its corresponding C_{max} observed in the phase 1 study, which were associated with acceptable safety findings.

3.4 Planned Study Duration

The duration of the study for an individual subject who participates in Treatment Period 1 and Treatment Period 2 is up to approximately 83 weeks if the duration of Treatment Period 2 is not extended (see Section 8.5.4.14).

This estimation is based on:

- A Screening Period of up to 4 weeks.
- A Run-in Period of up to 8 weeks.
- A treatment period of ~13 weeks (Treatment Period 1).
- A treatment period of at least ~44 weeks (Treatment Period 2).
- A Follow-up Period of ~14 weeks.

The overall study duration (ie, first subject's Screening Visit to last subject's final visit) is estimated to be 119 weeks, if Treatment Period 2 is not extended (see Section 8.5.4.14). Treatment Period 2 will extend until another CSL312 study is opened for subjects to join, or until the current study is discontinued.

3.5 Planned Number of Subjects

Up to 50 subjects are planned to be assigned to treatment with investigational product in Treatment Period 1, including:

- 8 subjects with C1-INH HAE who will be assigned to receive placebo q4wk.
- 8 subjects with C1-INH HAE who will be assigned to receive CCI mg CSL312 q4wk.
- 8 subjects with C1-INH HAE who will be assigned to receive CCI mg CSL312 q4wk.
- 8 subjects with C1-INH HAE who will be assigned to receive CCI mg CSL312 q4wk.
- Up to 8 subjects with C1-INH HAE who will be assigned to receive CCI mg CSL312 q2wk.

- Up to 10 subjects with FXII/PLG HAE who will be assigned to receive [redacted] mg CSL312 q4wk.

3.6 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) is defined as the date of the last study visit with the last subject at their Follow-up Visit (eg, Week 70 [Day 494] Visit if Treatment Period 2 is not extended [see Section 8.5.4.14]).

3.7 Study Oversight

3.7.1 Independent Data Monitoring Committee

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

3.7.2 Other Monitoring Committees

Not applicable

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 enter the Run-in Period, subjects must meet all of the following inclusion criteria:

1. Provides written informed consent.
2. Male or female.
3. Aged ≥ 18 to ≤ 65 years at the time of providing written informed consent.
4. A diagnosis of C1-INH HAE or FXII/PLG HAE:
   - Clinical diagnosis of C1-INH HAE, based on the following criteria:
     - For C1-INH HAE (type 1):
       - Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria).
       - CCI [redacted] < 50% of the lower limit of the reference range, as documented in the subject's medical record.
       - CCI [redacted] below the lower limit of the reference range, as documented in the subject's medical record.
     - For C1-INH HAE (type 2):
       - Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria).
       - CCI [redacted] < 50% of the lower limit of the reference range, as documented in the subject's medical record.
       - CCI [redacted] below the lower limit of the reference range, as documented in the subject's medical record.
   - Clinical diagnosis of FXII/PLG HAE, based on the following criteria:
     - Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria).
     - An HAE-associated FXII gene mutation (eg, FXII point mutation Thr328Lys or Thr328Arg, or deletion of 72 base pairs [c.971_1018 + 24del72], or duplication of 18 base pairs [c.892-909dup]), as documented in the subject's medical record, **OR** an HAE-associated PLG gene mutation (eg, PLG point mutation Lys330Glu), as documented in the subject's medical record.
     - CCI [redacted] 70 – 120 % of the normal level, as documented in the subject's medical record.

5. For subjects with C1-INH HAE: ≥ 4 HAE attacks over a consecutive 2-month period 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, ≥ 4 HAE attacks may be documented over any consecutive 2-month period during the 3 months before commencing the prophylactic therapy.
6. For subjects with FXII/PLG HAE: ≥ 1 HAE attack 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, 1 HAE attack may be documented during the 3 months before commencing the prophylactic therapy.
7. Willing to cease the use of C1-INH products, androgens or antifibrinolytics for routine prophylaxis against HAE attacks on the first day of the Run-in Period, after being assessed by the investigator to be able to adequately manage on-demand treatments of HAE attacks without assistance. Please see Section 7.3 for guidance.
8. Investigator believes that the subject understands the nature, scope and possible consequences of the study.

4.1.2 Exclusion Criteria for Entry into the Run-in Period

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

1. History of clinically significant arterial or venous thrombosis, or current clinically significant prothrombotic risk (including presence of a central venous access device [CVAD]).
2. History of an uncontrolled, abnormal bleeding event due to a coagulopathy, or a current clinically significant coagulopathy or clinically significant risks for bleeding events.
3. Any pre-planned surgeries during the trial that have an inherent clinically significant risk for thrombotic events or bleeding.
4. Known incurable malignancies at the time of Screening.
5. For subjects with a clinical diagnosis of C1-INH HAE, a clinically significant history of poor response to C1-INH therapy for the management of HAE.
6. Female subjects with C1-INH HAE who started taking or changed dose of any hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen / progesterone containing products) within 3 months before Screening.

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. Any previous treatment with any monoclonal antibody, recombinant protein bearing an Fc domain, ribonucleic acid (RNA) silencing, or gene transfer technologies.
9. Receiving any other therapy not permitted during the study at the time of Screening. **Note:** Prohibited therapies are described in Section 7.3.
10. Male or female subject of childbearing potential either not using or not willing to use a highly-effective method of contraception or not sexually abstinent at any time during Treatment Period 1 or Treatment Period 2 and during the Follow-up Period, or not surgically sterile. **Note:** Childbearing potential and the acceptable methods of contraception are defined in Section 7.4.
11. Intention to become pregnant or to father a child at any time during the study.
12. Pregnant or nursing mother.
13. Known or suspected hypersensitivity to the investigational product or to any excipients of the investigational product.
14. Employee of the study site, or spouse / partner or relative of the investigator or any sub-investigator.
15. Any other issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study.

4.1.3 Criteria for Entry into Treatment Period 1

Subjects will be eligible to exit the Run-in Period and begin Treatment Period 1 if they meet the following criteria:

1. Subject participated in the Run-in Period for at least 4 weeks (28 days).
2. For subjects with C1-INH HAE, confirmation of diagnosis by central laboratory testing:
   - For subjects with C1-INH HAE (type 1):
     - CCI [redacted] < 50% of the lower limit of the reference range.
     - CCI [redacted] below the lower limit of the reference range
   - For subjects with C1-INH HAE (type 2):
     - CCI [redacted] < 50% of the lower limit of the reference range.
     - CCI [redacted] below the lower limit of the reference range.

3. For subjects with C1-INH HAE: the occurrence of ≥ 2 HAE attacks within any consecutive 4-week period during the Run-in Period.
4. For subjects with FXII/PLG HAE: the occurrence of ≥ 1 HAE attack during the Run-in Period.
5. Do not have any clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments performed during Screening. **Note:** Subjects with ≥ 2 times the upper limit of normal for aspartate aminotransferase (AST) and / or alanine aminotransferase (ALT) may be eligible for participation if there is an explanation for this laboratory result and if the results are not clinically significant.

Note: Subjects should enter Treatment Period 1 no later than 14 days after the Week 9 (Day 57) Telephone Contact of the Run-in Period. If a subject is unable to enter Treatment Period 1 within the 14 days after the Week 9 (Day 57) Telephone Contact, then CSL approval is required for the subject to enter into Treatment Period 1.

4.2 Discontinuation of Treatment and / or Subject Withdrawal

4.2.1 Reasons for Discontinuation of Treatment and / or Subject Withdrawal

Subjects may discontinue treatment with investigational product or 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, due to an AE, protocol deviation, loss to follow-up, subject noncompliance, study terminated by CSL).

In accordance with International Conference on Harmonization (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 well-being 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.

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 or discontinuation of treatment with investigational product.

4.2.2 Procedures for Handling Withdrawals

If a subject declines further participation or is withdrawn from the study, attempts will be made to complete and document the assessments scheduled as described in Section 8.5.5.

If the subject is discontinued or withdrawn from the study after receiving investigational product, 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 discontinues or 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.

4.2.3 Replacement Policy

Subjects who discontinue or are withdrawn from the study will not be replaced.

5 Study Interventions

5.1 Description of Investigational Product

5.1.1 CSL312

CSL312 will be supplied ([redacted] mL per vial) as a sterile, preservative-free solution for injection, at pH [redacted] CSL312 is formulated in buffer containing [redacted]

Table 3 Description of CSL312

Substance number	CSL312
Active substance	Factor XIIa antagonist monoclonal antibody
Trade name	Not applicable
Dosage form	Solution for injection
Mode of administration	Intravenous and subcutaneous injection

CSL312 will be manufactured in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

Additional details related to the dosing and administration of the investigational product (ie, CSL312 or placebo) is presented in Section 6.2.

5.1.2 Placebo

The placebo will be supplied ([redacted] mL per vial) as a sterile, preservative-free solution for injection. The placebo is the same as the CSL312 formulation buffer, but does not contain the active substance (ie, factor XIIa antagonist monoclonal antibody).

Table 4 Description of Placebo

Substance number	Not applicable
Substance	Placebo
Trade name	Not applicable
Dosage form	Solution for injection
Mode of administration	Intravenous and subcutaneous injection

The placebo will be manufactured in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

Additional details related to the dosing and administration of the investigational product (ie, CSL312 or placebo) is presented in Section 6.2.

5.1.3 CSL312 Diluent

The CSL312 diluent is identical to placebo (see Section 5.1.2).

5.2 Packaging, Labeling, Supply and Storage

5.2.1 Packaging and Labeling

Investigational product will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines, and national legal requirements.

5.2.2 Supply and Storage

Investigational product will be supplied to the study sites or to a subject's home by CSL or delegate.

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

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

5.3 Accountability and Destruction

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

The unblinded pharmacist or delegate will confirm receipt of all shipments of investigational product (ie, CSL312 and placebo) in the interactive response technology (IRT) system.

All supplies of investigational product must be accounted for throughout the study in the IRT system.

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 unblinded pharmacist or delegate using the appropriate form or the IRT system.

The unblinded pharmacist or delegate must provide reasons for any discrepancies in records of drug accountability.

Any unused vials of investigational product must not be destroyed until the drug accountability documentation has been checked by the study monitor, and any necessary permission for destruction has been given by CSL. Any destruction of investigational product must be documented and certification provided to CSL.

All drug accountability records must be stored in the site file and must be readily available for inspection by the study monitor and / or auditor, and open to regulatory inspection at any time.

Further details regarding accountability and destruction of investigational product are provided in the site investigational product manual.

5.4 On-demand HAE Therapy

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

Subjects may use the on-demand medication of their choice to treat HAE attacks experienced during the study as described in Section 7.2.

5.5 Dose Modification

No modification of dose is planned in Treatment Period 1.

Subjects in Treatment Period 2 at a dose of CCI mg CSL312 q4wk who experience ≥ 3 HAE attacks within an 8-week period are eligible to have their CSL312 dose increased to CCI mg CSL312 q4wk. All CSL312 dose increases will be made in eligible subjects at the discretion of the investigator in consultation with CSL. All C1-INH HAE subjects receiving the CCI mg dose will have their dose reduced to CCI mg q4wk SC at their next scheduled study visit.

6 Allocation, Dosing, and Administration

6.1 Allocation to Treatment

6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number by the IRT. 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.

6.1.2 Randomization Procedures

Randomization will be conducted using an IRT. The investigator will be supplied with a user guide for the IRT. The randomization list will be generated according to the approved randomization specifications. The IRT service provider will keep the randomization code on file.

Treatment Period 1

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

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

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

Subjects with FXII/PLG HAE who are assigned to treatment in Treatment Period 1 will receive [redacted] mg CSL312 q4wk SC.

Treatment Period 1 will be conducted in a blinded manner for C1-INH HAE subjects who receive placebo, [redacted] mg CSL312, [redacted] mg CSL312, or [redacted] mg CSL312 q4wk. Emergency unblinding will be performed in the IRT (Section 6.1.3.2).

Treatment Period 1 will be conducted in an open-label manner for C1-INH HAE subjects who receive [redacted] mg CSL312 q2wk and for FXII/PLG HAE subjects who receive [redacted] mg CSL312 q4wk.

Treatment Period 2

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

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

- Subjects with FXII/PLG HAE will continue to receive [redacted] mg CSL312 q4wk in Treatment Period 2.

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

6.1.3 Blinding Procedures

6.1.3.1 Blinding Method

Treatment Period 1

Treatment Period 1 will be conducted in a blinded manner for subjects with C1-INH HAE who receive placebo, or [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk SC.

- For these treatments, all C1-INH HAE subjects will be blinded to their treatment assignment in Treatment Period 1.
- Except for the unblinded pharmacist or delegate, all investigational site staff (including the investigator) will also be blinded to the treatment assignment of subjects with C1-INH HAE in Treatment Period 1. The unblinded pharmacist or delegate will be responsible for the preparation of the investigational product, but will not administer the investigational product or assess subjects.
- Representatives from CSL and their delegates who have direct interaction with the study sites and / or subjects will be blinded to treatment assignment throughout Treatment Period 1. Adequate procedures are in place to ensure the integrity of the blinded data within CSL for those representatives who are blinded.

In order to maintain the blind, all doses of investigational product administered during Treatment Period 1 will be volume normalized (see Section 6.2). Volume normalization will permit administration of the same volume of investigational product to be administered to each subject, regardless of their treatment assignment.

- The unblinded pharmacist or delegate will dilute the assigned IV loading doses of CSL312 so that each is the same volume for administration as a dose of [redacted] mg CSL312 (ie, [redacted] mL).
- The unblinded pharmacist or delegate will dilute the assigned SC doses of CSL312 so that each is the same volume for administration as a dose of [redacted] mg CSL312 (ie, [redacted] mL).

After preparation of the investigational product and before the investigational product is delivered to the subject for administration, a physical blind (eg, opaque or colored syringe)

will be employed so that other site staff and study subjects are unable to detect any differences between CSL312 or placebo.

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

Treatment Period 1 will be conducted in an open-label manner for subjects with C1-INH HAE who receive CCI mg CSL312 q2wk SC. Investigational product will not be volume normalized for these subjects.

Treatment Period 1 will be conducted in an open-label manner for subjects with FXII/PLG HAE. Investigational product will not be volume normalized for these subjects.

Treatment Period 2

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

6.1.3.2 Breaking the Blind for an Emergency

The randomization code for all or individual subjects may be unblinded to a site using the IRT during the study in emergency situations for reasons of subject safety if knowing treatment assignment will change subject management. Whenever possible, the investigator should consult with the Medical Monitor before unblinding the randomization code. The reason for unblinding the randomization code must be fully documented and the investigator must follow the defined procedures provided in the study manual.

Additional details are presented in the IRT Manual.

6.2 Dosing and Administration

The investigator (or delegate) will only administer or dispense the investigational product to subjects included in this study following the procedures set out in this study protocol.

Table 5 Investigational Product Dosing Characteristics

Investigational product	**CSL312**		**Placebo**	
Route	**Intravenous infusion**	**Subcutaneous injection**	**Intravenous infusion**	**Subcutaneous injection**
Preferred anatomic location for administration	Arm	Abdomen [a]	Arm	Abdomen [a]
Total administration volume, Treatment Period 1	[redacted] mL [b]	[redacted] mL [c]	[redacted] mL [b]	[redacted] mL [c]
Total administration volume, Treatment Period 2	Not applicable	[redacted] mg CSL312 = [redacted] mL; [redacted] mg CSL312 = [redacted] mL	Not applicable	Not applicable
Recommended duration of administration	~ 1 mL / min	Maximum fixed rate of approximately 1 mL / min [d]	~ 1 mL / min	Maximum fixed rate of approximately 1 mL / min [d]

Abbreviations: min = minute

[a] Another anatomic location may be used, at the discretion of the investigator.

[b] In order to maintain the blind, [redacted] mg and [redacted] mg CSL312 will be volume normalized to a total administration volume that is equivalent to a dose of [redacted] mg CSL312.

[c] In order to maintain the blind, [redacted] mg and [redacted] mg CSL312 will be volume normalized to a total administration volume that is equivalent to a dose of [redacted] mg CSL312.

[d] The rate of administration may be adapted to the comfort level of the subject.

Additional information related to the dose and dosing regimen of investigational product is presented in Section 3.2.

Additional information related to modification of the dose of investigational product is presented in Section 5.5.

Additional information related to the volume normalization of investigational product in Treatment Period 1 is presented in Section 6.1.3.1.

Detailed investigational product preparation and administration instructions will be provided in the Investigational Medicinal Product Manual.

6.3 Treatment Compliance

For investigational product that is administered in Treatment Period 1, treatment compliance will be assessed using the administration details entered into the eCRF. For investigational product that is administered in Treatment Period 2, compliance will be assessed using the administration details entered into the eDiary.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

The following are considered contraindications for further administration of the investigational product for an individual subject:

- Anaphylaxis or severe and clinically significant allergic reaction that is causally related to the investigational product active substance or excipients.
- A diagnosis of a TEE (other than superficial thrombophlebitis and catheter-related thromboses), irrespective of causal relationship to the investigational product.
- A clinically significant, abnormal bleeding event, irrespective of causal relationship to the investigational product.
- The subject has been administered a prohibited therapy or has a prohibited change in concomitant therapy, at the discretion of the investigator in consultation with CSL.
- Any event that is considered by the investigator and / or CSL to be serious and clinically significant, and that would suggest significant hazard to the subject following further administration of the investigational product.

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, except those described in Section 7.3.
- Therapies to treat any AEs the subject experiences during the study, including non-prophylactic aspirin (eg, to treat a headache).

For C1-INH HAE subjects, estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) are PERMITTED if taken at a stable dose during the 3 months before Screening with no plans to change the dose during the study.

For FXII/PLG HAE subjects, estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) are PERMITTED without restriction.

The following on-demand HAE therapy is PERMITTED at any time during the study for the treatment of HAE attacks if that medication has previously been shown to be effective and if it 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 pre-procedure prevention of HAE attacks is PERMITTED at any time during the study (not to exceed 1 dose prior to each procedure).

The use of androgens is PERMITTED during the 3 months before the first day of the Run-in Period, but it is preferred that androgens are used only if at a stable dose **OR** if medically indicated for emergent medical conditions during this time.

Routine (long-term) prophylaxis to prevent HAE attacks, including the use of C1-INH products, androgens, or antifibrinolytics is PERMITTED during the Follow-up Period.

7.3 Prohibited Therapies

Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products or antifibrinolytics is PROHIBITED during the Run-in Period and at any time during Treatment Period 1 and/or Treatment Period 2.

The use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) is PROHIBITED during the Run-in Period and at any time during Treatment Period 1 and/or Treatment Period 2.

The following medications / therapies are PROHIBITED during the 3 months before Screening and at any time during the study:

- Angiotensin-converting enzyme (ACE) inhibitors.
- Any anticoagulant or antiplatelet therapy, including low-dose aspirin therapy taken prophylactically.

The use of any investigational drug or device is PROHIBITED during the study and 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.

The use of any therapeutic antibody other than CSL312 is PROHIBITED at any time during the study.

7.4 Lifestyle Restrictions

Subjects receiving investigational product will be provided with a wallet card specifying that their treatment may result in a prolonged CCI test result and that if assessment of CCI is required as a part of medical treatment then the subject's investigator should be contacted. Subjects are expected to carry this wallet card during participation in the study.

Female subjects of childbearing potential and all male subjects must use highly-effective methods of contraception from the first dose of investigational product and at any time during Treatment Period 1 or Treatment Period 2 and during the Follow-up Period.

Childbearing potential is assumed in all female subjects except:

- Female subjects aged > 45 years with amenorrhea for ≥ 12 months without an alternative medical cause.
- Female subjects who are surgically sterile for at least 3 months before providing informed consent.

Acceptable, highly-effective 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.
- Hormonal methods that are associated with inhibition of ovulation if used at a stable dose during the 3 months before Screening with no plans to change dose during the study; acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen / progestin vaginal ring, or contraceptive medication implant.

- Use of intrauterine device (placed more than 3 months before providing informed consent).
- Surgical sterilization (more than 3 months before providing informed consent) of subject or subject's partner.

7.5 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.

See Section 9.6.5 for overdose reporting requirements.

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 following schedules of assessments:

- Schedule of Assessments: Screening and Run-in Period [All Subjects]
- Schedule of Assessments: Treatment Period 1 [C1-INH HAE and FXII/PLG HAE Subjects Receiving Investigational Product Every 4 Weeks]
- Schedule of Assessments: Treatment Period 1 [C1-INH HAE Subjects Receiving Investigational Product Every 2 Weeks]
- Schedule of Assessments: Treatment Period 2 [All Subjects]

More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator.

8.1.1 Demographics and Safety Assessments

The clinical procedures to be conducted during this study related to the evaluation of population demographics and safety are provided in Table 6. All assessments are to be performed at time points as detailed in the schedules of assessments.

Table 6 Study Procedures: Demographics and Safety Assessments

Assessment	Description
Demographics	• Year of birth / age • Sex • Race and ethnicity
Medical history	• Relevant medical history, including HAE attack frequency and HAE diagnosis (C1-INH HAE or FXII/PLG HAE) • Contraception method • Prior (within 6 before Screening) / concomitant medications and therapies
Pregnancy test	• Serum [a] or urine test for Choriogonadotropin Beta (beta-human chorionic gonadotropin), for women of childbearing potential. A serum pregnancy test will be performed by the site if the result from urine testing is inconclusive.
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	• Refer to Section 9.
Vital signs	• Blood pressure (systolic and diastolic) • Respiratory rate • Pulse rate • Temperature • Height and body weight
Urinalysis [a]	• Bilirubin • Occult blood • Erythrocytes • Glucose • Ketones • Leukocyte esterase • Nitrite • pH • Protein • Specific gravity • Urobilinogen
Hematology [a]	• 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 [a]	• Sodium • Potassium • Chloride • Carbon dioxide • Albumin • Alkaline phosphatase (ALP) • Direct Bilirubin • Bilirubin, total • Aspartate aminotransferase (AST) • Protein – total • Calcium • Alanine aminotransferase (ALT) • Creatinine • Phosphate • Blood urea nitrogen (BUN) • Glucose
Coagulation [a]	• CCI • CCI • CCI • CCI • CCI • CCI
Viral serology [a]	• A blood sample will be retained for potential assessment of viral serology
Immunogenicity [a]	• Binding antibodies (inhibitory and non-inhibitory) specific to FXIIa antagonist monoclonal antibody.

Abbreviations: CCI; C1-INH HAE = Hereditary angioedema with C1-esterase inhibitor deficiency; FXIIa = activated factor XII; FXII/PLG HAE = Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE = hereditary angioedema.

Footnotes:

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

[b] CCI will be measured as a part of the coagulation panel for assessment of safety, but will also be analyzed as CCI (Table 7).

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 9.6.4 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 repeated as soon as possible after receiving the laboratory report to rule out laboratory error.

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 CCI Assessments

Pharmacokinetic and CCI analytes to be assessed during the study are provided in Table 7.

Details related to the collection, preparation and transfer of PK / CCI samples will be provided in the laboratory manual.

Table 7 Pharmacokinetic and CCI Analytes

Assessment	Description
Pharmacokinetic evaluations	• CSL312 concentration
CCI **evaluations**	• CCI • CCI • CCI • CCI • CCI • CCI

Abbreviations: CCI; CCI; CCI; CCI; CCI; CCI.

Note: CCI will be measured as a part of the coagulation panel (Table 6) for assessment of safety, but will also be analyzed as CCI.

8.1.3 Efficacy Assessments

At each subject visit, investigators will assess and document the occurrence of HAE attacks based on subject eDiary data. The following information will be documented in the subject eDiary:

- Date and time of HAE symptom onset.
- Date and time of HAE symptom resolution.
- Location of HAE symptom(s).
- Interference of symptom(s) with the subject's daily activities (yes / no).
- On-demand medication used to treat HAE symptoms (yes / no).
- Assistance by a healthcare professional during HAE symptoms (yes / no).
- If medication was needed to treat HAE symptoms:
  - On-demand HAE medication used (Berinert or other on-demand HAE medication [Kalbitor (ecallintide), Firazyr (icatibant), C1-INH other than Berinert, or other]).
  - Dose administered.
  - Date and time started.

8.1.4 Other Assessments

8.1.4.1 CCI

CCI

[redacted]

8.1.4.2 CCI

CCI

[redacted]

8.1.4.3 CCI

CCI

[redacted]

CCI

8.1.4.4 CCI

CCI

8.2 Blood Samples

During the study, blood will be taken from each subject for laboratory safety assessments and PK / CCI 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.

Refer to the Laboratory Manual for details about the collection, storage, handling and processing of blood samples.

8.3 Retention of Samples

Refer to the Laboratory Manual for further details about the collection, storage, and destruction of retention samples.

Retention Sample for Viral Serology

Blood samples for potential future assessment of viral serology will be obtained during Treatment Period 1 and Treatment Period 2. These samples will be shipped to CSL and stored at -70°C for potential testing of viral markers, and will be destroyed within 5 years after completion of the study.

Retention Samples for Non-genetic Testing Related to HAE

Informed consent / assent (as appropriate), independent to that for participating in the study, will be requested from subjects to allow left-over samples of their blood to be retained for up to 5 years after the end of the study for future, non-genetic research related to HAE. This consent / assent will not be valid for future research that involves genetic analysis of the retained samples or research that is unrelated to HAE.

8.4 Prior and Concomitant Medications and Therapies

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.

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 medications and therapies being administered to a subject at the time of the first administration of the investigational product, and which continue to be taken in addition to the investigational product during the study, are regarded as concomitant medications and therapies, and must be documented as such in the eCRF.

8.5 Visit Schedule

8.5.1 Screening / Run-in Period Visits

8.5.1.1 Screening

All subjects 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), and results from such assessments may be used in the determination of study eligibility.

The following procedures will be conducted at Screening:

- Written informed consent.
- Demographics.
- Medical history (including HAE attack frequency and HAE diagnosis).
- Physical examination.
- Vital signs, including height and body weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - CCI.

    Note: If a subject requires the use of on-demand medication to treat an HAE attack within 120 hours (ie, 5 days) 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 CCI (CCI).
- Confirm FXII or PLG mutation, based on the subject's medical record.
- Development of 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.
- Train subject on the use of the eDiary.
- Prior and concomitant medications and therapies.
- Begin to monitor AEs.
- Inclusion / exclusion criteria.

Screen Failure: If a subject is not eligible for entry into the Run-in Period, the primary reason for screen failure must be documented.

Re-screening: If a potential subject is not eligible for entry into the Run-in Period within 28 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). In the event that a potential subject is screened twice, all Screening assessments must be repeated during the second Screening Period, except for confirmation of FXII or PLG gene mutation in subjects with FXII/PLG HAE.

8.5.1.2 Run-in Period

8.5.1.2.1 Week 1 Telephone Contact

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:

- Open subject access to eDiary and review instructions with subject.
- Confirm access to on-demand HAE medication.
- Prior and Concomitant medications and therapies.
- Adverse events.

8.5.1.2.2 Week 3, Week 5, Week 7, and Week 9 Telephone Contacts

The following procedures will be conducted at the Week 3, Week 5, Week 7, and Week 9 Run-in Period Telephone Contacts for all subjects:

- Review eDiary data and assess / document HAE attacks.
- Confirm access to on-demand HAE medication.
- Concomitant medications and therapies
- Adverse Events.

Note 1: Subjects should enter Treatment Period 1 no later than 14 days after the Week 9 Telephone Contact. If a subject is unable to enter Treatment Period 1 within the 14 days after the Week 9 Telephone Contact, then CSL approval is required for the subject to enter into Treatment Period 1.

Note 2: Access to the eDiary should be closed within 14 days after the Week 9 Telephone Contact for subjects who will not participate in Treatment Period 1.

Note 3: Subjects who enter the Run-in Period, but are not eligible to enter Treatment Period 1 are considered screen failures. If a subject is not eligible to enter Treatment Period 1, the primary reason for screen failure must be documented. These subjects may not be re-screened.

8.5.2 Treatment Period 1 for C1-INH HAE and FXII/PLG HAE Subjects Receiving Investigational Product Every 4 Weeks

All subjects should remain at the study site for at least 30 minutes after the administration of investigational product when administered at the study site.

8.5.2.1 Week 1 (Day 1) Visit

The following procedures will be conducted at the Week 1 (Day 1) Visit:

- Confirm eligibility for entry into Treatment Period 1.
- Assignment to treatment with the investigational product.
- Physical examination.
- Vital signs, including weight.
- CCI
- CCI
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Viral serology (retention sample).
  - PK / CCI (pre-dose and 0.5, 4.0, and 8.0 hours post-dose).
  - Immunogenicity.
- Review eDiary instructions with subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.

- Confirm access to on-demand HAE medication.
- Intravenous administration of investigational product by investigator or delegate.
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note 1: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

Note 2: The PK / cci blood draws at 4.0 hours (± 60 minutes) post-dose and 8.0 hours (± 120 minutes) post-dose at the Week 1 (Day 1) Visit should occur ≥ 120 minutes apart.

8.5.2.2 Week 1 (Day 6) Visit

The following procedures will be conducted at the Week 1 (Day 6) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of blood to assess PK / cci
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.2.3 Week 5 (Day 35) Visit

The following procedures will be conducted at the Week 5 (Day 35) Visit:

- Physical examination.

- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / [redacted]
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.2.4 Week 9 (Day 63) Visit

The following procedures will be conducted at the Week 9 (Day 63) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.

- PK / CCI

  Note: The Week 9 (Day 63) and Week 9 (Day 66) Visits and corresponding PK / CCI blood draws should each occur at least 24 hours apart.

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
  Note: For subjects who do not participate in Treatment Period 2, this is the final dose of investigational product.
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.2.5 Week 9 (Day 66) Visit

The following procedures will be conducted at the Week 9 (Day 66) Visit:

- Collection of blood to assess PK / CCI
  Note: The Week 9 (Day 63) and Week 9 (Day 66) Visits and corresponding PK / CCI blood draws should each occur at least 24 hours apart. The Week 9 (Day 66) and Week 10 (Day 70) Visits and corresponding PK / CCI blood draws should each occur at least 72 hours apart.
- Concomitant medications and therapies.
- Adverse events.

8.5.2.6 Week 10 (Day 70) Visit

The following procedures will be conducted at the Week 10 (Day 70) Visit:

- Collection of blood to assess PK / CCI
  Note: The Week 9 (Day 66) and Week 10 (Day 70) Visits and corresponding PK / CCI blood draws should each occur at least 72 hours apart.
- Concomitant medications and therapies.

- Adverse events.

8.5.2.7 Week 11 (Day 77) Visit

The following procedures will be conducted at the Week 11 (Day 77) Visit:

- Collection of blood to assess PK / CCI
- Concomitant medications and therapies.
- Adverse events.

8.5.2.8 Week 12 (Day 84) Visit

The following procedures will be conducted at the Week 12 (Day 84) Visit:

- Collection of blood to assess PK / CCI
- Concomitant medications and therapies.
- Adverse events.

8.5.2.9 Week 13 (Day 91) Visit

The following procedures will be conducted at the Week 13 (Day 91) Visit:

- Physical examination.
- Vital signs, including weight.
- CCI
- CCI
- CCI
- CCI
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Retention Sample for viral serology.
  - PK / CCI

- Immunogenicity.

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Concomitant medications and therapies.
- Adverse events.

Note: For subjects who are taking part in Treatment Period 2, the Week 13 (Day 91) Visit is the first study visit in Treatment Period 2; refer to the Schedule of Events: Treatment Period 2 [All Subjects] and Section 8.5.4. If a subject is discontinued from the study before completing Treatment Period 1, the subject will undergo the assessments scheduled for the Week 13 (Day 91) Visit and then attend the Treatment Period 1 Follow-up Visit ~14 weeks later.

8.5.2.10 Treatment Period 1 Follow-up Visit

Subjects who do not participate in Treatment Period 2 will attend a Follow-up Visit at Week 26 (Day 186 ± 3 days).

The following procedures will be conducted at the Week 26 (Day 186) Treatment Period 1 Follow-up Visit:

- Collection of blood to assess PK / CCI
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Concomitant medications and therapies.
- Adverse events.
- Close eDiary access (for subjects who will not participate in Treatment Period 2).

Note 1: If a subject participates in Treatment Period 2, then the subject will not attend the Treatment Period 1 Follow-up Visit.

Note 2: The Treatment Period 1 Follow-up Visit may be waived in place of a telephone contact. If Treatment Period 1 Follow-up is not conducted as a visit, then the blood draw for assessment of PK / CCI is not required.

8.5.3 Treatment Period 1 for C1-INH HAE Subjects Receiving Investigational Product Every 2 Weeks

All subjects should remain at the study site for at least 30 minutes after the administration of investigational product when administered at the study site.

8.5.3.1 Week 1 (Day 1) Visit

The following procedures will be conducted at the Week 1 (Day 1) Visit:

- Confirm eligibility for entry into Treatment Period 1.
- Assignment to treatment with the investigational product.
- Physical examination.
- Vital signs, including weight.
- CCI
- CCI
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Viral serology (retention sample).
  - PK / CCI
  - Immunogenicity.
- Review eDiary instructions with subject.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.

- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.3.2 Week 3 (Day 15) Visit

The following procedures will be conducted at the Week 3 (Day 15) Visit:

- Collection of blood for PK / [redacted] analysis
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.3.3 Week 5 (Day 29) Visit

The following procedures will be conducted at the Week 5 (Day 29) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.

- PK / [redacted]

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks Confirm access to on-demand HAE medication.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.3.4 Week 7 (Day 43) Visit

The following procedures will be conducted at the Week 7 (Day 43) Visit:

- Collection of blood for PK / [redacted] analysis.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.3.5 Week 9 (Day 57) Visit

The following procedures will be conducted at the Week 9 (Day 57) Visit:

- Physical examination.
- Vital signs, including weight.

- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / [redacted]
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks Confirm access to on-demand HAE medication.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.3.6 Week 10 (Day 64) Visit (Optional)

The following procedures will be conducted at the Week 10 (Day 64) Visit:

- Collection of blood for PK / [redacted] analysis.
- Concomitant medications and therapies.
- Adverse events.

Note: The Week 10 (Day 64) Visit is optional, and blood for PK / [redacted] analysis may be collected off site.

8.5.3.7 Week 11 (Day 71) Visit

The following procedures will be conducted at the Week 11 (Day 71) Visit:

- Collection of blood for PK / [redacted] analysis.

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration of investigational product (SC).
  Note: For subjects who do not participate in Treatment Period 2, this is the final dose of investigational product.
- Accountability of investigational product.
- Concomitant medications and therapies.
- Adverse events.

Note: For subjects who do not participate in Treatment Period 2, this is the final dose of investigational product.

8.5.3.8 Week 12 (Day 77) Visit

The following procedures will be conducted at the Week 12 (Day 77) Visit:

- Collection of blood for PK / CCI analysis.
- Concomitant medications and therapies.
- Adverse events.

Note: Blood for PK / CCI analysis may be collected off-site. If blood is collected off-site, then a study visit is not required.

8.5.3.9 Week 13 (Day 85) Visit

The following procedures will be conducted at the Week 13 (Day 85) Visit:

- Physical examination.
- Vital signs, including weight.
- CCI
- CCI
- CCI
- CCI
- Collection of urine for urinalysis.

- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Viral serology (retention sample).
  - PK / [redacted]
  - Immunogenicity.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Concomitant medications and therapies.
- Adverse events.

Note: For subjects who are taking part in Treatment Period 2, the Week 13 (Day 85) Visit is the first study visit in Treatment Period 2; refer to the Schedule of Events: Treatment Period 2 [All Subjects] and Section 8.5.4. If a subject is discontinued from the study before completing Treatment Period 1, the subject will undergo the assessments scheduled for the Week 13 (Day 85) Visit and then attend the Treatment Period 1 Follow-up Visit ~14 weeks later.

8.5.3.10 Treatment Period 1 Follow-up Visit

Subjects who do not participate in Treatment Period 2 will attend a Follow-up Visit at Week 25 (Day 180 ± 3 days).

The following procedures will be conducted at the Week 25 (Day 180) Treatment Period 1 Follow-up Visit:

- Collection of blood to assess PK / [redacted]
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Concomitant medications and therapies.
- Adverse events.

- Close eDiary access (for subjects who will not participate in Treatment Period 2).

Note 1: If a subject participates in Treatment Period 2, then the subject will not attend the Treatment Period 1 Follow-up Visit.

Note 2: The Treatment Period 1 Follow-up Visit may be waived in place of a telephone contact. If Treatment Period 1 Follow-up is not conducted as a visit, then the blood draw for assessment of PK / CCI is not required.

8.5.4 Treatment Period 2

All subjects should remain at the study site for at least 30 minutes after the administration of investigational product when administered at study visits.

8.5.4.1 Week 13 (Day 85 / 91) Visit

For subjects who are participating in Treatment Period 2, the following procedures will be conducted at the Week 13 (Day 85 / 91) Visit:

- Assignment to treatment with CSL312.
- Physical examination.
- Vital signs, including weight.
- CCI
- CCI
- CCI
- CCI
- Collection of urine for urinalysis
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Viral serology (retention sample).
  - PK / CCI
  - Immunogenicity.

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration CSL312 (SC).
- Dispense CSL312.
- Accountability of CSL312.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.4.2 Week 17 (Day 119) Visit

The following procedures will be conducted at the Week 17 (Day 119) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / [redacted]
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration CSL312 (SC).
- Dispense CSL312.
- Accountability of CSL312.

- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.4.3 Week 21 (Day 147) Visit

The following procedures will be conducted at the Week 21 (Day 147) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / CCI
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Supervise subject self-administration CSL312 (SC).
- Dispense CSL312.
- Accountability of CSL312.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.4.4 Week 25 (Day 175) Activity

The following procedures will be conducted at approximately Week 25 (day 175):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.5 Week 29 (Day 203) Activity

The following procedures will be conducted at approximately Week 29 (Day 203):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.6 Week 33 (Day 231) Visit

The following procedures will be conducted at the Week 33 (Day 231) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - PK / [redacted]
  - Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Dispense CSL312.

- Accountability of CSL312.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.4.7 Week 37 (Day 259) Activity

The following procedures will be conducted at approximately Week 37 (Day 259):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.8 Week 41 (Day 287) Activity

The following procedures will be conducted at approximately Week 41 (Day 287):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.9 Week 45 (Day 315) Visit

The following procedures will be conducted at the Week 45 (Day 315) Visit:

- Physical examination.
- Vital signs, including weight.
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.

- Coagulation.
- PK / [redacted].

- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Dispense CSL312.
- Accountability of CSL312.
- Concomitant medications and therapies.
- Adverse events.

Note: The physical examinations, vital signs, weight measurement, and collection of blood and urine for laboratory assessments must occur before administration of the investigational product.

8.5.4.10 Week 49 (Day 343) Activity

The following procedures will be conducted at approximately Week 49 (Day 343):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.11 Week 53 (Day 371) Activity

The following procedures will be conducted at approximately Week 53 (Day 371):

- The test for beta-human chorionic gonadotropin will be performed for women of childbearing potential (only). A serum or urine pregnancy test may be used. A serum pregnancy test will be performed by the site if urine result is inconclusive. Documentation and tracking of pregnancy testing must be conducted by the site.

8.5.4.12 Week 57 (Day 399) Visit

The following procedures will be conducted at the Week 57 (Day 399) Visit:

- Physical examination.
- Vital signs, including weight.

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Collection of urine for urinalysis.
- Collection of urine or blood for pregnancy test (for women of childbearing potential). A serum pregnancy test will be performed by the site if urine result is inconclusive.
- Collection of blood to assess:
  - Hematology.
  - Biochemistry.
  - Coagulation.
  - Viral serology (retention sample).
  - PK / CCI [redacted].
  - Immunogenicity.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Confirm access to on-demand HAE medication.
- Dispense CSL312 (only if Treatment Period 2 is extended).
- Accountability of CSL312 (only if Treatment Period 2 is extended).
- Concomitant medications and therapies.
- Adverse events.

Note: If a subject is discontinued from the study before completing Treatment Period 2, the subject will undergo the assessments scheduled for the Week 57 (Day 399) Visit in Treatment Period 2, and will then attend the Treatment Period 2 Follow-up Visit ~14 weeks later.

8.5.4.13 Treatment Period 2 Follow-up Visit

The Treatment Period 2 Follow-up Visit will be conducted ~14 weeks after the final visit in Treatment Period 2. If Treatment Period 2 is not extended, then Treatment Period 2 Follow-up will be conducted at the Week 70 (Day 494) Visit.

The following procedures will be conducted at the Treatment Period 2 Follow-up Visit:

- Collection of blood to assess PK / CCI.
- Review eDiary data, including investigator assessment of HAE symptoms and documentation of HAE attacks.
- Concomitant medications and therapies.
- Adverse events.
- Close eDiary access.

Note: The Treatment Period 2 Follow-up Visit may be waived in place of a telephone contact. If Treatment Period 2 Follow-up is not conducted as a visit, then the blood draw for assessment of PK / CCI is not required.

8.5.4.14 Extension of Treatment Period 2

Treatment Period 2 will extend until another CSL312 study is opened for enrollment, or until the current study is discontinued. If Treatment Period 2 is extended, procedures from the Week 45 (Day 315) Visit will be repeated approximately every 12 weeks starting 12 weeks after all listed assessments are completed at the Week 57 (Day 399) Visit. In the instance of an extension of Treatment Period 2, investigational product will be dispensed and accountability of investigational product will be conducted at the Week 57 (Day 399) Visit. If Treatment Period 2 is extended, then all assessments scheduled for the Week 57 (Day 399) Visit will be repeated at each subject's final Treatment Period 2 visit (approximately 4 weeks after the last dose of study treatment). The Follow-up Visit will occur ~14 weeks after each subject's final Treatment Period 2 visit.

8.5.5 Subject Withdrawal / Discontinuation

If a subject declines further participation or is withdrawn from the study for any reason, attempts will be made to complete and document all scheduled assessments:

- Any subjects who discontinue or are withdrawn during the Run-in Period should complete assessments scheduled for the Week 9 Telephone Contact of the Run-in Period.
- C1-INH HAE subjects who received placebo, CCI mg, CCI mg, or CCI mg CSL312 q4wk during Treatment Period 1, and who discontinue or are withdrawn during Treatment Period 1 should complete assessments for the Week 13 (Day 91) Visit of Treatment Period 1, and then attend a Treatment Period 1 Follow-up Visit ~14 weeks later.

- FXII/PLG HAE subjects who discontinue or are withdrawn during Treatment Period 1 should complete assessments for the Week 13 (Day 91) Visit of Treatment Period 1, and then attend a Treatment Period 1 Follow-up Visit ~14 weeks later.
- C1-INH HAE subjects who received [redacted] mg CSL312 q2wk during Treatment Period 1, and who discontinue or are withdrawn during Treatment Period 1 should complete assessments for the Week 13 (Day 85) Visit of Treatment Period 1, and then attend a Treatment Period 1 Follow-up Visit ~14 weeks later.
- Any subjects who discontinue or are withdrawn during Treatment Period 2 should complete assessments for the Week 57 (Day 399) Visit of Treatment Period 2, and then attend a Treatment Period 2 Follow-up Visit ~14 weeks later.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH guidelines, 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.
- 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.

9.1.2 Adverse Event of Special Interest

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

The following events will be considered AEs of special interest:

- Disorders of coagulation:
  - Thromboembolic events (TEEs).
    - 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 in the opinion of the investigator are considered SAEs and should be reported as such. Additionally, any bleeding event not considered abnormal that meets the criteria for an SAE must be reported as an SAE.
- Anaphylaxis.
  - All events of anaphylaxis are considered SAEs and should be reported as such.

9.1.3 Serious Adverse Event

A serious adverse event (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 1 of the above outcomes listed as an SAE criterion.

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

9.2 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 **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to investigational product. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to the investigational product.

The degree of certainty with which an AE is attributed to the 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 the 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 the investigational product, drug withdrawal or reproduced on rechallenge).

9.4 Observation Period for Adverse Events

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

- The Week 9 Telephone Contact for any subject who enters the Run-in Period and does not participate in Treatment Period 1.
- Follow-up at the Week 26 (Day 186) Visit for C1-INH HAE subjects who are assigned to receive placebo, [redacted] mg, [redacted] mg, or [redacted] mg CSL312 q4wk during Treatment Period 1.
- Follow-up at the Week 26 (Day 186) Visit for FXII/PLG HAE subjects who take part in Treatment Period 1.
- Follow-up at the Week 25 (Day 180) Visit for C1-INH HAE subjects who are assigned to receive [redacted] mg CSL312 q2wk during Treatment Period 1.
- Follow-up at the Week 70 (Day 494) Visit for subjects taking part in Treatment Period 1 and Treatment Period 2, if Treatment Period 2 is not extended.

- Follow-up at the Treatment Period 2 Follow-up Visit taking place ~14 weeks (ie, 95 days [± 3 days]) after each subject's final Treatment Period 2 study visit for subjects taking part in Treatment Period 1 and Treatment Period 2, if Treatment Period 2 is extended.

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 to the investigational product, the event must be reported to CSL (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. AEs will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the final study visit, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

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

9.6.2 Adverse Events of Special Interest

In order to guarantee the rapid communication of AESIs from investigator to CSL, information relating to any AESI must be entered into the eCRF within 24 hours.

If an AESI is considered serious, the event must be reported to CSL as described in Section 9.6.3 (Serious Adverse Event Reporting).

9.6.3 Serious Adverse Event Reporting

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 the investigational product, must be entered into the eCRF immediately (within 24 hours of the investigator becoming aware of the event). An assessment of causality to the investigational product must be included.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to the investigational product that meet 1 or more of the seriousness criteria 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 final study visit that is considered to be causally related to the investigational product must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL.**

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number.
- Suspected medicinal product and / or procedure.
- Event term.
- Reporting source identification (Note: the reporting source must be medically qualified).

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) / Independent Ethics Committee (IEC) during the timeframe specified by the IRB / IEC.
- 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.

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 Abnormal Laboratory Values

During Screening, any laboratory values that deviate from the reference ranges and are considered clinically significant by the investigator must be documented on the medical history page of the eCRF.

For laboratory safety parameters, any instances of absolute values being outside the reference range and/or changes at any visit after study start that are considered by the investigator as clinically significant must 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:

- Increases in CCI will not be classified as AEs because CSL312 is expected to cause increase in this parameter.
- 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).

9.6.5 Overdose

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 (eg, volume, location of infusions, infusion rate) of overdose of the investigational product (defined in Section 7.5) 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 must notify the investigator immediately and at any time during the study (see Section 9.4).

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

During the study, CSL must be notified within 5 days of the investigator becoming aware of the pregnancy (by entry of appropriate data into the eCRF).

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to the 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 responsibility to comply with the requirements for IRB / IEC notification. CSL will provide investigators with all details of all SAEs reported to regulatory authorities.

10 Statistics

10.1 Sample Size Estimation

Subjects with C1-INH HAE

Seven subjects assigned to each treatment (Placebo, or CCI mg, CCI mg, or CCI mg CSL312 q4wk) are needed to reach power of ~82% for the comparisons of CCI mg CSL312 q4wk versus placebo q4wk and CCI mg CSL312 q4wk versus placebo q4wk in Treatment Period 1. This is based on the following assumptions:

- The time-normalized number of HAE attacks is 2.9 attacks per month during treatment with placebo. This number was derived from CSL study CSL830_3001, using the lower bound of the distribution-free 95% confidence interval for the median of the first placebo treatment period.
- The time-normalized number of HAE attacks is 0.6 attacks per month during treatment with CCI mg CSL312 q4wk or CCI mg CSL312 q4wk. The number was derived from CSL study CSL830_3001, using the upper bound of the distribution-free 95% confidence interval for the median of the combined active treatment periods.
- Alpha is 2.5% for each of the 2 two-sided Mann-Whitney Tests of CCI mg CSL312 q4wk or CCI mg CSL312 q4wk against placebo.

CCI [redacted]. The sample size of 7 subjects for this arm is not driven by an efficacy comparison, but instead, by consistency with other treatment arms and for maintenance of blinding of the study. No testing for efficacy of the CCI mg CSL312 dose against placebo is planned and no power calculation has been done. An additional subject may be added to each of these 4 treatment arms to account for drop outs during Treatment Period 1, resulting in 8 subjects in each treatment arm.

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

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

Subjects with FXII/PLG HAE

Up to 10 subjects with FXII/PLG HAE will take part in the study.

10.2 Description of Study Analysis Populations

10.2.1 Screening Population

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

10.2.2 Intent-to-Treat Population

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

10.2.3 Per Protocol Population

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

10.2.4 Safety Population

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

10.2.5 Pharmacokinetic Population

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

10.2.6 CCI [redacted]

CCI [redacted]

10.3 Statistical Analyses and Methods

The data from Treatment Period 1 and Treatment Period 2 will be analyzed separately.

In addition, Treatment Period 1 and Treatment Period 2 will be analyzed together for subjects who are being continuously administered the same dose of CSL312 in both treatment periods, unless otherwise specified. For C1-INH subjects having a dose reduction from CCI mg to CCI mg in Treatment Period 2, only data until the date and time of the dose reduction will be included.

Subjects with C1-INH HAE who are treated with placebo or CCI mg, CCI mg, or CCI mg CSL312 q4wk will be analyzed separately from subjects with C1-INH HAE who are treated with CCI mg CSL312 q2wk. Subjects with FXII/PLG HAE will be analyzed separately from subjects with C1-INH HAE.

Subject disposition will be summarized using all Subjects. Demographic and subject characteristics will be summarized using the ITT and PP populations. Safety data will be summarized using the Safety population. The primary efficacy endpoint will be summarized using the ITT and PP populations. CCI [redacted]. Pharmacokinetic data will be summarized using the PK population. CCI [redacted]

Continuous variables will be described by using mean values with their respective 95% confidence intervals (CI); standard deviation; 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 CCI data. The geometric mean and its respective 90% CI will be calculated for PK and CCI 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, study site, subject, time point, and item number (if applicable).

The evaluation periods for assessment of efficacy will be:

- **The Run-in Period (all subjects):** From Week 1 (Day 1) of the Run-in Period until the date / time of the first administration of investigational product in Treatment Period 1 (ie, at the Week 1 [Day 1] Visit of Treatment Period 1).
- **Treatment Period 1 (subjects who receive an IV loading dose of investigational product and who participate in Treatment Period 2):** From the date / time of the first SC administration of investigational product in Treatment Period 1 (ie, at the Week 1 [Day 6] Visit) until the date / time of the first administration of investigational product in Treatment Period 2 (ie, at the Week 13 [Day 91] Visit).
- **Treatment Period 1 (subjects who receive an IV loading dose of investigational product and who do NOT participate in Treatment Period 2):** From the date / time of the first SC administration of investigational product in Treatment Period 1 (ie, at the Week 1 [Day 6] Visit) until the Week 13 (Day 91) Visit date and time.
- **Treatment Period 1 (CCI [redacted]):** From the date / time of the second SC administration of investigational product in Treatment Period 1 (ie, at the Week 3 [Day 15] Visit) until the date / time of the first administration of investigational product in Treatment Period 2 (ie, at the Week 13 [Day 85] Visit).
- **Treatment Period 1 (CCI [redacted]):** From the date / time of the second SC administration of investigational product in Treatment Period 1 (ie, at the Week 3 [Day 15] Visit) until the Week 13 (Day 85) Visit date and time.
- **Treatment Period 2 (subjects assigned to CCI mg):** From the date / time of the third administration of investigational product in Treatment Period 2 (ie, at the Week 21 [Day 147] Visit) until the Week 57 (Day 399) Visit date and time.
- **Treatment Period 2 (subjects assigned to CCI mg):**
  - From the date / time of the third administration of investigational product in Treatment Period 2 (ie, at the Week 21 [Day 147] Visit) until the Week 57 (Day 399) Visit date and time OR time point of planned switch to CCI mg (per protocol Amendment 2), whatever occurs first OR
  - From the date / time of planned switch to CCI mg (per protocol Amendment 2) until the Week 57 (Day 399) Visit date and time.

The evaluation period for assessment of efficacy in Treatment Period 2 will be extended to the subject's final Treatment Period 2 visit for subjects who are in the Extended Treatment Period 2.

Hereditary angioedema attacks with a start date between the first and second administrations of the investigational product in Treatment Period 1 will not be included in the analyses of efficacy, but will be presented in a listing (only).

A complete description of the statistical analyses and methods will be available in a statistical analysis plan (SAP). The SAP will be finalized within 2 months after the first subject is entered into the Run-in Period.

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

The following will be presented in summary tables for all subjects who have provided informed consent / assent (as appropriate) by treatment and overall:

- The number of subjects who provide informed consent.
- The number of subjects who undergo Screening.
- The number of subjects who enter the Run-in Period.
- The number of subjects who are not assigned to treatment.
- The number of subjects who are assigned to treatment in Treatment Period 1.
- The number of subjects who are assigned to treatment in Treatment Period 2.
- The number of subjects who have a dose reduction from cci mg to cci mg in Treatment Period 2 (per protocol Amendment 2).
- The number of subjects who complete Treatment Period 1.
- The number of subjects who complete Treatment Period 2.
- The number of subjects who completed the study.
- The number of subjects who discontinued participation in the study (overall and for Treatment Period 1 and Treatment Period 2; including the reason for discontinuation).

The number of subjects in each analysis population will be summarized by treatment and overall.

Subjects with C1-INH HAE and subjects with FXII/PLG HAE will be presented combined and separately.

Reasons for discontinuations / withdrawals will be listed by subject.

10.3.1.2 Subject Characteristics

All demographic and subject characteristics will be summarized by treatment and overall for the ITT Population and Per Protocol Population. These will include:

- Demographics (age, sex, race, ethnicity, height, body weight, body mass index).
- Medical history.
- HAE history (including confirmation of HAE diagnosis, identification of HAE type, and number of HAE attacks in the 3 months before Screening).

10.3.2 Efficacy Analyses

10.3.2.1 Primary Efficacy Analysis

10.3.2.1.1 The Primary Analysis

The primary endpoint (time-normalized number of HAE attacks) will be analyzed using the ITT and PP Populations. The ITT population will be used for the primary analysis and the PP will be used as the secondary analysis.

The evaluation periods for efficacy, including for the time-normalized number of HAE attacks are specified in Section 10.3. For the primary analysis, only the efficacy period for Treatment Period 1 and subjects with q4wk dosing, as defined in Section 10.3, is applicable.

Subjects are to enter HAE symptoms into their eDiary. HAE attacks are based upon review of patient diaries and review of relevant interim medical history by the investigator, including hospital / medical records and any information provided by the subject. Using medical judgment, the investigator is to determine the occurrence of an HAE attack.

The time-normalized number of HAE attacks per month during treatment 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 for Treatment Period 1 as: [the date / time of the first SC dose of investigational product in Treatment Period 2 – the date / time of the first SC dose of investigational product in Treatment Period 1].

The time-normalized number of HAE attacks will be summarized descriptively by median (primary) and mean (secondary) with corresponding 95% CIs by treatment (ie, placebo, or CCI mg, CCI mg, or CCI mg CSL312 q4wk).

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

To account for multiple testing, the alpha level of 5% will be evenly split between the hypotheses tested. Therefore, the CCI mg CSL312 q4wk or CCI mg CSL312 q4wk CSL312 doses (in subjects with C1-INH HAE) will each be evaluated against placebo at alpha = 0.025 for each test:

H01: a1 = 0 vs H11: a1 ≠ 0

and

H02: a2 = 0 vs H12: a2 ≠ 0

In the above hypotheses, the term "a1" is the shift between the 2 distributions of CCI mg CSL312 q4wk and placebo and the term "a2" is the shift between the distributions of CCI mg CSL312 q4wk and placebo, respectively.

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

There will be no testing of the of CCI mg CSL312 q2wk dose against placebo for subjects with C1-INH HAE or the CCI mg CSL312 q4wk dose against placebo for subjects with FXII/PLG HAE.

10.3.2.1.2 Supportive Analyses

The primary endpoint (the time-normalized number of HAE attacks) will also be summarized descriptively for the CCI mg CSL312 q2wk regimen (for subjects with C1-INH HAE) and the CCI mg CSL312 q4wk regimen (for subjects with FXII/PLG HAE) for the evaluation period of Treatment Period 1.

The primary endpoint will also be summarized descriptively for the CSL312 q4wk regimens for the following (see Section 10.3):

- Treatment Period 2 evaluation period (alone).
- Treatment Period 1 and Treatment Period 2 evaluation periods (combined).

For the difference in the primary endpoint between the 2 treatments CCI mg and CCI mg CSL312 q4wk in Treatment Period 1, a comparison will be performed as an CCI [redacted] using a two-sided Mann Whitney test at alpha = 0.05: [H01: a3 = 0 vs H11: a3 ≠ 0] (CCI mg tested against CCI mg CSL312 q4wk) where the term "a3" is the shift in the 2 distributions of the 2 CSL312 doses compared against each other.

CCI [redacted].

There will be no testing of the of CCI mg CSL312 q2wk dose for subjects with C1-INH HAE or the CCI mg CSL312 q4wk dose against placebo for subjects with FXII/PLG HAE.

10.3.2.2 Secondary Efficacy Analyses

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

Subjects with C1-INH HAE who are treated with placebo or CCI mg, CCI mg, or CCI mg CSL312 q4wk, will be analyzed separately from subject with C1-INH HAE who are treated with CCI mg q2wk. Subjects with FXII/PLG HAE will be analyzed separately from subjects with C1-INH HAE.

The number and percentage of responders and non-responders will be presented by treatment and for all CSL312 doses combined with corresponding 95% CI. A subject is classified as a responder if the percentage reduction in HAE attacks is ≥ 50%. The percentage reduction in the time-normalized number of HAE attacks per subject is calculated within a subject as: 100% * [1 – (the time-normalized number of HAE attacks with CSL312 per month) / (the time-normalized number of HAE attacks per month during the Run-in Period)].

CCI [redacted]

The number and percentage of subjects who do not experience an HAE attack will be presented by treatment and for all CSL312 doses combined. Additionally, the median time, the 25th percentile of time, and the 75th percentile of time of the subjects being attack-free will be calculated for each treatment.

The total number and percentage of mild, moderate, or severe HAE attacks as well as the time-normalized number per month will be presented by treatment. The number of subjects having at least 1 mild, moderate, or severe HAE attacks will also be presented.

The number, the time-normalized number, and the percentage of treated and untreated attacks overall and by severity will be presented by treatment. The above will also be presented as rate per month. A treated HAE attack will be defined as a treatment-emergent HAE attack during which on-demand medication to treat HAE attacks was taken. The number and percentage of subjects with at least 1 treated attack, the number and percentage of subjects with only treated attacks, the number and percentage of subjects with attacks but without treated attacks, and the number and percentage of subjects with no attacks at all will be presented by treatment. These analyses will be repeated including moderate or severe attacks only. The above will also be presented as rate per month.

10.3.3 Safety Analyses

AEs with a start date and time on or after the first injection date and time of investigational product are considered treatment-emergent AEs. AEs with missing or partial start date or time will also be considered treatment-emergent following the worst case principle, unless the partial date clearly indicates that the AE started before first injection date and time.

Adverse events with a start date occurring after administration of IV investigational product and occurring before the first administration of SC investigational product will be analyzed separately from AEs with a start date occurring after the first administration of SC investigational product.

Only treatment-emergent AEs will be included in analyses, 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 system organ class (SOC) and preferred term.
- Incidence of subjects with SAEs by SOC and preferred term.
- Incidence of subjects with AEs by severity and SOC and preferred term.
- Incidence of subjects with AEs by relationship to investigational product and SOC and preferred term.
- Incidence of subjects with AEs leading to discontinuation by SOC and preferred term.
- Incidence of subjects with TEEs by SOC and preferred term.
- Incidence of subjects with bleeding events by SOC and preferred term.
- Incidence of subjects with anaphylaxis by SOC and preferred term.
- 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.

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, preferred term, and treatment.

Summaries of ISRs will be presented by treatment and also by MedDRA System Organ Class and Preferred Term, 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 adverse event. 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 deaths will be listed.

10.3.4 Pharmacokinetic Analyses

PK parameters for CSL312 in plasma will be derived using non-compartmental analyses, and will include:

- Maximum concentration (C_{max}).
- Time to reach C_{max} in plasma (T_{max}).
- Area under the concentration-time curve in 1 dosing interval ($AUC_{0\text{-}tau}$).
- Total systemic clearance (CL_{tot}).
- Apparent clearance (CL/F).
- Apparent volume of distribution (Vd/F).
- Volume of distribution during the elimination phase (Vz).
- Terminal elimination half-life ($T_{1/2}$).

All PK values will be listed by individual subject and summarized descriptively by time point and treatment.

10.3.5 CCI

CCI

10.3.6 Pharmacokinetic / CCI Relationships

Additional PK / CCI analyses may be conducted, and the relevant details will be provided in the SAP.

10.3.7 Other Analyses

Analyses of CCI will be described in the SAP.

10.3.8 Interim Analysis

An interim analysis of data from Treatment Period 1 will be conducted after all C1-INH HAE subjects who received placebo or CCI mg, CCI mg, CCI mg CSL312 q4wk complete Treatment Period 1.

An interim analysis of data from subjects with FXII/PLG HAE will be conducted after subjects with FXII/PLG HAE complete Treatment Period 1.

Additional interim analyses may be conducted, as outlined in the SAP.

Additional details regarding planned interim analyses will be provided in supporting documents (eg, SAP, IDMC charter).

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 regulatory authority (eg, United States Food and Drug Administration). Regulatory 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 a Food and Drug Administration Investigational New Drug application and will be documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this 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 protocol and informed consent forms (ICFs) must be submitted 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.

12.3 Subject Information and Informed Consent

Informed consent of study subjects according to the standards of GCP 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 must be given ample opportunity to inquire about details of the study.

The subject must be provided with a copy of the signed informed consent form.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), then 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 regulatory 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 Agreement for the study (see Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Agreement

This study will be conducted under a Clinical Trial 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 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 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 study protocol registration record.

13.3 Implementation of the Protocol / Protocol Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed 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 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 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.

13.4 Protocol Deviations

All instances where the requirements of the 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. 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 the investigational product and 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 who takes part in 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 who take part 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 who takes part in the study and signed by the investigator (or delegate).

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 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 regulatory 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 in writing. If the study is suspended or terminated for safety reasons, then all investigators and the relevant regulatory agencies will be immediately notified of the action, as well as the reason for the suspension / termination. The investigator 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, if applicable, a nominated coordinating investigator (or delegate). In this case, it is required by CSL 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.

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15 Appendices

Appendix 1 Signature on Behalf of Sponsor

Study Title:	A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with hereditary angioedema
Protocol Number:	CSL312_2001

I have read the Clinical Study Protocol titled "A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with hereditary angioedema" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

PPD

PPD

Date

Appendix 2 Signature of Principal Investigator

Study Title:	A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with hereditary angioedema
Protocol Number:	CSL312_2001 **Site Number:**

I have read the Clinical Study Protocol titled "A multicenter, randomized, placebo-controlled, parallel-arm study to investigate the efficacy, pharmacokinetics, and safety of CSL312 in subjects with 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 Behring and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

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

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

Signature Page

CSL312_2001 - Protocol Amendment - 2 - 20Mar2020

Signed By	Date (GMT)
PPD	25-Mar-2020 15:19:13
Approved-PPD Approval	
PPD	25-Mar-2020 17:02:23
Approved-Clinical Safety Physician Approval	
PPD	25-Mar-2020 17:34:15
Approved-PPD Approval	

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