



CLINICAL STUDY PROTOCOL

An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema

Country-Specific Protocol Amendment No. 1 (United States)

Study Number:	CSL830_3002
Study Product:	CSL830
Development Phase:	3b
Sponsor:	CSL Behring GmbH (CSL) Emil-von-Behring-Strasse 76 35041 Marburg Germany
Protocol Version:	Country-Specific Amendment No. 1 (United States)
EudraCT Number:	2014-001054-42
IND Number:	CCI
Protocol Date:	10 July 2015
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.

This protocol includes information and data that contain trade secrets and privileged or confidential information that is the property of the sponsor (“CSL”). This information must not be made public without written permission from CSL. These restrictions on disclosure will apply equally to all future information supplied to you. This material may be disclosed to and used by your staff and associates as may be necessary to conduct the clinical study.

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.

Signature on Behalf of Sponsor

Study Title: An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.

Protocol Number: CSL830_3002

I have read the protocol titled “An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema” and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD
PPD

PPD

Date PPD
(DD MMM YYYY)

Signature of Investigator

Study Title: An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.

Protocol Number: CSL830_3002

I have read the protocol titled “An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.”

By signing this 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 protocol, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), and applicable regulatory requirements.

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

I will ensure that study staff fully understand and follow the protocol.

Name of investigator
Affiliation of investigator

Date
(DD MMM YYYY)

Protocol Synopsis

Title	An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema
Study Number	CSL830_3002
Sponsor	CSL Behring GmbH (CSL)
Development Phase	3b
Study Product	CSL830
Indication	Hereditary Angioedema (Type I and II)
Study Summary	<p>This is a multicenter, randomized, open-label, parallel-arm, phase 3b study designed to investigate the clinical safety and efficacy of subcutaneously administered CSL830 in the prophylactic treatment of hereditary angioedema (HAE). The study will consist of 2 treatment periods. Treatment Period 1 (24 weeks) will be a fixed-dose period. Treatment Period 2 (28 weeks) will be a dose-adjustment period to allow for individual optimization of prophylaxis. Subjects from the United States who complete Treatment Period 2 will be allowed to participate in an Extension Period to continue to receive treatment with open-label CSL830.</p> <p>Subjects belonging to the following categories will undergo assessment at a Screening Visit in order to confirm their eligibility:</p> <ul style="list-style-type: none"> • “CSL830-Naïve” Subjects (subjects who did not participate in study CSL830_3001; subjects who participated in study CSL830_3001 but did not receive blinded investigational product). • “CSL830-Interrupted” Subjects (subjects who completed participation in study CSL830_3001, but who delayed entry into the current study [ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1]). <p>Subjects belonging to the following category will not have a Screening Visit:</p> <ul style="list-style-type: none"> • “CSL830-Continuation” Subjects (subjects who complete participation in study CSL830_3001 and who continue directly on to participate in the current study [ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1]). <p>The eligibility of “CSL830-Continuation” Subjects will include</p>

evaluation based upon assessments performed in CSL830_3001 (see additional details in the protocol body).

Treatment Period 1 will begin with the Day 1 Visit and will end with the Week 25 Visit. Treatment Period 2 will begin *either* during the Week 25 Visit (if CSL830 is administered at the study visit) *or* immediately following the Week 25 Visit. Treatment Period 2 will end with the Week 53 Visit.

Eligible subjects will be randomized to 1 of the following CSL830 treatment groups at the first visit in Treatment Period 1:

- 40 IU/kg CSL830 treatment group, **OR**
- 60 IU/kg CSL830 treatment group.

CSL830 will be administered as a single subcutaneous injection twice weekly either independently (ie, self-administered by the subject) or with assistance (ie, with the help of a caretaker such as a parent or guardian) at home during Treatment Period 1 and Treatment Period 2. Treatment will be administered in an open-label manner.

During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, ≥ 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. Dose increases during Treatment Period 1 are intended as rescue prophylaxis, to provide the opportunity for subjects who have very frequent HAE attacks to continue in the study during this otherwise fixed-dose treatment period.

Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. Dose increases during Treatment Period 2 are intended to allow investigators to adjust/optimize the dose for subjects who may need a higher dose for prophylaxis.

An evaluation period for any dose increase in either Treatment Period 1 or Treatment Period 2 is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830).

Subjects will attend a Follow-up Visit occurring 14 days (\pm 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit. During the Follow-up Period, subjects will be followed for HAE attacks, the emergence of new adverse events (AEs), and the use of concomitant medication.

Primary Objective(s) The primary objective is to assess the clinical safety of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.

Primary Endpoint(s) The primary endpoints are the person-time incidence rates of each of the following:

- Adverse events leading to premature study discontinuation.
- Thromboembolic events (TEEs).
- Anaphylaxis.
- HAE attacks resulting in in-patient hospitalization (where hospitalization is the consequence of the need for emergent medical care).
- Solicited AEs (injection site reactions at the CSL830 injection site) graded as severe by the investigator.
- Related serious adverse events (SAEs), other than events specified above.
- Anti-C1-INH (anti-C1-esterase inhibitor) antibodies (inhibitory or non-inhibitory).

The person-time incidence rates are the number of subjects experiencing each primary endpoint safety event during treatment with CSL830, divided by the sum of each subject's time at risk.

The primary endpoints will be assessed for Treatment Period 1, Treatment Period 2 and Treatment Periods 1 and 2 together. The primary endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

Secondary Objective(s) The secondary objectives are the following:

1. To further characterize the clinical safety of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.
2. To characterize the clinical efficacy of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.

**Secondary
Endpoint(s)**

1. The secondary safety endpoints are the following:
 - a) The percentage of subjects experiencing the following events: SAEs, temporally-related AEs, increased risk scores for deep vein thrombosis (DVT) or pulmonary embolism (PE), TEEs, inhibitory anti-C1-INH antibodies, or clinically significant abnormalities in laboratory assessments (ie, lab abnormalities reported as AEs).
 - b) The percentage of administrations of CSL830 resulting in solicited local AEs (discomfort [eg, pain, burning], swelling, bruising, or itching at the CSL830 injection site).
 - c) The percentage of subjects who have at least 1 solicited local AE (discomfort [eg, pain, burning], swelling, bruising, or itching at the CSL830 injection site).
 - d) The percentage of subjects who become seropositive for human immunodeficiency virus types 1 or 2 (HIV-1/-2), hepatitis B virus (HBV), or hepatitis C virus (HCV).

The secondary safety endpoints will be assessed for Treatment Period 1, Treatment Period 2, and Treatment Periods 1 and 2 (together). The secondary safety endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

2. Efficacy endpoints considered as secondary include the following:
 - a) The percentage of subjects who experience a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.
 - b) The percentage of subjects who are responders. "Response" is defined as a $\geq 50\%$ relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks that is used to qualify the subject for participation in the study.

The secondary efficacy endpoints will be assessed for Treatment Period 1, and Treatment Periods 1 and 2 (together). The secondary efficacy endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

**Exploratory
Objective(s)**

CCI
[Redacted text]

**Exploratory
Endpoint(s)**

CCI
[Redacted text]

CCI
[Redacted text block]

Study Design Multicenter, randomized, open-label, parallel-arm, phase 3b study

Number of Subjects The study plans to enroll subjects who complete participation in CSL830_3001. Additional subjects who have not participated in study CSL830_3001 will be enrolled so that the total number of subjects randomized is approximately 110.

Assuming that up to 10% of subjects withdraw before the completion of the study, 100 subjects are planned to complete the study.

Subjects from the United States who have completed Treatment Period 1 and Treatment Period 2 are eligible to enroll in the Extension Period. Approximately 50 of these subjects are anticipated to enroll in the Extension Period.

Study Duration **Treatment Period 1 and Treatment Period 2**
The duration of the study for an individual subject is expected to be up to 58 weeks. This estimation is based on:

- A Screening Period lasting up to 4 weeks (≤ 28 days), as needed.
- Two treatment periods totaling 52 weeks (367 days \pm 2 days).
- A Follow-up Period lasting 2 weeks (14 days \pm 3 days).

Extension Period (Optional)

The Extension Period (88 weeks) followed by the Extension Period follow-up (2 weeks) will begin at first subject first visit in the Extension Period and result in an anticipated total study duration of up to approximately 146 weeks for participating subjects. Subjects who have any Extension Period visits that occur within 6 weeks before the study end date will be handled as completers. These subjects will attend the final study visit (Extension Period Week 88) in place of their next study visit or telephone contact and will receive follow-up telephone contact (Extension Period Week 90 \pm 3 days). Subjects who roll-over into the Extension Period prior to the Treatment Period 2 Follow-up Visit will be regarded as completers. All subjects who are not withdrawn from the study will be considered completers of the study.

Study Population and Main Criteria for Eligibility**Subjects must meet all of the following inclusion criteria in order to be enrolled (randomized) into the study:**

- Male or female.
- Aged 6 years or older at the time of providing written informed consent/assent (as appropriate).
- A diagnosis of HAE type I or II, as determined by the following: a clinical history consistent with HAE *and* C1-INH functional activity levels $< 50\%$, concurrent with C4 antigen concentrations below normal limits. **NOTE:** Additional details on the application of this criterion to “CSL830-Continuation/-Interrupted/-Naïve” Subjects are presented in the protocol body.
- Have experienced HAE attacks (requiring acute treatment, medical attention or causing significant functional impairment), as described below:
 - For “CSL830 Naïve” Subjects:
 - “CSL830-Naïve” Subjects using intravenous C1-INH as routine (long-term) prophylaxis against HAE attacks must have experienced 4 HAE attacks over *any* consecutive 2-month period before the initiation of intravenous C1-INH prophylaxis and before the CSL830_3002 Screening Visit, as documented in the subject medical records.
 - All other “CSL830-Naïve” Subjects (eg, treated using oral HAE prophylaxis against HAE attacks or on-demand

treatment) must have experienced 4 HAE attacks over a consecutive 2-month period within the 3 months before the CSL830_3002 Screening Visit, as documented in the subject medical records.

- For “CSL830-Continuation” Subjects AND “CSL830-Interrupted” Subjects: Subjects must have experienced 4 HAE attacks over a consecutive 2-month period within the 3 months before the CSL830_3001 Screening Visit, as documented in the subject medical records (ie, the HAE attack frequency required for eligibility to participate in study CSL830_3001).
- For subjects who have used oral medication for prophylaxis against HAE attacks (ie, androgens, tranexamic acid, progestins) during the 3 months before the first study visit: use of a *stable* regimen of oral prophylactic medication (ie, dose and administration frequency) during the 3 months before the first study visit and willingness to continue the stable regimen for at least 25 weeks.

Subjects meeting any of the following exclusion criteria must not be enrolled (randomized) into the study:

- Known incurable malignancies at the time of the first study visit.
- Any clinical condition that is likely to interfere with evaluation of CSL830 or satisfactory conduct of the study.
- A clinically significant history of poor response to C1-INH therapy for the management of HAE.
- A suspected or confirmed diagnosis of acquired HAE or HAE with normal C1-INH (ie, HAE type III).
- Assessed by the investigator as unable to have their HAE adequately managed pharmacologically with on-demand treatment, when that on-demand treatment is administered independently or with assistance.

Study Product Dose, Dosing Regimen and Administration

CSL830 is a C1-INH concentrate, which is a volume-reduced formulation of the marketed product, Berinert, currently licensed for the acute treatment of HAE attacks. CSL830 is a lyophilized powder (1500 IU C1-INH per single-use vial) reconstituted with 3 mL water for injection.

During Treatment Periods 1 and 2, subjects who do not increase their dose of CSL830 will administer CSL830 (40 IU/kg or 60 IU/kg, per randomization) via a single SC injection, twice weekly. During Treatment Periods 1 and 2, the actual dose of CSL830 that is assigned will be rounded up to the nearest 500 IU,

as this corresponds with a practical volume of 1 mL of CSL830. During the Extension Period, the actual dose of CSL830 that is assigned will be rounded (ie, up *or* down) to the nearest 1000 IU for subjects weighing ≥ 40 kg; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU).

Subjects who are randomized to treatment with 40 IU/kg CSL830 may undergo up to 2 independent 20 IU/kg dose increases, for a maximum final dose of 80 IU/kg. Subjects who are randomized to treatment with 60 IU/kg CSL830 may undergo a single 20 IU/kg dose increase, for a maximum final dose of 80 IU/kg. All dose increases will be made in eligible subjects only and at the discretion of investigator.

40 IU/kg CSL830 is equivalent to a volume of 0.08 mL/kg;
60 IU/kg CSL830 is equivalent to a volume of 0.12 mL/kg;
80 IU/kg CSL830 is equivalent to a volume of 0.16 mL/kg.

During the Extension Period, each subject will continue to be eligible for dose escalation in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for Treatment Period 2 (see above).

Efficacy Assessments

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Safety Assessments

The safety of CSL830 for the long-term prophylactic treatment of HAE will be assessed based on the following:

- Vital signs.
- Physical examination.
- Clinical scores of risk assessment for DVT and PE.

- Solicited local AEs (injection site reactions).
- Other AEs, including SAEs.
- Clinical laboratory assessments:
 - Hematology, biochemistry and coagulation profiles.
 - Viral serology.
 - Anti-C1-INH antibodies.
 - Urinalysis.

Pharmacokinetics

CCI [Redacted]

Pharmacodynamics

CCI [Redacted]

Other Assessments

CCI [Redacted]

Statistical Analyses

Continuous variables will be described using mean with the relevant 95% confidence intervals (CI); geometric mean and the relevant 90% CI; standard deviation; range; 25th, 50th (median), and 75th percentiles; geometric coefficient of variation expressed as a percentage (applicable to PK and PD data only); and counts of missing and non-missing values. Categorical values will be described using counts and percentages.

Safety Analyses

Treatment Period 1 and Treatment Period 2

Safety analyses will be performed by treatment group (ie, by subjects who are randomized to 40 IU/kg CSL830 and by subjects who are randomized to 60 IU/kg CSL830). Data collected from those subjects will be included in the 40 IU/kg and 60 IU/kg CSL830 treatment groups, respectively, until the time they undergo the final study visit or undergo a CSL830 dose increase, whichever comes first.

A secondary safety analysis will be performed by treatment group [ie, by subjects who are randomized to 40 IU/kg CSL830 and by subjects who are randomized to 60 IU/kg CSL830, regardless of any dose increase(s)]. Data collected from those subjects will be included in the 40 IU/kg and 60 IU/kg CSL830 treatment groups,

respectively, until the time they undergo the final study visit.

The analyses will be done both for Treatment Period 1 (only) and for Treatment Period 1 and 2 (together), unless otherwise noted.

Furthermore, safety analyses will be summarized by subjects who are randomized to 40 IU/kg CSL830 and who have 1 dose increase; by subjects who are randomized to 40 IU/kg CSL830 and who have 2 dose increases; by subjects who are randomized to 60 IU/kg CSL830 and who have 1 dose increase. These dosing groups will be given separately for Treatment Periods 1 and 2, depending if the dose increase takes place in Treatment Period 1 or 2.

The person-time incidence rate of each primary endpoint safety event will be assessed as primary safety analysis, as defined above and overall.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). Serious AEs, temporally-related AEs, increased risk scores for DVT or PE, thromboembolic events, inhibitory anti-C1-INH antibodies, or clinically significant abnormalities in laboratory assessments occurring during treatment will be summarized for the safety analyses.

Extension Period

Data collected during the Extension Period will be summarized as follows:

- For the Extension Period only (separate from data collected during Treatment Period 1 and Treatment Period 2 using descriptive statistics.)
- For Treatment Period 1, Treatment Period 2 and the Extension Period (combined)

Only data collected from subjects who are enrolled the Extension Period will be included in these analyses.

Interim Analyses

Interim analyses will be conducted on an as-needed basis in order to support regulatory activities. The results of interim analyses are not intended to be used to stop or adapt the study. Additional details will be provided in the statistical analysis plan (SAP).

Schedule of Events for “CSL830-Continuation” Subjects ^A

	Treatment Period 1 ^{B, C}							Treatment Period 2 ^C							Follow-up ^D	
	Week	1	5	9	13	17	21	25	29	33	37	41	45	49		53
	Day	1	29	57	85	113	141	169	197	225	253	281	309	337		367
Window (days)		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	
Study center visit	X		X		X		X	X		X		X		X	X	
Telephone contact		X		X		X			X		X		X			
Informed Consent / Assent (as applicable) ^E	X															
Inclusion / exclusion criteria	X															
Individual acute action plan ^F	X															
Enrollment and randomization	X															
Demographics and medical history ^G	X															
Physical examination	X ^H		X				X	X		X					X	
Indwelling catheter (yes/no)	X														X	
Vital signs, including body weight	X ^H		X		X		X	X		X		X		X	X	
Height	X															
Assess risk of DVT and PE	X ^H		X		X		X	X		X		X		X		
CCI							X								X	
CCI	X		X				X	X		X					X	
Clinical Laboratory Assessments ^I	X		X				X	X		X					X	
Dispense CSL830 / other supplies	X		X		X		X	X		X		X				
Confirm access to on-demand HAE medication	X		X		X		X	X		X		X		X		
Assess for CSL830 dose increase		←—————→ ^K						←—————→ ^L								
Train subject / observe CSL830 admin ^J	X															
CSL830 accountability	X		X		X		X	X		X		X		X		
Prior and concomitant therapy	←—————→															
Adverse events	←—————→															
Dispense eDiary	X															
Review eDiary / record attacks in eCRF			X		X		X	X		X		X		X	X	

	Treatment Period 1 ^{B, C}							Treatment Period 2 ^C							Follow-up ^D
Week	1	5	9	13	17	21	25	29	33	37	41	45	49	53	See Footnote D.
Day	1	29	57	85	113	141	169	197	225	253	281	309	337	367	
Window (days)		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	
Collect eDiary															X ^M
Schedule next visit / contact	X		X		X		X	X		X		X		X	

[Abbreviations and footnotes are presented on the following page.]

Abbreviations used in the Schedule of Events for “CSL830-Continuation” Subjects:

DVT = deep vein thrombosis; eCRF = electronic case report form; eDiary = electronic diary; CCI

; HAE = hereditary angioedema; CCI ; PE =

pulmonary embolism; CCI

Notes to the Schedule of Events for “CSL830-Continuation” Subjects:

- A:** “CSL830-Continuation” Subjects are subjects who complete participation in study CSL830_3001 and who continue directly on to participate in the current study (ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).
- B:** “CSL830-Continuation” Subjects:
- Must meet the eligibility criteria presented in [Section 4.1.2](#) and [Section 4.1.3](#) in order to participate in CSL830_3002.
 - May use the results of assessments conducted in CSL830_3001 in order to support the assessment of CSL830_3002 eligibility, as described in [Section 8.4.3.1](#).
 - Should schedule the final study visit of CSL830_3001 on the same day as the Day 1 Visit of CSL830_3002 Treatment Period 1, where possible.
- C:** During Treatment Periods 1 and 2, subjects will administer CSL830 twice per week (eg, Monday and Thursday of each week) independently or with assistance; the final administration of CSL830 should occur prior to the Week 53 Visit in Treatment Period 2.
- D:** Subjects will attend a Follow-up Visit occurring 14 days (± 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit.
- E:** Written informed consent/assent (as appropriate) must be provided before any study-specific assessments or procedures are performed.
- F:** The investigator should create/update the individual acute action plan, as appropriate, and review with the subject on Day 1 of Treatment Period 1.
- G:** Demographics and clinically significant medical history will be updated (as needed) to provide a complete CSL830_3002 subject record.
- H:** If these assessments were conducted at the CSL830_3001 End of Study Visit, then they do not need to be repeated on Day 1 of Treatment Period 1.
- I:** The clinical laboratory assessments to be conducted are presented in the [Schedule of Events for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects](#).
- J:** CSL830 injection technique and dosing regimen, and use of eDiary will be reviewed with each subject; the administration of CSL830 will be observed.
- K:** During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, ≥ 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.

- L:** Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.
- M:** The subject eDiary will not be collected from subjects at the last visit of Treatment Period 2 (Follow-up Visit) if they plan to participate in the Extension Period.

Schedule of Laboratory Assessments for “CSL830-Continuation” Subjects ^A

	Treatment Period 1							Treatment Period 2							Follow-up ^B
Week	1	5	9	13	17	21	25	29	33	37	41	45	49	53	See Footnote B.
Day	1	29	57	85	113	141	169	197	225	253	281	309	337	367	
Window (days)		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	
Study center visit	X		X		X		X	X		X		X		X	X
Telephone contact		X		X		X			X		X		X		
Blood samples: • Hematology • Biochemistry • Coagulation	X ^C		X				X	X		X				X	
CCI	X ^D		X				X	X		X				X	
Blood sample for anti-C1-INH antibody	X ^C						X							X	
Blood sample for viral serology	X ^C						X							X	
Urine sample for urinalysis	X ^C		X				X	X		X				X	
Urine sample for pregnancy test ^E	X		X				X			X				X	

C1-INH = C1-esterase inhibitor; CCI [redacted]; CCI [redacted].

Notes to the Schedule of Laboratory Assessments for “CSL830-Continuation” Subjects:

- A:** “CSL830-Continuation” Subjects are subjects who complete participation in study CSL830_3001 and who continue directly on to participate in the current study (ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).
- B:** Subjects will attend a Follow-up Visit occurring 14 days (± 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit.
- C:** If these assessments are or have been conducted at the CSL830_3001 End of Study Visit, then they do not need to be repeated here.
- D:** CCI [redacted]

E: The urine test for beta-human chorionic gonadotropin will be performed at the study site. All females are to be tested to assess eligibility prior to randomization and dosing. A urine pregnancy test will be conducted to assess eligibility ONLY if the CSL830_3001 End of Study Visit and the first visit of CSL830_3002 Treatment Period 1 (ie, Day 1) occur on different days.

Schedule of Events for “CSL830-Interrupted” Subjects ^A and “CSL830-Naïve” Subjects ^B

	Screening ^C	Treatment Period 1 ^D							Treatment Period 2 ^D							Follow-up ^E	
Week	-4 to -1	1	5	9	13	17	21	25	29	33	37	41	45	49	53	See Footnote E.	
Day	-28 to -1	1	4	29	57	85	113	141	169	197	225	253	281	309	337		367
Window (days)		+ 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2		
Study center visit	X	X	X ^F		X		X		X	X		X		X		X	
Telephone contact				X		X		X			X		X		X		
Informed Consent / Assent (as applicable) ^G	X																
Inclusion / exclusion criteria	X	X															
Individual acute action plan ^H	X	X															
Monitor / Document HAE Attacks ^I	X																
Enrollment and randomization		X															
Demographics and medical history	X																
Physical examination	X				X				X	X		X				X	
Indwelling catheter (yes/no)	X															X	
Vital signs, including body weight ^J	X				X		X		X	X		X		X		X	
Assess risk of DVT and PE	X				X		X		X	X		X		X		X	
CCI									X							X	
CCI		X			X				X	X		X				X	
Clinical Laboratory Assessments ^K	X	X			X				X	X		X				X	
Dispense CSL830 / other supplies			X		X		X		X	X		X		X			
Confirm access to on-demand HAE med	X	X	X		X		X		X	X		X		X		X	
Assess for CSL830 dose increase			← ^M							← ^N							
Train subject / observe CSL830 admin ^L		X	X														
CSL830 accountability		X	X		X		X		X	X		X		X		X	
Prior and concomitant therapy	←																
Adverse events	←																
Dispense eDiary		X															
Review eDiary / record attacks in eCRF			X		X		X		X	X		X		X		X	
Collect eDiary																X ^O	
Schedule next visit / contact	X	X	X		X		X		X	X		X		X		X	

[Abbreviations and footnotes are presented on the following page.]

Abbreviations used in the Schedule of Events for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects:

DVT = deep vein thrombosis; eCRF = electronic case report form; eDiary = electronic diary; CCI
; HAE = hereditary angioedema; CCI ; med = medication; PE = pulmonary embolism; CCI

Notes to the Schedule of Events for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects:

- A:** “CSL830-Interrupted” Subjects are subjects who completed participation in study CSL830_3001, but who delayed entry into the current study (ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).
- B:** “CSL830-Naïve” Subjects include the following:
- Subjects who did not participate in study CSL830_3001;
 - Subjects who participated in study CSL830_3001 but did not receive blinded investigational product as part of that study.
- C:** The Screening Visit and the Day 1 Visit of Treatment Period 1 can occur on the same day. If a subject fails Screening at a combined Screening Visit / Day 1 Visit, then the subject will be treated as a screen failure.
- D:** During Treatment Periods 1 and 2, subjects will administer CSL830 twice per week (eg, Monday and Thursday of each week) independently or with assistance; the final administration of CSL830 should occur prior to the Week 53 Visit in Treatment Period 2.
- E:** Subjects will attend a Follow-up Visit occurring 14 days (\pm 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit.
- F:** The Day 4 Visit may be waived for “CSL830-Interrupted” Subjects (only) if the investigator has confirmed that the subject can adequately treat themselves with CSL830 (ie, no further training is necessary). In this case, all activities scheduled for the Day 4 visit may be conducted at the Day 1 Visit.
- G:** Written informed consent/assent (as appropriate) must be provided before any study-specific assessments or procedures are performed.
- H:** The investigator should create/update the individual acute action plan, as appropriate, and review with the subject on Day 1 of Treatment Period 1.
- I:** Beginning after the Screening Visit until Day 1 of Treatment Period 1, HAE attacks should be monitored and documented independently of the eDiary.
- J:** Height will be collected at the Screening Visit, only.
- K:** The clinical laboratory assessments to be conducted are presented in the [Schedule of Events for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects](#).
- L:** CSL830 injection technique and dosing regimen, and use of eDiary will be reviewed with each subject; the administration of CSL830 will be observed.
- M:** During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, \geq 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.
- N:** Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience \geq 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.

O: The subject eDiary will not be collected from subjects at the last visit of Treatment Period 2 (Follow-up Visit) if they plan to participate in the Extension Period.

Schedule of Laboratory Assessments for “CSL830-Interrupted” Subjects ^A and “CSL830-Naïve” Subjects ^B

	Screening	Treatment Period 1								Treatment Period 2						Follow-up ^C	
Week	-4 to -1	1	5	9	13	17	21	25	29	33	37	41	45	49	53	See Footnote C.	
Day	-28 to -1	1	4	29	57	85	113	141	169	197	225	253	281	309	337		367
Window (days)		+ 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2		± 2
Study center visit	X	X	X		X		X		X	X		X		X		X	X
Telephone contact				X		X		X			X		X		X		
Blood samples: • Hematology • Biochemistry • Coagulation		X			X				X	X		X					X
CCI [REDACTED]	X ^E	X			X				X	X		X					X
Blood sample for anti-C1-INH antibody		X							X								X
Blood sample for viral serology		X							X								X
Urine sample for urinalysis		X			X				X	X		X					X
Urine sample for pregnancy test ^D		X			X				X			X					X

C1-INH = C1-esterase inhibitor; CCI [REDACTED]; [REDACTED].

Notes to the Schedule of Laboratory Assessments for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects:

- A:** “CSL830-Interrupted” Subjects are subjects who completed participation in study CSL830_3001, but who delayed entry into the current study (ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1)
- B:** “CSL830-Naïve” Subjects include the following:
 - Subjects who did not participate in study CSL830_3001;
 - Subjects who participated in study CSL830_3001 but did not receive blinded investigational product as part of that study.
- C:** Subjects will attend a Follow-up Visit occurring 14 days (± 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit.
- D:** The urine test for beta-human chorionic gonadotropin will be performed at the study site. All females are to be tested to assess eligibility prior to randomization and dosing.

E: CCI



Visit / Contact #	1 ^A	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 ^B	Follow-up ^C
Extension Period Week	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	88	90
Extension Period Day	1	43	85	127	169	211	253	295	337	379	421	463	505	547	589	617	631
Window (days)	+ 30 ^D	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 3
Review eDiary / record attacks in eCRF ¹	X ^E		X		X		X		X		X		X		X	X	
Collect eDiary																X	
Schedule next visit / contact	X		X		X		X		X		X		X		X	X	
		6		22			46			70							
		26				50				74							

Abbreviations used in the Schedule of Events for the Extension Period:

C1-INH = C1-esterase inhibitor; DVT = deep vein thrombosis; eCRF = electronic case report form; eDiary = electronic diary; CCI [redacted];
 CCI [redacted]; HAE = hereditary angioedema; CCI [redacted];
 IU = international units; med = medication; CCI [redacted]; PE = pulmonary embolism; CCI [redacted];
 CCI [redacted]

[Footnotes are presented on the following page.]

Notes to the Schedule of Events for the Extension Period:

- A:** This is the first visit of the Extension Period; the last visit of Treatment Period 2 and the first visit of the Extension Period should occur on the same day, when possible (however, subjects can elect to take a rest period of up to 30 days between the final visit of Treatment Period 2 and the first visit of the Extension Period).
- B:** This is the last on-site visit of Extension Period.
- C:** This is the Extension Period Follow-up Contact. Subjects will attend a Follow-up Visit occurring 14 days (\pm 3 days) after the final visit in the Extension Period or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn.
- D:** Visit 1 of the Extension Period can occur within 30 days after the last visit of Treatment Period 2.
- E:** To be repeated at Extension Period Visit 1 only if the Final Visit of Treatment Period 2 and Extension Period Visit 1 are conducted on different days.
- F:** The subject will be advised to resume usual medical care upon completion of the study.
- G:** Starting with the Extension Period Visit 1, the subject's CSL830 by-weight dose will be rounded to the nearest (ie, up *or* down) 1000 IU for subject weighing \geq 40 kg; subjects weighing $<$ 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU).
- H:** Beginning with the Extension Period Visit 1 and throughout the Extension Period, subjects who experience \geq 3 HAE attacks (as determined per protocol) within an 8 week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). See [Section 3.2](#) for additional details.
- I:** The subject diary will not be collected from subjects at the last visit of Treatment Period 2 (Follow-up Visit) if they plan to participate in the Extension Period. For subjects who elect to take a rest period between Treatment Period 2 and the Extension Period, the diary will not be used after the already planned Treatment Period 2 follow-up period (approximately 2 weeks); however, information for the period during which no diary is in use will be recorded (see [Section 8.4.6.1.2](#) for additional details). The subject diary will only be used at the first visit of the Extension Period.
- J:** The Quality of Life Questionnaire for Patients with Recurrent Swelling Episodes (AE Quality of Life) will be self-administered and assessed by the subjects at Weeks 6, 22, 46 and 70 of the Extension Period.
- K:** The Hereditary Angioedema Quality of Life Questionnaire (HAE Quality of Life) will be self-administered and assessed by the subjects at Weeks 26, 50 and 74 of the Extension Period.

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List of Abbreviations

Abbreviation	Definition
ACS	Abnormal, clinically significant
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
C1-INH	C1-esterase inhibitor
CSL	CSL Behring GmbH
DVT	Deep vein thrombosis
eCRF	Electronic case report form
eDiary	Electronic diary
F1 + 2	Prothrombin fragments 1 and 2
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
CCI	CCI
HAE	Hereditary Angioedema
HIV	Human immunodeficiency virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICH	International Conference on Harmonisation
ICF	Informed consent form
IEC	Independent ethics committee
CCI	CCI
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent to Treat
IU	International unit
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
C	CCI
PE	Pulmonary embolism
PEF	Peak expiratory flow
C	CCI
PP	Per-protocol

Abbreviation	Definition
CCI	CCI
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
CCI	CCI
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
CCI	CCI
U	Unit
VAS	Visual analog scale
CCI	CCI

1 Introduction

1.1 Background

Hereditary angioedema (HAE) is a rare genetic disorder with 3 known types (I, II, and III) [Rosen et al 1965; Bork et al 2000]. Type I and II HAE are autosomal dominant inherited disorders, which are associated with a deficiency in C1-esterase inhibitor (C1-INH) [Donaldson and Evans 1963]. In type I HAE (common form genotype), an impaired synthesis of a normal and functionally active C1-INH molecule occurs [Rosen et al 1965]. This causes a reduction in the availability of functionally active C1-INH levels to between 6% and 25% of normal [Rosen et al 1965]. In type II HAE (variant form genotype), normal levels of a functionally impaired C1-INH molecule are synthesized, but the normal form of C1-INH is considerably reduced in the circulation. Type III HAE is even less frequent and is not associated with C1-INH deficiency [Bork et al 2000]. The prevalence of type I and II HAE is estimated to be in the order of 1:50,000 [Göring et al 1998, Kunschak et al 1998], with approximately 85% of subjects having type I HAE and approximately 15% of subjects having type II HAE [Longhurst and Bork 2006].

HAE is a debilitating disease and subjects with frequent attacks are severely affected in their quality of life. Clinically, type I and II HAE are characterized by local subcutaneous (SC) / submucosal swellings of the skin (ie, edema of the extremities, facial edema, and edema of the genitals), abdominal pain attacks, and, rarely, life-threatening attacks of laryngeal edema [Bork 2008]. Attacks typically follow a course in which the edema increases for 24 to 36 hours and then slowly decreases during the following 48 to 72 hours [Zuraw 2008].

Treatment for type I and II HAE can be subdivided into the acute treatment of attacks and prophylaxis. The treatment of choice in the event of an HAE attack is the rapid replacement of the functionally missing plasma protein (ie, by intravenous [IV] administration of C1-INH concentrate or fresh frozen plasma) [Bork 2008, Gompels et al 2005, Longhurst 2005]. Recently, compounds including a kallikrein inhibitor and a bradykinin receptor antagonist have been added to the spectrum of anti-HAE medications [Cicardi et al 2010a, Cicardi et al 2010b]. Attenuated androgens or antifibrinolytics are effective in some subjects as prophylactic therapy, but may have significant side effects [Banerji et al 2008, Göring et al 1998]. Regular IV infusions of C1-INH can also be used for HAE prophylaxis [Zuraw et al 2010]. However, repeated IV administration may not be practical for all patients, and IV access can become progressively more difficult with time.

A more convenient route of administration (eg, SC) may facilitate the use of C1-INH in HAE prophylaxis. The pharmacokinetics (PK) of subcutaneously administered C1-INH in patients with HAE have been investigated using a currently available formulation [[Martinez-Saguer et al 2013](#)]. The study examined 1000 units (U) of C1-INH, in a volume of 20 mL, administered intravenously or subcutaneously; subcutaneously administered C1-INH had a bioavailability of approximately 40%, and was generally well tolerated [[Martinez-Saguer et al 2013](#)].

To further enhance the feasibility of SC administration of C1-INH, CSL830 has been developed as a human plasma-derived C1-INH concentrate that can be reconstituted in a low volume. CSL830 is being investigated for the prevention of HAE attacks.

1.2 Background Information on CSL830

1.2.1 Overview

CSL830, which is a C1-INH concentrate, is a volume-reduced formulation of the marketed product, Berinert. Berinert is currently licensed for the acute treatment of HAE attacks in more than 30 countries. The manufacturing process of CSL830 is almost identical to that of Berinert. The major difference between these 2 products is the concentration of C1-INH after reconstitution; CSL830 contains 1500 IU of C1-INH to be reconstituted in 3 mL whereas Berinert contains 500 IU of C1-INH to be reconstituted in 10 mL.

1.2.2 Nonclinical Evaluation

Berinert has been assessed in nonclinical evaluations. Berinert was well tolerated and no toxicity was observed in single-dose toxicity studies in rats and mice and a repeat dose toxicity study in rats. Information on nonclinical safety studies conducted with Berinert is available in the European Summary of Product Characteristics for Berinert and in the US Prescribing Information.

Because CSL830 has a higher local protein concentration compared with Berinert, 2 nonclinical local tolerance studies with CSL830 have been conducted in rabbits. In these 2 nonclinical studies, administration of a single injection of CSL830 (3 mL; IV, SC, intra-arterial, and intramuscular injection) revealed no findings of clinical significance and was locally well tolerated.

1.2.3 Previous Clinical Experience

Currently, clinical data are available from two studies that were conducted with CSL830: study CSL830_1001 and study CSL830_2001.

Study CSL830_1001 was conducted in healthy subjects in order to compare the safety and PK of intravenously administered CSL830 and Berinert (the currently marketed C1-INH concentrate). CSL830 had acceptable safety and local tolerability profiles. There were no adverse events (AEs) causally related to CSL830 or Berinert, and there were no clinically significant abnormalities in laboratory parameters, viral safety assessments, vital signs, physical examinations, or electrocardiogram results. No anti-C1-INH antibodies were detected in any subject. There were no thromboembolic events (TEEs), and no surrogate markers suggestive of pulmonary embolism (PE) or deep vein thrombosis (DVT) were identified. CSL830 and Berinert also had comparable PK profiles following single-dose, IV administration.

Study CSL830_2001 was conducted in subjects with HAE (type I or II) in order to characterize the PK, pharmacodynamics (PD), and safety of SC administration. Functional levels of C1-INH activity and levels of C1-INH antigen and C4 antigen were achieved with each CSL830 dosing regimen that was tested. Subcutaneous administration of CSL830 of up to 6,000 IU was tolerated with local site events. Safety events were not related to either absolute CSL830 dose or dose per body weight. There was no evidence of a dose-response relationship between the administered dose of CSL830 and the intensity of treatment-emergent adverse events (TEAEs). Inhibitory auto- antibodies to C1-INH did not develop in any of the subjects in the study. Further, there were no TEEs.

The efficacy and safety of SC CSL830 are currently being assessed in a double-blind, randomized, placebo-controlled, crossover phase 3 study (study identifier CSL830_3001) that is enrolling at least 80 subjects with HAE. During participation in CSL830_3001 subjects are randomly assigned to either a 40 IU/kg CSL830 or 60 IU/kg CSL830 treatment sequence. Each sequence consists of 2 consecutive treatment periods. Each subject receives the assigned dose of CSL830 in 1 treatment period and placebo in the other treatment period. Subjects who participate in study CSL830_3001 will be eligible to participate in this long-term safety study if they meet all eligibility criteria (see [Section 4.1](#)).

1.3 Study Overview

This is a multicenter, randomized, open-label, parallel-arm, phase 3b study to investigate the clinical safety and efficacy of subcutaneously administered CSL830 in the prophylactic treatment of HAE. [Section 3](#) presents a detailed overview of the study design and other supporting information.

1.4 Potential Risks and Benefits

Potential for Virus Transmission

CSL830 contains human plasma-derived C1-INH and, therefore, has the potential for virus transmission to recipients. However, CSL830 has a high margin of virus safety. The risk of virus transmission is minimized by stringent donor selection and screening criteria, and by reducing enveloped and non-enveloped viruses using pasteurization, nanofiltration methods, and chromatography [De Serres et al 2003].

During study CSL830_2001 (see [Section 1.2.3](#)), no new viral infections were detected in subjects who received CSL830. No changes in serology results for HIV (human immunodeficiency virus), hepatitis A virus, HBV (hepatitis B virus), HCV (hepatitis C virus) were observed from baseline to study exit.

During this 12-month safety study, evidence of potential viral transmission will be collected as part of the safety evaluations.

Immunogenicity or Anaphylactic-type Reactions

Immunologic or anaphylactic-type reactions have been rarely reported with the use of C1-INH. Antibodies against C1-INH have been identified in patients with HAE, irrespective of whether they have received C1-INH. However, the presence of antibodies against C1-INH does not appear to inhibit the activity of C1-INH [data on file at CSL; [Farkas et al 2007](#)].

The immunogenicity of CSL830 was examined as a part of study CSL830_2001 (see [Section 1.2.3](#)). C1-INH antibodies were detected for 7/18 subjects during that study; however, the presence of C1-INH antibodies was not associated with inhibition of C1-INH activity. There was no apparent relationship between the dose of CSL830 administered and the presence of C1-INH antibodies.

The development of immune reactions to CSL830 will be monitored in this study, and will include testing for and characterization of (eg, idiotyping) anti-C1-INH antibodies.

Thromboembolic Events

Thromboembolic events have been occasionally reported following the use of C1-INH, especially in patients receiving off-label high doses of up to 500 U/kg IV in the setting of cardiac surgery and extracorporeal circulation. At the recommended IV doses, a causal relationship between TEEs and the use of C1-INH has not been established.

During study CSL830_2001 (see [Section 1.2.3](#)) no TEEs were reported. Further, no subject treated with CSL830 was considered to be at risk for DVT, when assessed using a clinical model scoring system.

TEEs including DVT and PE will be monitored during this study (see [Section 8.1.2](#)).

Local Tolerance

Because of the SC route of administration and the high protein concentration of CSL830, transient local reactions may occur at CSL830 injection sites.

During study CSL830_2001, a small proportion of subjects administered CSL830 experienced local administration site reactions. The reactions were mostly mild to moderate in intensity, most resolved within 3 days.

Local reactions will be documented as part of the safety evaluation during this study.

Efficacy

Intravenous C1-INH has been demonstrated to be effective in the prevention of HAE attacks [[Zuraw et al 2010](#)]. However, the efficacy of SC C1-INH for prophylaxis of HAE attacks has not been established, but is under evaluation as a part of the pivotal study CSL830_3001 (see [Section 1.2.3](#)). As such, throughout the current study, eligible subjects will be permitted to use medication for the treatment of breakthrough HAE attacks.

Overview

This clinical study may contribute to the development of a new therapy to effectively manage HAE. Given the low probability of potential risks and the study procedures that will closely monitor the safety of study subjects, the associated risk-benefit assessment of the study is acceptable for subjects enrolled in the study.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

The primary objective is to assess the clinical safety of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.

2.1.2 Primary Endpoints

The primary endpoints are the person-time incidence rates of each of the following:

- Adverse events leading to premature study discontinuation.
- Thromboembolic events.
- Anaphylaxis.
- HAE attacks resulting in in-patient hospitalization (where hospitalization is the consequence of the need for emergent medical care).
- Solicited AEs (injection site reactions at the CSL830 injection site) graded as severe by the investigator.
- Related serious adverse events (SAEs), other than events specified above.
- Anti-C1-INH antibodies (inhibitory or non-inhibitory).

The person-time incidence rates are the number of subjects experiencing each primary endpoint safety event during treatment with CSL830, divided by the sum of each subject's time at risk.

The primary endpoints will be assessed for Treatment Period 1, Treatment Period 2 and Treatment Periods 1 and 2 (together). The primary endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives are the following:

1. To further characterize the clinical safety of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.
2. To characterize the clinical efficacy of subcutaneously administered CSL830 in the long-term prophylactic treatment of HAE.

2.2.2 Secondary Endpoints

1. The secondary safety endpoints are the following:
 - a. The percentage of subjects experiencing the following events: SAEs, temporally-related AEs, increased risk scores for DVT or PE, TEEs, inhibitory anti-C1-INH antibodies, or clinically significant abnormalities in laboratory assessments (ie, lab abnormalities reported as AEs).
 - b. The percentage of administrations of CSL830 resulting in solicited local AEs (discomfort [eg, pain, burning], swelling, bruising, or itching at the CSL830 injection site).
 - c. The percentage of subjects who have at least 1 solicited local AE (discomfort [eg, pain, burning], swelling, bruising, or itching at the CSL830 injection site).
 - d. The percentage of subjects who become seropositive for HIV-1/-2, HBV, or HCV.

The secondary safety endpoints will be assessed for Treatment Period 1, Treatment Period 2 and Treatment Periods 1 and 2 (together). The secondary safety endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

2. Efficacy endpoints considered as secondary include the following:
 - a. The percentage of subjects who experience a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.
 - b. The percentage of subjects who are responders. “Response” is defined as a $\geq 50\%$ relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks that is used to qualify the subject for participation in this study (see [Section 4.1.2](#) [inclusion criterion 5]).

The secondary efficacy endpoints will be assessed for Treatment Period 1, and Treatment Periods 1 and 2 (together). The secondary efficacy endpoints will also be assessed for the Extension Period (only) and for the treatment periods overall for subjects who are included in the Extension Period.

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

2.3.2 Exploratory Endpoints

CCI [Redacted]

[Redacted]

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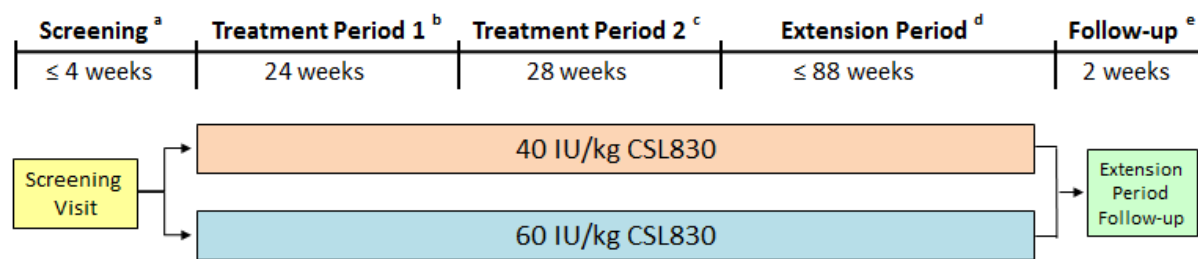
[Redacted]

3 Study Design

3.1 Study Design and Rationale

This is a multicenter, randomized, open-label, parallel-arm, phase 3b study designed to investigate the clinical safety and efficacy of subcutaneously administered CSL830 in the prophylactic treatment of HAE. An overview of the study is depicted in Figure 1.

Figure 1: Study Overview



Footnotes to Figure 1:

- ^a “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects will participate in a Screening Visit in order to confirm their eligibility. “CSL830-Continuation” Subjects will not be required to participate in a Screening Visit. Instead, data from study CSL830_3001 will be used to confirm their eligibility (see [Section 8.4.3.1](#)). **NOTE:** The definitions for “CSL830-Continuation” Subjects, “CSL830-Interrupted” Subjects, and “CSL830-Naïve” Subjects are presented in [Section 4.1.1](#).
- ^b During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, ≥ 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.
- ^c Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details.
- ^d For subjects (from the United States) enrolled in the Extension Period, their CSL830 dose will be escalated in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for Treatment Period 2 (see [Section 3.2](#)), but their CSL830 by-weight dose will be rounded to the nearest (ie, up *or* down) 1000 IU based on their assigned dose for subjects weighing ≥ 40 kg; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU).
- ^e Subjects will undergo a 2-week (± 3 days) follow-up contact after either completing or discontinuing/withdrawing from the Extension Period.

3.1.1 Screening Visit

A Screening Visit will be conducted within the 4 weeks before Treatment Period 1 in order to confirm the eligibility of the following subjects belonging to groups of subjects:

- **“CSL830-Naïve” Subjects:** subjects who did not participate in study CSL830_3001; subjects who participated in study CSL830_3001 but did not receive blinded investigational product as a part of that study.
- **“CSL830-Interrupted” Subjects:** subjects who completed participation in study CSL830_3001, but who delayed entry into the current study (ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).

The first visit in Treatment Period 1 (ie, the Day 1 Visit) may occur on the same day as the Screening Visit.

“CSL830-Continuation” Subjects will not have a Screening Visit. “CSL830-Continuation” Subjects are subjects who complete participation in CSL830_3001 and who continue directly on to participate in the current study [ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1].

The eligibility of “CSL830-Continuation” Subjects will include evaluation based upon the assessments performed during study CSL830_3001 as described in [Table 6](#) (see [Section 8.4.3.1](#)). For “CSL830-Continuation” Subjects, the End of Study Visit of CSL830_3001 and the first study visit of Treatment Period 1 of CSL830_3002 may occur on the same day.

3.1.2 Treatment Periods 1 and 2

Treatment Period 1 will begin with the Day 1 Visit and will end with the Week 25 Visit. Treatment Period 2 will begin *either* during the Week 25 Visit (if CSL830 is administered at the study visit) *or* immediately following the Week 25 Visit. Treatment Period 2 will end with the Week 53 Visit.

Eligible subjects will be randomized to 1 of the following CSL830 treatment groups at the first visit in Treatment Period 1:

- 40 IU/kg CSL830 treatment group, **OR**
- 60 IU/kg CSL830 treatment group.

CSL830 will be administered as a single subcutaneous injection twice weekly at home either independently (ie, self-administered by the subject) or with assistance (ie, with the help of a caretaker such as a parent or guardian) during Treatment Period 1 and Treatment Period 2.

During the study, an investigator may increase a subject's CSL830 dose if that subject is eligible for dose increase. A subject's eligibility for a dose increase is related to the frequency of their HAE attacks and the rules are different during the "fixed dose" Treatment Period 1 and the "dose optimization" Treatment Period 2. During Treatment Period 1, dose increases are intended as potential rescue prophylaxis for subjects who have very frequent attacks; these increases are intended to provide an opportunity for such subjects to remain in the study. During Treatment Period 2, dose increases are intended to allow the investigator to optimize the dose for subjects whom the investigator considers may benefit from a higher prophylaxis dose. Dose increase rules are presented in [Section 3.2](#).

The last visit of Treatment Period 2 will be the Week 53 Visit.

3.1.3 Extension Period

The Extension Period will follow Treatment Period 2. The last visit (Week 53 Visit, Day 367) of Treatment Period 2 will serve as the first visit of the Extension Period (Extension Period Day 1), unless there is a rest period of up to 30 days. In this case, the first visit of the Extension Period will be a new (separate) visit. The Extension Period is intended to allow subjects from the United States who complete Treatment Period 2 according to the protocol to continue to receive treatment with open-label CSL830. During the Extension Period (unlike during Treatment Periods 1 and 2 during which the assigned by-weight dose was rounded up to the nearest 500 IU) for subjects weighing ≥ 40 kg, each subject's dose will be rounded to the nearest 1000 IU (up *or* down) based on his/her assigned by-weight dose; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU). During the Extension Period, each subject will continue to be eligible for dose escalation in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for Treatment Period 2 (see [Section 3.2](#)).

3.1.4 Post-treatment Follow-up

Subjects will attend a Follow-up Visit occurring 14 days (± 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit.

3.1.5 Enrollment Stopping Rules

There will be no pre-specified enrollment stopping rules for safety or efficacy reasons.

3.1.6 Enrollment Re-starting Rules

Not Applicable.

3.1.7 Study Termination Rules

There will be no pre-specified study termination rules for safety or efficacy reasons.

3.2 Dose and Dosing Regimen

The doses of CSL830 (40 IU/kg and 60 IU/kg) to be assessed in the current study were selected based on the results of the CSL830_2001 study. Body weight-adjusted doses can provide a more appropriate exposure to study drug, especially at low and high body weights. A dosing regimen of 40 IU/kg twice a week is expected to achieve a mean steady-state trough CCI of approximately 40%, which is a target level that may be associated with clinical efficacy [Späth et al 1984]. Dosing regimens of 60 IU/kg and 80 IU/kg can achieve a mean steady-state trough CCI of approximately 60% and 80% (respectively), with sufficient safety experience from the previous study to justify its assessment without body weight restrictions.

During all treatment periods, subjects who do not increase the dose of CSL830 to which they were assigned will administer CSL830 (40 IU/kg or 60 IU/kg) via a single SC injection, twice weekly. 40 IU/kg CSL830 is equivalent to a volume of 0.08 mL/kg; 60 IU/kg CSL830 is equivalent to a volume of 0.12 mL/kg. During Treatment Periods 1 and 2, the actual dose of CSL830 that is assigned will be rounded up to the nearest 500 IU, as this corresponds with a practical volume of 1 mL of CSL830. During the Extension Period, the actual dose of CSL830 that is assigned will be rounded (ie, up *or* down) to the nearest 1000 IU for subjects weighing ≥ 40 kg; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU).

To promote compliance, the twice weekly administration of CSL830 should be scheduled on fixed days of the week (eg, Monday and Thursday). The suggested interval between each administration of CSL830 is 3 or 4 days. In addition, CSL830 should be administered at approximately the same time on each day. A missed injection should be administered as soon as possible, unless within 24 hours of the next scheduled injection; in this situation, the

missed injection should be omitted, and the administration of CSL830 should occur at the next scheduled day and time.

If a subject requires the use of C1-INH medication for the treatment of breakthrough HAE attacks within 24 hours before a scheduled injection of CSL830, the scheduled injection may be delayed by up to 24 hours.

Additional information on the dosing regimen can be found in [Section 6.2](#).

CSL830 Dose Increase

Some subjects may be eligible to increase the dose of CSL830 to which they were assigned at the beginning of Treatment Period 1.

During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, ≥ 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. Dose increases during Treatment Period 1 are intended as rescue prophylaxis, to provide the opportunity for subjects who have very frequent HAE attacks to continue in the study during this otherwise fixed-dose treatment period.

Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. Dose increases during Treatment Period 2 are intended to allow investigators to adjust/optimize the dose for subjects who may need a higher prophylactic dose.

During the Extension Period (unlike during Treatment Periods 1 and 2 during which the assigned by-weight dose was rounded up to the nearest 500 IU) for subjects weighing ≥ 40 kg, each subject's dose will be rounded to the nearest 1000 IU (up *or* down) based on his/her assigned by-weight dose; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU). During the Extension Period, each subject will continue to be eligible for dose escalation in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for Treatment Period 2 (see above).

An evaluation period for any dose increase in Treatment Period 1, Treatment Period 2, or the Extension Period is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830).

All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. CSL830 dose increases may be made in increments of 20 IU/kg up to a maximum dose of 80 IU/kg. Subjects who are randomized to treatment with 40 IU/kg CSL830 and who are eligible for a dose increase may undergo up to 2 independent 20 IU/kg dose increases (at the sole discretion of the investigator), up to a maximum dose of 80 IU/kg. Subjects who are randomized to treatment with 60 IU/kg CSL830 and who are eligible for a dose increase may undergo a single 20 IU/kg dose increase (at the sole discretion of the investigator), up to a maximum dose of 80 IU/kg.

Assessment of Subject Weight

The weight of the subject is assessed at study visits. The baseline body weight for “CSL830-Naïve” and “CSL830-Interrupted” Subjects will be recorded at Screening. The baseline body weight for “CSL830-Continuation” Subjects will be recorded at the CSL830_3001 End of Study Visit.

The actual dose of CSL830 will be adjusted, if necessary. The actual dose administered will be based on the weight at Day 1 of Treatment Period 1 and will only be adjusted if the patient has a body weight change of more than 10% compared to baseline. If a new body weight is used, this weight will become the new baseline weight and subsequent weight measures will be compared to this. If there is a change of more than 10% compared to this new baseline weight the dose will be adjusted again. This will be repeated throughout the study.

3.3 Planned Study Duration

Treatment Period 1 and Treatment Period 2

The duration of the study for an individual subject is expected to be up to 58 weeks. This estimation is based on:

- A Screening Period lasting up to 4 weeks (≤ 28 days), as needed.
- Two treatment periods totaling 52 weeks (367 days \pm 2 days).
- A Follow-up Period lasting 2 weeks (14 days \pm 3 days).

The overall study duration (ie, from the first subject’s first Screening Visit to the last subject’s Follow-up Visit) is planned to be 26 months, but will depend on recruitment.

Extension Period (Optional)

The Extension Period (88 weeks) followed by the Extension Period follow-up (2 weeks) will begin at first subject first visit in the Extension Period and result in an anticipated total study duration of up to approximately 146 weeks for participating subjects. Subjects who have any Extension Period visits that occur within 6 weeks before the study end date will be handled as completers. These subjects will attend the final study visit (Extension Period Week 88) in place of their next study visit or telephone contact and will receive follow-up telephone contact (Extension Period Week 90 ± 3 days). Subjects who roll-over into the Extension Period prior to the Treatment Period 2 Follow-up Visit will be regarded as completers. All subjects who are not withdrawn from the study will be considered completers of the study.

3.4 Planned Number of Sites

The study is planned to be conducted at approximately 50 study sites, with approximately 12 United States sites conducting the Extension Period portion of the study.

3.5 Planned Number of Subjects

The study plans to enroll subjects who complete participation in CSL830_3001. Additional subjects who have not participated in study CSL830_3001 will be enrolled so that the total number of subjects randomized is approximately 110.

Assuming that up to 10% of subjects withdraw before the completion of the study, 100 subjects are planned to complete the study.

Subjects from the United States who have completed Treatment Period 1 and Treatment Period 2 according to the study protocol are eligible to enroll in the Extension Period. Approximately 50 of these subjects are anticipated to enroll in the Extension Period.

3.6 Study Monitoring Procedures**3.6.1 Steering Committee**

A Steering Committee has been established to provide scientific advice and safety monitoring for the study.

Members of the Steering Committee will be listed in the Investigator Study File.

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 [Section 4.1.2](#) and [Section 4.1.3](#), respectively.

Subjects who have completed participation in CSL830_3001 will be offered treatment with CSL830 as a part of the study if they meet the eligibility criteria presented here. Additional subjects (ie, “CSL830-Naïve” Subjects [see Section 4.1.1]) will be eligible to participate in the current study in order to meet the planned sample size.

Subject eligibility will be reviewed and documented by an appropriately medically qualified member of the investigator’s study team before a subject is enrolled in the study.

4.1.1 Subject Classification

Before subject eligibility can be assessed against the inclusion and exclusion criteria, each subject will be classified into 1 of the following categories:

Treatment Period 1 and Treatment Period 2

- “CSL830-Naïve” Subjects: subjects who did not participate in study CSL830_3001; subjects who participate in study CSL830_3001 but did not receive blinded investigational product as a part of that study.
NOTE: For “CSL830-Naïve” Subjects, the first study visit is the Screening Visit.
- “CSL830-Interrupted” Subjects: subjects who completed participation in study CSL830_3001, but who delay entry into the current study (ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).
NOTE: For “CSL830-Interrupted” Subjects, the first study visit is the Screening Visit.
- “CSL830-Continuation” Subjects: subjects who complete participation in study CSL830_3001 and who continue directly on to participate in the current study (ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).
NOTE: For “CSL830-Continuation” Subjects, the first study visit is the first study visit in Treatment Period 1. For these subjects, the last study visit of CSL830_3001 and the first study visit of Treatment Period 1 from CSL830_3002 may occur on the same day.

Extension Period

- “Extension Period” Subjects: subjects from the United States who complete participation in CSL830_3002 Treatment Period 2 and who continue on to participate in the Extension Period.

NOTE: For “Extension Period” Subjects, the last study visit of CSL830_3002 Treatment Period 2 and the first study visit of the Extension Period may occur on the same day.

4.1.2 Inclusion Criteria

Subjects meeting all of the following inclusion criteria may be enrolled (randomized) into the study:

1. Capable of providing written informed consent/assent (as appropriate) and willing and able to adhere to all protocol requirements, and/or the subject’s parent(s) or legally acceptable representative(s) capable of providing written informed consent.
2. Male or female.
3. Aged 6 years or older at the time of providing written informed consent/assent (as appropriate).
4. A diagnosis of HAE (type I or II), as determined by the following: a clinical history consistent with HAE *and* CCI [REDACTED]
[REDACTED]
 - For “CSL830-Naïve” Subjects: Historically documented CCI [REDACTED]
[REDACTED] that are compatible with participation will be accepted; however, if historical documentation is unavailable, then the tests may be conducted at Screening. Biochemical confirmation of HAE (type I or II) diagnosis must be established for a subject before starting the Treatment Period 1.
 - For “CSL830-Interrupted” Subjects AND “CSL830-Continuation” Subjects: The documentation that was used to confirm eligibility in CSL830_3001 will be used to verify the required value for inclusion in the current study (CSL830_3002).
5. Have experienced HAE attacks (requiring acute treatment, medical attention or causing significant functional impairment) as described below:

- For “CSL830-Naïve” Subjects:
 - “CSL830-Naïve” Subjects using intravenous C1-INH as routine (long-term) prophylaxis against HAE attacks must have experienced 4 HAE attacks over *any* consecutive 2-month period before the initiation of intravenous C1-INH prophylaxis and before the CSL830_3002 Screening Visit, as documented in the subject medical records.
 - All other “CSL830-Naïve” Subjects (eg, treated using oral HAE prophylaxis against HAE attacks or on-demand treatment) must have experienced 4 HAE attacks over a consecutive 2-month period within the 3 months before the CSL830_3002 Screening Visit, as documented in the subject medical records.
 - For “CSL830-Continuation” Subjects AND “CSL830-Interrupted” Subjects:

Subjects must have experienced 4 HAE attacks over a consecutive 2-month period within the 3 months before the CSL830_3001 Screening Visit, as documented in the subject medical records (ie, the HAE attack frequency required for eligibility to participate in study CSL830_3001).
6. For subjects who have used oral medication for prophylaxis against HAE attacks (ie, androgens, tranexamic acid, progestins) within 3 months of their first study visit: Use of a *stable* regimen of oral prophylactic medication (ie, dose and administration frequency) during the 3 months before their first study visit and willingness to continue the stable regimen for at least 25 weeks.

NOTE: Subjects using oral medication for HAE prophylaxis are to maintain their stable, pre-study dose during Treatment Period 1, but may decrease their dose after entering Treatment Period 2.
 7. Investigator assesses that the subject is willing and able to adhere to all protocol requirements.
 8. Assessed by the investigator as able to appropriately store CSL830, and is capable of being trained to administer CSL830 (independently or with assistance) outside of the study center setting.
 9. Assessed by the investigator as able to have access to medication to treat breakthrough HAE attacks, and is capable of using medication to treat breakthrough attacks (independently or with assistance) outside of the study center setting.

4.1.3 Exclusion Criteria

Subjects meeting any of the following exclusion criteria must not be enrolled (randomized) into the study:

1. Subjects who were enrolled in CSL830_3001 but who were withdrawn before completion of that study for any reason.
2. Known incurable malignancies at the time of the first study visit.
3. Any clinical condition that is likely to interfere with evaluation of CSL830 or satisfactory conduct of the study.
4. A clinically significant history of poor response to C1-INH therapy for the management of HAE.
5. A suspected or confirmed diagnosis of acquired HAE or HAE with normal C1-INH (ie, HAE type III).
6. Assessed by the investigator as unable to have their HAE adequately managed pharmacologically with on-demand treatment, when that on-demand treatment is administered independently or with assistance.
NOTE: This must be documented by the investigator in an individual acute action plan.
7. Female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception or not sexually abstinent during the study, or not surgically sterile.
8. Female subjects who started taking or changed dose of any hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen / progesterone containing products) during the 3 months before their first study visit, or who intend to initiate these therapies during the course of the study.
9. Intention to become pregnant during the course of the study.
10. Pregnancy or nursing mother.
11. Participated in an interventional clinical study (other than CSL830_3001) during the 30 days before the first administration of the investigational product or at any time during the study.
12. Alcohol, drug or medication abuse within 1 year before the study.

13. Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study.
14. Known or suspected hypersensitivity to CSL830, or to any excipients of CSL830.
15. Employee at the study site, or spouse / partner or relative of the investigator or sub-investigators.
16. Any other issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study.

4.2 Subject Withdrawal and Replacement

4.2.1 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (eg, due to an AE, protocol violation, loss to follow-up, subject noncompliance, and study termination).

In accordance with International Conference on Harmonisation (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.

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

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 for the last visit in Treatment Period 2 (ie, the Week 53 Visit) (see [Section 8.4.4.7](#)) or the last visit in the Extension Period (Extension Period Week 88)(see [Section 8.4.6.20](#)). These subjects will then attend a Follow-up Visit occurring 14 days (\pm 3 days) after a visit resulting in study discontinuation, unless informed consent/assent has been withdrawn (see [Section 8.4.5.1](#)). If the subject is withdrawn from the study after receiving CSL830, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study, and also withdraws consent/assent (as appropriate) for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent/assent (as appropriate).

In the event that a subject withdraws from the study, the investigator should record the reason and date of withdrawal in the electronic case report form (eCRF) and in the subject's medical records.

Subjects who discontinue or withdraw from Treatment Periods 1 or 2 will not be eligible to participate in the Extension Period.

4.2.3 Replacement Policy

Subjects who discontinue participation in or are otherwise withdrawn from the study will not be replaced. Assuming that up to 10% of subjects withdraw before the completion of the study, 100 subjects are planned to complete the study.

5 Study Interventions

5.1 Description of Investigational Product

5.1.1 CSL830

Table 1: Description of CSL830

Substance number	CSL830
Active substance	C1-esterase inhibitor (C1-INH)
Trade name	Not Applicable
Dosage form	Lyophilized powder for reconstitution; 1500 IU C1-INH per single-use vial.
Dose for Treatment Periods 1 and 2	40 IU/kg and/or 60 IU/kg and/or 80 IU/kg (rounded up to the nearest 500 IU), as described in Section 3.2 .
Dose for Extension Period	40 IU/kg and/or 60 IU/kg and/or 80 IU/kg (rounded up <i>or</i> down to the nearest 1000 IU for subjects weighing \geq 40 kg; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 [ie, rounded up to the nearest 500 IU]), as described in Section 3.2 .
Mode of administration	Subcutaneous injection

Before use, each vial of CSL830 will be reconstituted with 3 mL water for injection. Each vial of CSL830 requires a reconstitution time of 10 minutes. 40 IU/kg CSL830 is equivalent to a volume of 0.08 mL/kg; 60 IU/kg CSL830 is equivalent to a volume of 0.12 mL/kg; 80 IU/kg CSL830 is equivalent to a volume of 0.16 mL/kg.

CSL830 will be manufactured by CSL in accordance with Good Manufacturing Practice guidelines and local regulatory requirements.

5.1.2 Comparator Product

Not Applicable.

5.2 Packaging, Labeling, Supply and Storage

5.2.1 Packaging and Labeling

CSL830 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

CSL830 will be supplied to the study sites by CSL.

CSL830 must be stored under temperature-monitored conditions in a secure storage area as specified in the CSL830 Handling Instructions.

5.3 Accountability and Destruction

All supplies of CSL830 must be accounted for throughout the study. At the end of the study, the original Drug Inventory Log, dated and signed by the investigator or delegate (eg, pharmacist), must be retained at the study site as verification of final accountability of CSL830.

Records for the delivery of CSL830 to the study site, the inventory at the study site, the use by each subject, and the destruction or return of CSL830 to CSL must be maintained by the investigator (or delegate). The records will include dates, quantities, batch numbers and unique code numbers assigned to CSL830 and unique code numbers assigned to the subjects.

Information on the destruction of CSL830 is provided in the CSL830 Handling Instructions.

5.4 Other Intervention(s)

Not applicable.

6 Allocation, Dosing and Administration

6.1 Allocation to Treatment

6.1.1 Subject Assignment

After providing written informed consent/assent (as appropriate), the subject will be issued with a study-level unique subject identification number. Each “CSL830-Continuation” and “CSL830-Naïve” Subject will re-use the subject numbers they used in study CSL830_3001. 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.

Subjects who are enrolled in the Extension Period will continue to receive the CSL830 dose that they were originally administered during Treatment Period 2. This CSL830 dose may be escalated in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for Treatment Period 2 (see [Section 3.2](#)).

6.1.2 Randomization Procedures

A stratified block randomization scheme will be used to ensure that subjects are randomized to a starting dose of CSL830 of either 40 IU/kg or 60 IU/kg in a balanced manner and to ensure that “CSL830-Continuation” Subjects, “CSL830-Interrupted” Subjects, and “CSL830-Naïve” Subjects are distributed evenly between the 2 CSL830 treatment groups.

Eligible subjects will be randomized to 1 of the 2 treatment groups (CSL830 40 IU/kg or CSL830 60 IU/kg) by means of interactive response technology (IRT). The IRT will assign the appropriate study treatment to each subject. CSL will supply the investigator with a user guide for the IRT.

6.1.3 Blinding Procedures

Not applicable.

6.2 Dosing and Administration

6.2.1 Administration of the Investigational Product

The investigator (or delegate) will only dispense the investigational product (ie, CSL830) to subjects included in this study following the procedures set out in this study protocol. CSL830 will be administered either independently (ie, self-administered by the subject) or with assistance (ie, with the help of a caretaker such as a parent or guardian) at home via a single SC injection in the abdomen. The injection site should be changed for each new administration of CSL830; ideally, the site of injection should alternate between the right and left sides of the abdomen and should be at least 5 cm (2 inches) away from the previous injection site.

The abdomen is the preferred injection location in this study. However, if the investigator believes that another SC injection site (eg, outer thigh, upper arm) is more clinically appropriate for an individual subject, this location can also be used.

Additional information on the CSL830 dose and dosing regimen can be found in [Section 3.2](#).

6.2.2 Subject Training for Self-Administration of the Investigational Product

The investigator must ensure that all subjects or their caregivers have been trained sufficiently to allow for home therapy to occur in Treatment Periods 1 and 2 and the

Extension Period. Mandatory formal training will be performed on Day 1 of Treatment Period 1 for all subjects. “CSL830-Naïve” Subjects and “CSL830-Interrupted” Subjects will also have a second round of follow-up training on Day 4 of Treatment Period 1. During these training visits, subjects (or their caregivers, as appropriate) will administer CSL830 under the supervision of the investigator. Additional training (including at additional visits) may be conducted for any subject by the study site personnel, if required. Subjects weighing ≥ 40 kg who enroll in the Extension Period will receive training on the new dose rounding scheme (up *or* down to the nearest 1000 IU) on Visit 1 of the Extension Period; subjects weighing < 40 kg will continue to undergo rounding as during Treatment Periods 1 and 2 (ie, rounded up to the nearest 500 IU).

NOTE: The Day 4 Visit may be waived for “CSL830-Interrupted” Subjects (only) if the investigator has confirmed that the subject can adequately treat themselves with CSL830 (ie, no further training is necessary). In this case, all activities scheduled for the Day 4 visit may be conducted at the Day 1 Visit.

The training for self-administration of investigational product (ie, CSL830) will include the following:

- Correct storage.
- Correct reconstitution technique.
- Correct administration technique.
- Signs and symptoms of hypersensitivity reactions.
- Procedures in case of suspected hypersensitivity reactions.
- Correct completion of the eDiary (eg, recording of HAE symptoms, medication for the treatment of breakthrough HAE attacks, AE reporting).

Complete instructions for the handling, reconstitution, and administration of CSL830 will be detailed in the CSL830 Handling Instructions. These instructions will be provided to each study center prior to enrollment of the first subject. Subjects will also be provided with written instructions for the preparation and administration of CSL830.

6.3 Treatment Compliance

Subjects will record the dose and date of injection of CSL830 in the eDiary. In addition, subjects will bring their used / partially used vials of CSL830 to every study visit. Subjects will return all vials (ie, used, partially used, and unused) of CSL830 to the site at last visit in

Treatment Period 2 and last visit in the Extension Period. Treatment compliance will be monitored by counting the used vials of CSL830, the results of which will be documented.

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 (ie, CSL830) for an individual subject:

- Anaphylaxis or severe and clinically significant allergic reaction causally related to CSL830.
- Any other CSL830-related SAE or CSL830-related important medical event that is considered by the investigator and / or CSL to be serious and clinically significant, or that would suggest significant hazard to the subject following further administration of CSL830.
- Administration of a prohibited concomitant therapy or a prohibited change in concomitant therapy (see [Section 7.3](#)).

7.2 Permitted Therapies

The following therapies are PERMITTED during the Screening Period, Treatment Period 1, Treatment Period 2, the Follow-up Period, and the Extension Period:

- Prescribed medication(s) required for the management of acute or chronic medical conditions, except those described in [Section 7.3](#).
- Over the counter medications and dietary supplements.
- Medications (eg, IV C1-INH) for the pre-procedure prevention of acute HAE attacks, not to exceed 1 dose prior to each procedure.
- Medications for the treatment of breakthrough HAE attacks, including the following:
 - Berinert (IV C1-INH).
 - Other plasma-derived or recombinant C1-INH, other than CSL830.
 - Firazyr (Icatibant).
 - Kalbitor (Ecallantide).
 - Fresh frozen plasma.

The following therapy is PERMITTED during the Screening and Follow-up Periods (only):

- Intravenous C1-INH for routine prophylaxis against HAE attacks.

The following therapies are PERMITTED if used at a *stable* dose for 3 months before the first study visit and used at the same dose during Treatment Period 1*:

- Oral medications for HAE prophylaxis (eg, androgens, tranexamic acid, progestins) if used at a stable dose for 3 months before the first study visit*.

NOTE: Subjects using oral medication for HAE prophylaxis may decrease their dose after entering Treatment Period 2 and the Extension Period.

* For “CSL830-Naïve” Subjects AND “CSL830-Interrupted” Subjects: the first study visit is the Screening Visit;
For “CSL830-Continuation” Subjects: the first study visit is the first study visit in Treatment Period 1.

7.3 Prohibited Therapies

Use of the following therapy is NOT permitted during Treatment Period 1, Treatment Period 2, and the Extension Period for subjects who are using CSL830:

- Intravenous C1-INH for routine prophylaxis against HAE attacks.

NOTE: Use of IV C1-INH for the pre-procedure prevention of acute HAE attacks is permitted, not to exceed 1 dose prior to each procedure.

Dose changes, including initiation or discontinuation, in the following therapy are NOT permitted during the 3 months before the first study visit* and throughout the study:

- Hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen / progesterone containing product).

* For “CSL830-Naïve” Subjects AND “CSL830-Interrupted” Subjects: the first study visit is the Screening Visit;
For “CSL830-Continuation” Subjects: the first study visit is the first study visit in Treatment Period 1.

7.4 Dietary and Lifestyle Restrictions

Not Applicable.

7.5 Overdose

Overdose is defined as the accidental or intentional infusion or ingestion of any dose of a product that is considered excessive. In a previous study (CSL830_2001), doses up to 6000 IU (up to 120 IU/kg) were administered twice weekly for 4 weeks without any safety issues. The effects of any potential overdose with CSL830 have not been otherwise studied.

The development of thrombosis has been reported after administering IV C1-INH doses up to 500 U/kg body weight when used off label in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.

There is no specific antidote for excessive dosing of CSL830; in these circumstances, appropriate supportive management should be instituted.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

8.1.1 Demographics and Safety Assessments

The clinical procedures that will be conducted during this study related to the evaluation of population demographics and safety are provided in [Table 2](#). Refer to the Laboratory Manual for details about the collection, storage, handling and transportation of biological specimens, and how the assessments should be performed.

Table 2: Clinical Procedures: Demographics and Safety Evaluation

Assessment	Description		
Demographics	Year of birth, age, sex, race and ethnicity.		
Medical history	Relevant medical history for the previous 6 months. Diagnosis of HAE and disease type. Prior therapy relating to HAE in the past 3 months. Contraception method (if relevant). Current therapies.		
Dipstick pregnancy test	Urine test for beta-human chorionic gonadotropin (test conducted at the study site).		
Physical examination	As per the site's standard procedure.		
Vital signs	Blood pressure (systolic and diastolic) and respiratory rate. Pulse rate (per minute) will be measured from the radial pulse counted manually or with an automatic blood pressure monitor over ≥ 15 seconds. Body temperature. Body weight and height (height measurement at Screening only or from CSL830_3001, as appropriate); body mass index will be determined from height and weight values.		
Urinalysis (Central laboratory)	Bilirubin. Glucose. Nitrite. Specific gravity.	Blood. Ketones. pH. Urobilinogen.	Erythrocytes. Leukocyte esterase. Protein.
Hematology (Central laboratory)	Hemoglobin. Blood cell counts: basophils, eosinophils, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, platelets.	Hematocrit.	
Biochemistry (Central laboratory)	ALT. Creatinine. Protein. Albumin. Calcium.	Chloride. Lactate dehydrogenase. Total bilirubin. AST. Sodium.	GGT. Glucose. Potassium. Urea.
Coagulation (Central laboratory)	INR. D-dimer.	APTT. F1+2.	Fibrinogen.
Viral serology (Central laboratory)	Blood samples to be tested for HIV-1/-2, HBV, and HCV.		
Immunogenicity (Central laboratory)	Serum analyzed for the presence of binding antibodies specific to C1-INH.		

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; F1+2 = prothrombin fragment 1+2; GGT = Gamma glutamyl transferase; HAE = hereditary angioedema; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio.

8.1.2 Risk Assessments for Deep Vein Thrombosis and Pulmonary Embolism

The clinical model scoring system that will be used for the risk assessment of DVT is described in Table 3.

Table 3: Scoring System for the Risk Assessment of Deep Vein Thrombosis

Clinical feature ¹	Score
Active cancer (treatment ongoing or within previous 6 months or palliative).	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities.	+1
Recently bedridden for more than 3 days or major surgery, within 4 weeks.	+1
Localized tenderness along the distribution of the deep venous system.	+1
Entire leg swollen.	+1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity).	+1
Pitting edema (greater in the symptomatic leg).	+1
Collateral superficial veins (non-varicose).	+1
Alternative diagnosis as likely or greater than that of deep vein thrombosis.	-2

¹In subjects with symptoms in both legs, the more symptomatic leg is used. From [Wells et al 1997](#).

If a subject has a risk score of ≥ 1 , a lower extremity ultrasound examination will be arranged by the investigator to exclude DVT. If a DVT is confirmed on ultrasound examination, the event will be classified as an AE of special interest (AESI) (see [Section 9.1.2](#)) and will be reported as an SAE.

The clinical model scoring system that will be used for the risk assessment of PE is described in Table 4.

Table 4: Scoring System for the Risk Assessment of Pulmonary Embolism

Clinical feature ¹	Score
Previous pulmonary embolism or deep vein thrombosis.	+1.5
Heart rate >100 beats per minute.	+1.5
Immobilization or surgery in the previous 4 weeks.	+1.5
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins).	+3
Alternative diagnosis less likely than pulmonary embolism.	+3
Hemoptysis.	+1
Malignancy (on treatment, treated within the last 6 months, or palliative).	+1

¹From [Wells et al 2000](#).

If a subject has a risk score of ≥ 2 , a computerized tomographic angiogram or appropriate investigation will be arranged by the investigator to exclude PE. If PE is confirmed on investigation, the event will be classified as an AESI (see [Section 9.1.2](#)) and will be reported as an SAE.

8.1.3

CCI

CCI

CCI

CCI

CCI

8.2 Retention of Samples

Informed consent/assent (as appropriate), independent to that for participating in the study, will be requested from subjects to allow 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.

8.3 Prior and Concomitant Therapies

All drugs and/or procedures being administered to a subject at the time of signing informed consent/assent (as appropriate), and which continue to be taken in addition to the investigational product (ie, CSL830) during the study, are regarded as prior and/or concomitant therapies, and must be documented as such in the eCRF.

Additionally, all medications used to treat HAE (ie, HAE prophylaxis or on-demand treatment for HAE) within the 3 months before each subject's first study visit will also be captured in the eCRF.

8.4 Visit Schedule

The timing and frequency of all clinical procedures are described in the following tables:

- [Schedule of Events for “CSL830-Continuation” Subjects.](#)
- [Schedule of Laboratory Assessments for “CSL830-Continuation” Subjects.](#)
- [Schedule of Events for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects.](#)
- [Schedule of Laboratory Assessments for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects.](#)
- [Schedule of Events for the Extension Period.](#)

8.4.1 Informed Consent / Assent

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

Subjects who participate in the Extension Period are to provide written informed consent/assent (as appropriate) before any study-specific assessments or procedures are performed during the Extension Period.

8.4.2 Screening

The eligibility of “CSL830-Naïve” Subjects and “CSL830-Interrupted” Subjects will be assessed at a Screening Visit conducted within the 4 weeks before Treatment Period 1.

The Screening Visit and the Day 1 Visit of Treatment Period 1 can occur on the same day. If a subject fails Screening at a combined Screening Visit / Day 1 Visit, then the subject will be treated as a screen failure.

“CSL830-Naïve” Subjects include the following:

- Subjects who did not participate in CSL830_3001.
- Subjects who participated in CSL830_3001 but did not receive blinded investigational product as a part of that study.

NOTE: For “CSL830-Naïve” Subjects, the first study visit is the Screening Visit.

“CSL830-Interrupted” Subjects include the following:

- Subjects who completed participation in study CSL830_3001, but who delayed entry into the current study (ie, > 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1).

NOTE: For “CSL830-Interrupted” Subjects, the first study visit is the Screening Visit.

If a potential subject was not entered into Treatment Period 1 of the current study within the 4 weeks following the Screening Visit, the potential subject may attend a second Screening Visit (for a maximum of 2 Screening Visits per subject). In the event that a potential subject is screened twice, all Screening Period assessments including medical history must be repeated at the second Screening Visit and these finding / results will supersede those from the previous Screening Visit. CCI [REDACTED]

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

- Written informed consent/assent (as appropriate).
- Review of inclusion and exclusion criteria.
- Develop an individual acute action plan, including assessment of subject’s ability to manage HAE attacks independently or with assistance.
- Demographics.
- Clinically significant history from the previous 6 months.
- Vital signs, including weight and height.
- Physical examination.
- Indwelling venous catheter is present (yes/no).
- Assess risk of DVT and PE.

- CCI [REDACTED]

CCI

- Start monitoring of AEs.
- Record prior / concomitant therapies, including therapy relating to HAE in the previous 3 months.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Begin monitoring / documenting HAE attacks; investigators and subjects should maintain good communication during the Screening Period to allow capture of the appropriate information from the Screening Visit to the start of Treatment Period 1.
- Schedule the next study visit.

Subjects who complete all of these assessments and who fulfill the inclusion/exclusion criteria (ie, eligible subjects) will be entered into Treatment Period 1. If the subject is not eligible for the Treatment Period 1, the primary reason for screen failure must be entered in the eCRF.

8.4.3 Treatment Period 1

8.4.3.1 Week 1, Day 1

The first study visit in Treatment Period 1 will occur on Week 1, Day 1. There is no visit window for the visit.

“CSL830-Continuation” Subjects (subjects who complete participation in CSL830_3001 and who continue directly on to participate in the current study [ie, ≤ 1 week between the End of Study Visit of CSL830_3001 and the first visit of CSL830_3002 Treatment Period 1]) will not have a Screening Visit. For these subjects, the last study visit of CSL830_3001 and the first study visit of Treatment Period 1 from CSL830_3002 should occur on the same day, where possible.

Eligibility of “CSL830-Continuation” Subjects (see [Section 4.1.2](#) and [Section 4.1.3](#)) will be assessed using CSL830_3001 data, as described in [Table 6](#); if the required CSL830_3001 data is not available on the Day 1 Visit of the current study, then the corresponding assessment must be conducted.

If a subject did not participate in a Screening Visit (ie, “CSL830-Continuation” Subjects), then written informed consent/assent (as appropriate) must be obtained before any study-

specific assessments or procedures are performed at the first visit in Treatment Period 1 (the Day 1 Visit).

Table 6: Results from Study CSL830_3001 to be used for Study CSL830_3002 Eligibility Assessment of “CSL830-Continuation” Subjects

Assessment	Source
Demographics	CSL830_3001 Screening Visit ^A
Medical History	CSL830_3001 Screening Visit ^A
Ongoing Adverse Events	CSL830_3001: End of Study Visit ^A
Concomitant Medication	Within 3 months of and including the CSL830_3001: End of Study Visit ^A
Physical Examination	CSL830_3001: End of Study Visit
Vital Signs, including Weight	CSL830_3001: End of Study Visit
CCI [REDACTED]	CCI [REDACTED]
Pre-CSL830_3001 HAE Attacks	Results used to qualify for CSL830_3001
Urine Pregnancy Test	CSL830_3001: End of Study Visit ^B

^A To be updated (as needed) in order to provide a complete CSL830_3002 subject record.

^B The results of the urine pregnancy test conducted at the end of study visit can only be used to satisfy the applicable eligibility criterion if the CSL830_3001 End of Study Visit and the first visit of CSL830_3002 Treatment Period 1 (ie, Day 1) occur on the same day. Otherwise, a new pregnancy test must be performed at the first study visit in CLS830_3002 Treatment Period 1 in order to confirm eligibility.

Subjects who fulfill the inclusion/exclusion criteria (ie, eligible subjects) will be entered (randomized) into Treatment Period 1. If the subject is not eligible for the Treatment Period 1, the primary reason for screen failure must be entered in the eCRF.

The following assessments will be conducted by the investigator or delegate for all study subjects, unless otherwise noted:

- Review of inclusion / exclusion criteria in order to confirm eligibility to participate in the current study.
- Update demographics and medical history (as needed).
- Enroll subject into the study and randomize subject to a study treatment arm via interactive response technology.
- Dispense eDiary to subject.
- CCI [REDACTED]

- Obtain blood samples for the following [applicable to all “CSL830-Naïve” and “CSL830-Interrupted” Subjects AND “CSL830-Continuation” Subjects who did not complete the assessments at the CSL830_3001 End of Study Visit, only]:
 - Hematology.
 - Biochemistry.
 - Coagulation.
 - Viral serology.
 - Assessment of antibodies against C1-INH.
- Assess risk of DVT and PE [applicable to “CSL830-Continuation” Subjects who did not complete the assessments at the CSL830_3001 End of Study Visit, only].
- **CCI** [REDACTED]
- Obtain a urine sample for urinalysis [applicable to all “CSL830-Naïve” and “CSL830-Interrupted” Subjects AND “CSL830-Continuation” Subjects who did not complete the assessments at the CSL830_3001 End of Study Visit, only].
- For female subjects, obtain a urine sample for dipstick pregnancy testing to assess eligibility prior to randomization and dosing [applicable to all “CSL830-Naïve” Subjects and “CSL830-Interrupted” Subjects; also applicable to all “CSL830-Continuation” subjects if their CSL830_3001 End of Study Visit and their first visit of CSL830_3002 Treatment Period 1 (ie, Week 1, Day 1) occur on different days].
- Subject height [applicable to “CSL830-Continuation” Subjects, only].
- Indwelling venous catheter is present (yes/no) [applicable to “CSL830-Continuation” Subjects, only].
- Dispense CSL830 and other study supplies [applicable to “CSL830-Continuation” Subjects, only].
- Perform CSL830 accountability.
- Confirm subject is capable of using medication for the treatment of breakthrough HAE attacks (independently or with assistance).
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record prior / concomitant therapies.

- Review the individual acute action plan with subject.
- Train subject:
 - Instruct on use of the eDiary.
 - Instruct on the CSL830 injection technique.
 - Instruct on the CSL830 dosing regimen.
 - Supervise (observe) subject's first administration of CSL830.
 - Provide written instructions on the handling, reconstitution, and self-administration of CSL830; the suggested interval between each administration of CSL830 is 3 or 4 days.
- Schedule the next telephone contact and the next study visit.

8.4.3.2 Week 1, Day 4

“CSL830-Naïve” Subjects and “CSL830-Interrupted” Subjects will attend a study visit on Day 4 (+ 1 day).

The Day 4 Visit may be waived for “CSL830-Interrupted” Subjects (only) if the investigator has confirmed that the subject can adequately treat himself/herself with CSL830 (ie, no further training is necessary). In this case, all activities scheduled for the Day 4 Visit may be conducted at the Day 1 Visit.

“CSL830-Continuation” Subjects are not required to attend a study visit on Day 4.

The following procedures will be performed by the investigator or delegate:

- Review subject eDiary; record information on HAE attacks in eCRF.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Train subject:
 - Instruct on use of the eDiary.
 - Instruct on the CSL830 injection technique.
 - Instruct on the CSL830 dosing regimen.
 - Supervise subject's second administration of CSL830.
- Dispense CSL830/study supplies to subject.
- Perform CSL830 accountability.
- Schedule the next telephone contact and the next study visit.

8.4.3.3 Week 5

Subjects will be contacted by telephone on Day 29 (± 2 days) to record AEs and concomitant therapies.

8.4.3.4 Week 9

Subjects will attend a study visit on Day 57 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs, including weight.
- Physical examination.
- Assess risk of DVT and PE.
- CCI [REDACTED]
- Obtain blood samples for the following:
 - Hematology.
 - Biochemistry.
 - Coagulation.
- CCI [REDACTED]
- Obtain a urine sample for urinalysis.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Assess subject for CSL830 dose continuation or CSL830 dose increase.
 - During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, ≥ 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). A dose increase in Treatment Period 1 is intended as rescue prophylaxis, to provide the opportunity for subjects who have very frequent HAE attacks to continue in the study during the otherwise fixed-dose Treatment Period 1.

- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.3.5 Week 13

Subjects will be contacted by telephone on Day 85 (\pm 2 days) to record AEs and concomitant therapies.

8.4.3.6 Week 17

Subjects will attend a study visit on Day 113 (\pm 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs, including weight.
- Assess risk of DVT and PE.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Assess subject for CSL830 dose continuation or CSL830 dose increase.
 - During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (ie, \geq 12 attacks, as defined per protocol, within a 4-week evaluation period) are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). A dose increase in Treatment Period 1 is intended as rescue prophylaxis, to provide the opportunity for subjects who have very frequent HAE attacks to continue in the study during the otherwise fixed-dose Treatment Period 1.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.

- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.3.7 Week 21

Subjects will be contacted by telephone on Day 141 (± 2 days) to record AEs and concomitant therapies.

8.4.3.8 Week 25

Subjects will attend a study visit on Day 169 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Physical examination.
- Assess risk of DVT and PE.
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Obtain blood samples for the following:
 - Hematology.
 - Biochemistry.
 - Coagulation.
 - Viral serology.
 - Assessment of antibodies against C1-INH.
- CCI [REDACTED]
- Obtain a urine sample for urinalysis.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Assess subject for CSL830 dose continuation or CSL830 dose increase.

- Beginning with the Week 25 Visit and throughout Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). A dose increase in Treatment Period 2 is intended to allow investigators to adjust/optimize the dose for subjects who may need a higher prophylactic dose.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.4 Treatment Period 2

8.4.4.1 Week 29

All subjects will attend a study visit on Day 197 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs, including weight.
- Physical examination.
- Assess risk of DVT and PE.
- CCI [REDACTED]
- Obtain blood samples for the following:
 - Hematology.
 - Biochemistry.
 - Coagulation.

- CCI [REDACTED]

- CC [REDACTED]
- Obtain a urine sample for urinalysis.
 - Review subject eDiary; record information on HAE attacks in eCRF.
 - Assess subject for CSL830 dose continuation or CSL830 dose increase.
 - During Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details. A dose increase in Treatment Period 2 is intended to allow investigators to adjust/optimize the dose for subjects who may need a higher prophylactic dose.
 - Perform CSL830 accountability.
 - Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
 - Record AEs.
 - Record concomitant therapies.
 - If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
 - Dispense CSL830/study supplies to subject.
 - Schedule the next telephone contact and the next study visit.

8.4.4.2 Week 33

Subjects will be contacted by telephone on Day 225 (± 2 days) to record AEs and concomitant therapies.

8.4.4.3 Week 37

Subjects will attend a study visit on Day 253 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Physical examination.
- Assess risk of DVT and PE.

CC [REDACTED]
[REDACTED]

- Obtain blood samples for the following:
 - Hematology.
 - Biochemistry.
 - Coagulation.
- **CCI** [REDACTED]
- Obtain a urine sample for urinalysis.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Assess subject for CSL830 dose continuation or CSL830 dose increase.
 - During Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details. A dose increase in Treatment Period 2 is intended to allow investigators to adjust/optimize the dose for subjects who may need a higher prophylactic dose.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.4.4 Week 41

Subjects will be contacted by telephone on Day 281 (± 2 days) to record AEs and concomitant therapies.

8.4.4.5 Week 45

Subjects will attend a study visit on Day 309 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Assess subject for CSL830 dose continuation or CSL830 dose increase.
 - During Treatment Period 2, subjects who experience ≥ 3 HAE attacks (as determined per protocol) within an 8-week evaluation period are eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases are optional, and will be made only in subjects who are eligible, at the sole discretion of investigator. An evaluation period for any dose increase is defined as beginning after a dose-stable period (ie, 2 weeks after the initiation or dose increase of CSL830). See [Section 3.2](#) for additional details. A dose increase in Treatment Period 2 is intended to allow investigators to adjust/optimize the dose for subjects who may need a higher prophylactic dose.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.4.6 Week 49

Subjects will be contacted by telephone on Day 337 (± 2 days) to record AEs and concomitant therapies.

8.4.4.7 Week 53

Subjects will attend a study visit on Day 367 (± 2 days). See also [Section 8.4.6.1](#) for the Week 53 Visit of the Extension Period, which may also be the first visit of the Extension Period.

All subjects (including “CSL830_Naive” subjects), will attend the Week 53 Visit is to occur no earlier than 365 days after randomization.

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Physical examination.
- Assess risk of DVT and PE.
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Obtain blood samples for the following:
 - Hematology.
 - Biochemistry.
 - Coagulation.
 - Viral serology.
 - Assessment of antibodies against C1-INH.
- CCI [REDACTED]
- Obtain a urine sample for urinalysis.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Indwelling venous catheter is present (yes/no) [if status has changed, then provide a reason for the change (where available) and date of change (where available), and cross-check with AEs recorded in the eCRF for consistency (where applicable)].
- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Schedule the next study visit.

8.4.5 Subject Follow-up

8.4.5.1 Follow-up Visit

Subjects will attend a Follow-up Visit occurring 14 days (\pm 3 days) after the final visit in Treatment Period 2 or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn or if the Extension Period starts prior to the scheduled Follow-up Visit. See Section 8.4.6 for information on how subjects may continue onto the Extension Period from Treatment Period 2.

The following procedures will be performed by the investigator or delegate:

- Review subject eDiary; record information on HAE attacks in eCRF.
- Collect eDiary from subject (only if subject is not going to participate in the Extension Period).
- Record AEs.
- Record concomitant therapies.

8.4.6 Extension Period

8.4.6.1 Extension Period Week 1

The assessments performed for the Extension Period Visit 1 depend on whether a subject starts the Extension Period on the same day as the final visit for Treatment Period 2. Please see the specific instructions as noted below.

8.4.6.1.1 Extension Period Starts on the Same Day as Treatment Period 2 Completion (Week 53 of Treatment Period 2)

The following procedures will be performed by the investigator or delegate for subjects who start the Extension Period on the same day that they complete Treatment Period 2 in addition to the procedures performed on the final visit of Treatment Period 2. The Extension Period Visit 1 procedures will not be repeated if they were already performed for the final visit of Treatment Period 2 (see [Section 8.4.4.7](#)).

- Ensure that the subject completed an informed consent form (ICF) if he/she did not already consent to participate in the Extension Period.
- Schedule the next study visit.
- Instruct the subject on dosing volume. Note: Determine volume to be administered based on new algorithm for subjects weighing \geq 40 kg (subjects weighing $<$ 40 kg

will continue to undergo rounding as during Treatment Periods 1 and 2 [ie, rounded up to the nearest 500 IU]: 1. Determine weight-based dose. Round (up *or* down to the nearest 1000 IU), 2. Determine the volume to be administered, and 3. Instruct the subject on the volume to be administered twice weekly.

- Dispense CSL830 and other supplies to subjects.

Table 7 shows the assessments from Treatment Period 2 (Week 53 Visit) that will be used for Visit 1 of the Extension Period when the Extension Period starts on the Same Day and Treatment Period 2.

Table 7: Assessments from Treatment Period 2 (Week 53 Visit) to Be Used for Visit 1 of the Extension Period When the Extension Period Starts on the Same Day as Treatment Period 2

Assessments from Treatment Period 2 (Week 53 Visit)
Study Center Visit
Physical Examination
Indwelling Catheter (yes/no)
Vital Signs, including Body Weight
Assess Risk of DVT and PE
Urine Pregnancy Test ^A
Confirm Access to On-demand HAE Medication
CSL830 Accountability
Concomitant Medication
Adverse Events

Abbreviations: DVT = deep vein thrombosis; HAE = hereditary angioedema; PE = pulmonary embolism.

^A The results of the urine pregnancy test can only be used to satisfy the applicable eligibility criterion if the Treatment Period 2 End of Study Visit and the first visit of the Extension Period (ie, Day 367) occur on exactly the same day. Otherwise, a new pregnancy test must be performed at the first study visit in the Extension Period in order to confirm eligibility.

8.4.6.1.2 Extension Period Does Not Start on the Same Day as Treatment Period 2 Completion

It is strongly preferred that subjects initiate the Extension Period on the same day they complete Treatment Period 2; however, a period of up to 30 days is allowed between the final visit of Treatment Period 2 and the first visit of the Extension Period.

The procedures outlined above in [Section 8.4.6.1.1](#) will be conducted with the following exceptions for subjects who do not start the Extension Period on the same day that they

complete Treatment Period 2. For subjects who have an interrupted course/elect to take a rest period (of up to 30 days) of CSL830 treatment between Treatment Period 2:

1. The Treatment Period 2 End-of-Study Follow-up Visit will remain an on-site visit and will occur 14 days (\pm 3 days) after the last visit (Week 53) in Treatment Period 2 if the subject's Extension Period starts after the scheduled Follow-up Visit. (No Treatment Period 2 Follow-up Visit is required if the subject's Extension Period starts prior to the scheduled Follow-up Visit), and
2. The diary will not be used after the already planned Treatment Period 2 follow-up period (approximately 2 weeks); however, the following information will be reviewed, documented in the medical record, and recorded at the Extension Period Visit 1 for the period during which no diary is in use:
 - Any additional information on relevant medical history,
 - Any HAE attacks,
 - Any medication taken, and
 - Any adverse events

[Table 8](#) shows the assessments from Treatment Period 2 (Week 53 Visit) that will be repeated for Visit 1 of the Extension Period when the Extension Period does not start on the Same Day and Treatment Period 2.

Table 8: Assessments from Treatment Period 2 (Week 53 Visit) to Be Repeated for Visit 1 of the Extension Period When the Extension Period Does Not Start on the Same Day as Treatment Period 2

Assessments from Treatment Period 2 (Week 53 Visit)
Study Center Visit
Physical Examination
Indwelling Catheter (yes/no)
Vital Signs, including Body Weight
Assess Risk of DVT and PE
Urine Pregnancy Test ^A
Confirm Access to On-demand HAE Medication
CSL830 Accountability
Concomitant Medication
Adverse Events

Abbreviations: DVT = deep vein thrombosis; HAE = hereditary angioedema; PE = pulmonary embolism.

^A The results of the urine pregnancy test can only be used to satisfy the applicable eligibility criterion if the Treatment Period 2 End of Study Visit and the first visit of the Extension Period (ie, Day 367) occur on exactly the same day. Otherwise, a new pregnancy test must be performed at the first study visit in the Extension Period in order to confirm eligibility.

8.4.6.2 Extension Period Week 6

Subjects will be contacted by telephone at the Extension Period Week 6 Visit (± 2 days) to record AEs and concomitant therapies and self-administer the AE QoL questionnaire.

8.4.6.3 Extension Period Week 12

Subjects will attend a study visit at Extension Period Week 12 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- CCI [Redacted]
- CCI [Redacted]
- CCI [Redacted]
- CCI [Redacted]

- [REDACTED]
- Review subject eDiary; record information on HAE attacks in eCRF.
 - Perform CSL830 accountability.
 - Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
 - Record AEs.
 - Record concomitant therapies.
 - Dispense CSL830/study supplies to subject.
 - Schedule the next telephone contact and the next study visit.

8.4.6.4 Extension Period Week 18

Subjects will be contacted by telephone at the Extension Period Week 18 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.5 Extension Period Week 22

Subjects will self-administer the AE QoL questionnaire at Extension Period Week 22 (± 2 days).

8.4.6.6 Extension Period Week 24

Subjects will attend a study visit at Extension Period Week 24 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Physical examination.
- Assess risk of DVT and PE.
- Obtain blood sample for assessment of antibodies against C1-INH.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.6.7 Extension Period Week 26

CCI

8.4.6.8 Extension Period Week 30

Subjects will be contacted by telephone at the Extension Period Week 30 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.9 Extension Period Week 36

Subjects will attend a study visit at Extension Period Week 36 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- CCI
- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.6.10 Extension Period Week 42

Subjects will be contacted by telephone at the Extension Period Week 42 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.11 Extension Period Week 46

Subjects will self-administer the AE QoL questionnaire at Extension Period Week 46 (± 2 days).

8.4.6.12 Extension Period Week 48

Subjects will attend a study visit at Extension Period Week 48 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Physical examination.
- Assess risk of DVT and PE.
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Obtain blood samples for the following:
 - ALT/AST
 - Coagulation.
 - Assessment of antibodies against C1-INH.
 - Viral serology.
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Dispense CSL830/study supplies to subject.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Perform CSL830 accountability.
- Record concomitant therapies.
- Record AEs.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Schedule the next telephone contact and the next study visit.

8.4.6.13 Extension Period Week 50

CCI [REDACTED]

8.4.6.14 Extension Period Week 54

Subjects will be contacted by telephone at the Extension Period Week 54 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.15 Extension Period Week 60

Subjects will attend a study visit at Extension Period Week 60 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- CCI [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.6.16 Extension Period Week 66

Subjects will be contacted by telephone at the Extension Period Week 66 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.17 Extension Period Week 70

CCI [REDACTED]
[REDACTED]

8.4.6.18 Extension Period Week 72

Subjects will attend a study visit at Extension Period Week 72 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- Obtain blood sample for assessment of antibodies against C1-INH.
- For female subjects, obtain urine sample for dipstick pregnancy testing.

- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Record AEs.
- Record concomitant therapies.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.6.19 Extension Period Week 74

CCI

8.4.6.20 Extension Period Week 78

Subjects will be contacted by telephone at the Extension Period Week 78 Visit (± 2 days) to record AEs and concomitant therapies.

8.4.6.21 Extension Period Week 84

Subjects will attend a study visit at Extension Period Week 84 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Vital signs including weight.
- Assess risk of DVT and PE.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks.
- Perform CSL830 accountability.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Dispense CSL830/study supplies to subject.
- Schedule the next telephone contact and the next study visit.

8.4.6.22 Extension Period Week 88 (Final Visit)

Subjects will attend a study visit at Extension Period Week 88 (± 2 days).

The following procedures will be performed by the investigator or delegate:

- Physical examination.
- Vital signs including weight.
- Assess risk of DVT and PE.

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Obtain blood samples for the following:
 - ALT/AST
 - Coagulation.
 - Viral serology.
 - Assessment of antibodies against C1-INH.
- CCI [REDACTED]
- Obtain a urine sample for urinalysis.
- Indwelling venous catheter is present (yes/no) [if status has changed, then provide a reason for the change (where available) and date of change (where available), and cross-check with AEs recorded in the eCRF for consistency (where applicable)].
- For female subjects, obtain urine sample for dipstick pregnancy testing.
- Review subject eDiary; record information on HAE attacks in eCRF.
- Perform CSL830 accountability.
- Confirm access to on-demand medication for the treatment of breakthrough HAE attacks. The subject will be advised to resume usual medical care upon completion of the study
- Record AEs.
- Record concomitant therapies.
- Schedule the next telephone contact.
- Collect eDiary.

8.4.6.23 Extension Period Week 90 (Follow Up)

Subjects will be contacted by telephone 14 days (\pm 3 days) after the final visit (Extension Period Week 88) of the Extension Period, or any visit resulting in study discontinuation, unless informed consent/assent has been withdrawn to record AEs and concomitant therapies.

8.4.7 Unscheduled Visits

Unscheduled visits can be arranged at any time point during the study (eg, to reinstruct subject on correct injection technique, dosing regimen, or use of eDiary; to repeat a study procedure; to pick up new study medication), at the discretion of the investigator or upon request of the subject.

8.4.8 Subject Assessments

During Treatment Periods 1 and 2 and the Extension Period, subjects will report the following information in the eDiary:

- Details of the administration of CSL830 (ie, dose, date, start time of injection, location of injection, and needle type used).
- Local reactions at the site of CSL830 administration (discomfort [eg, pain, burning], swelling, bruising, itching) (yes/no).
- Prodromal symptoms experienced (fatigue, rash, muscle aches, nausea, tingling) (yes/no).
- HAE symptoms experienced (yes/no).
- Day and time of HAE symptom onset.
- Location of HAE symptom(s) from most severe to least severe (face/lips; tongue/inside mouth; throat/voice box; abdominal; genitourinary; extremities [right arm, left arm, right leg, left leg]).
- Location of primary HAE symptom (face/lips; tongue/inside mouth; throat/voice box; abdominal; genitourinary; extremities [right arm, left arm, right leg, left leg]).
- Severity of HAE symptom(s) (mild, moderate, or severe).
- Medication for the treatment of breakthrough HAE attacks is needed (yes/no).
- If medication for the treatment of breakthrough HAE attacks is needed:
 - Medication used (Berinert, Kalbitor, Firazyr, C1-INH other than Berinert, fresh frozen plasma, other).
 - Dose administered.
 - Day and time started.
 - Administration of medication by a health-care professional (yes/no).
- Other AEs (yes/no).
- Other concomitant medication (yes/no).

CCI

CCI

CCI
[REDACTED]CCI
[REDACTED]

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 subject 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/assent (as appropriate) until the Follow-up Visit (see [Section 8.4.5](#) and [Section 8.4.6](#)).

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/assent (as appropriate) but before the investigational product administration.
- Intercurrent illnesses with an onset after administration of the investigational product.

Adverse events do not include:

- Events identified at Screening that meet exclusion criteria
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
 - Planned hospitalizations due to pre-existing conditions, which have not worsened.

NOTE: A pre-planned surgery must have been pre-planned prior to the subject's participation in the study (ie, at the time of signing informed consent/assent [as appropriate]). This information must be presented in the subject's source documentation.

- 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.
- Overdose of the investigational product or any concomitant therapy that does not result in any adverse signs or symptoms.
- HAE attacks; unless the attack meets the criteria of an SAE (see [Section 9.1.3](#)) or unless the attack significantly worsens following on-demand treatment (eg, with IV Berinert).

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

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

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

9.1.2 Adverse Event of Special Interest

There are several AEs that will be monitored closely as AESIs to enable an adequate risk-benefit evaluation of CSL830 versus standard therapy. Additional data may be requested for these events. The AESIs will be:

- Thrombotic or thromboembolic events.

- Anaphylaxis (defined as severe and clinically relevant systemic allergic reaction with sudden onset and rapid progression. Clinical criteria for the diagnosis of anaphylaxis are presented in Table 9).

Table 9: Clinical Criteria for the Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least 1 of the following:
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF = peak expiratory flow; BP = blood pressure.

* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Reference: [Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117\(2\):391-7.](#)

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 non-serious AEs.

9.2 Severity of Adverse Events

9.2.1 Unsolicited Adverse Events

The severity of each AE (ie, non-serious and serious AEs) is to be assessed using the following criteria:

Table 10: Severity of Unsolicited Adverse Events

Severity	Definition ¹
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.

¹ CDISC SDTM Severity Intensity Scale for Adverse Event Terminology

9.2.2 Solicited Local Adverse Events (Injection Site Reactions)

Solicited local AEs are injection site reactions at the CSL830 injection site that are specifically asked for and recorded.

Subjects will record the occurrence of local AEs (injection site reactions) in their eDiary by answering the following question: “Have you experienced any local reactions at the injection site (eg, discomfort, swelling, bruising, or itching)? (yes/no)”. Subjects will be instructed to take notes (outside of the diary) to describe any local AEs they experience and to report that information to their investigator. Each investigator will use the information from the diary and the subject to identify and grade the intensity of each symptom. Each symptom will be entered as an independent AE.

Solicited local AEs are defined and graded as follows:

Table 11: Intensity of Solicited Local Adverse Events

Solicited Local Adverse Event	Intensity Grading		
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Discomfort at the injection site after the injection procedure (eg, pain, burning)	Present but does not interfere with activity	Repeated use of non-narcotic pain reliever for over 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Swelling at the injection site worse than at the end of the injection procedure	Up to 2.5 cm larger than at the end of the injection procedure and does not interfere with activity	2.6 to 5.0 cm larger than at the end of the injection procedure or interferes with activity	Over 5.0 cm larger than at the end of the injection procedure or prevents daily activity
Bruising at the injection site	Up to 2.5 cm	2.6 to 5.0 cm	Greater than 5.0 cm
Itching at the injection site	Present but does not interfere with activity	Interferes with activity	Prevents daily activity

9.3 Causality of Adverse Events

The causal relationship of an AE to CSL830 must always be assessed by the investigator. All AEs will be classified as either related or not related to CSL830. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to CSL830.

The degree of certainty with which an AE is attributed to CSL830 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 CSL830.
- 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 CSL830, drug withdrawal or reproduced on re-challenge).

9.4 Observation Periods for Adverse Events

Treatment Period 1 and Treatment Period 2

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent/assent (as appropriate) for participation in this study and finish with the final study visit.

Extension Period

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent/assent (as appropriate) for participation in the Extension Period and finish with the follow-up visit contact.

If the investigator becomes aware of an SAE that has started after the observation period has finished, and the event could in some way be associated with the investigational product, then this must also be reported to CSL Global Clinical Safety and Pharmacovigilance (see [Section 9.6](#)).

9.5 Adverse Event Reporting

9.5.1 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 for 30 days after the final administration of CSL830, whichever is sooner.

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

9.5.2 Adverse Events of Special Interest

Adverse events of special interest should be considered medically significant and are therefore SAEs. The expedited reporting procedures for SAEs are described in detail in [Section 9.6.1](#).

9.6 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 AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the Investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator. In this case, the investigator should follow-up with a completed, signed, and dated electronic document.

All SAEs that occur during the course of the study, whether or not causally related to CSL830, must be reported immediately (within 24 hours of the investigator becoming aware of the event) to CSL.

Adverse events occurring in the period between the time the subject gave written informed consent/assent (as appropriate) and the first exposure to CSL830 that meet 1 or more of the seriousness criteria for AEs must be reported to CSL 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 CSL830 must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL.**

Contact details and guidance for reporting SAEs will be provided to study site before the study starts.

9.6.1 Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate reporting of SAEs include:

- Identifiable subject.
- Suspected medicinal product and / or procedure.
- Event term.
- Identifiable reporting source.

In addition, the investigator must:

- Report all SAEs to the relevant institutional review board (IRB) / independent ethics committee (IEC) within the timeframe specified by the IRB / IEC.
- Submit follow-up reports to CSL Clinical Safety and Pharmacovigilance until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

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

When submitting SAE reports and any other related reports (eg, discharge summaries) to CSL, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name, date of birth, or address.

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).

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in [Section 9.4](#).

9.7 Other Significant Event Reporting

9.7.1 Overdose

Details (ie, volume, location of infusions, infusion rate) of overdose of CSL830 or any concomitant therapy must be recorded in the eCRF. Any overdose of CSL830 that results in any adverse signs or symptoms, and considered by the investigator to be medically significant, must be reported as an SAE (see [Section 9.1.3](#)).

9.7.2 Pregnancy and Lactation

Females who are pregnant, intending to be pregnant or nursing are not eligible to enroll or continue to participate in this study. C1-esterase inhibitor approved for intravenous treatment or prophylaxis of HAE is a Pregnancy Category C medication.

A female subject who becomes pregnant while participating in the study must notify the investigator immediately. The subject must discontinue treatment with CSL830. If the female subject is in the active Treatment Period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in [Section 4.2](#).

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

Whenever possible, a pregnancy in a 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.

If the partner of a male subject participating in this study becomes pregnant, the male subject should inform the investigator as soon as possible. The investigator will attempt to obtain written permission directly from the pregnant female that her gynecologist can be contacted by the investigator and/or the sponsor. In this case, the investigator may contact the gynecologist of the pregnant female to review potential risks of C1-INH and the pregnancy will be followed to its outcome.

9.8 IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and CSL830-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.

9.9 Follow-up of Adverse Events

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study. A subject with an SAE will be followed until the SAE has resolved or stabilized. A subject with a non-serious AE will be followed for as long as a period of 30 days after the final administration of the investigational product, if the AE has not resolved before that time. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. For SAEs, details of the subject's progress should also be submitted to CSL Global Clinical Safety and Pharmacovigilance. Contact details for CSL Global Clinical Safety and Pharmacovigilance will be provided to each site at the time of study start.

10 Assessments

10.1 Subject Characteristics

Subject characteristics to be evaluated will include:

- Demographics (eg, sex, race, height, body weight).
- Clinically significant medical history.
- Confirmation of HAE diagnosis and identification of HAE type (see [Section 4.1.2](#)).
- Frequency of HAE attacks in the 2 month period that was used to qualify subjects for participation in the current study (see [Section 4.1.2](#)).
- Frequency of HAE attacks during the Screening Period (for "CSL830-Naïve" Subjects and "CSL830-Interrupted" Subjects, only [ie, subjects who participate in the Screening Period]).
- Prior and/or concomitant therapy, including therapy related to HAE.

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10.3 Safety Assessments

Safety will be assessed using:

- Vital signs.
- Physical examination.
- Clinical scores of risk assessment for DVT and PE.
- Solicited local AEs (ie, injection site reactions).
- Other AEs, including SAEs.
- Clinical laboratory assessments:
 - Hematology.
 - Biochemistry.
 - Coagulation profile
 - Viral serology.
 - Anti-C1-INH antibodies.
 - Urinalysis.

Clinical laboratory tests will be performed at time points as detailed in the schedule of assessments (the [Schedule of Laboratory Assessments for “CSL830-Continuation” Subjects](#), the [Schedule of Laboratory Assessments for “CSL830-Interrupted” Subjects and “CSL830-Naïve” Subjects](#), and the [Schedule of Events for the Extension Period](#)). More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator. The laboratory values will be entered into the eCRF using the same units as provided by the laboratory. Verification of the laboratory values, if applicable, will be recorded in the source data.

All abnormal laboratory values will require a comment by the investigator on the respective eCRF or the laboratory report. The following codes should be used:

- Error (ER) (eg, laboratory error, improper sample preparation, hemolysis, delayed transit to laboratory).
- Abnormal, not clinically significant (ANCS).

- Abnormal, clinically significant (ACS).

Tests resulting in abnormal laboratory values during the study period that have been classified by the investigator as ACS should be repeated as soon as possible after receiving the laboratory report to rule out laboratory error.

Any laboratory values that deviate from the reference ranges and are considered by the investigator as clinically significant (ie, classified as an ACS value) at any visit after baseline also must be documented in the eCRF as an AE.

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11 Statistics

11.1 Sample Size Estimation

100 subjects are planned to complete Treatment Periods 1 and 2 of the study. The sample size is based on guidelines issued by the International Conference on Harmonisation [ICH 1994] and not on other statistical calculations. This allows observation of ≥ 1 adverse event with a probability of 3% at 95% confidence.

Only subjects from the United States who completed Treatment Period 2 are eligible to participate in the Extension Period. Approximately 50 of these subjects are expected to enroll in the Extension Period.

11.2 Description of Analysis Datasets

11.2.1 Screening Population

The Screening Population will comprise all subjects who provide informed consent/assent (as appropriate) (see [Section 8.4.1](#)).

11.2.2 Intent to Treat Population

The Intent to Treat (ITT) Population will comprise all subjects who provide informed consent/assent (as appropriate) and are randomized, regardless of whether or not they receive CSL830.

11.2.3 Safety Population

The Safety Population will comprise all subjects, who provide informed consent/assent (as appropriate), who are randomized, and who received at least 1 dose or a partial dose of CSL830.

11.2.4 Per-Protocol Population

The Per-protocol (PP) Population will comprise all subjects in the ITT Population, excluding subjects who have a significant protocol violation. Further details will be defined in the statistical analysis plan.

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11.2.7 CCI [REDACTED]

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11.3 Statistical Analyses and Methods

Subject disposition and HAE attacks during the Screening Period will be summarized using the Screening Population. Demographic and subject characteristics will be summarized using the ITT and Safety Populations. Adverse events that occur during the Screening will be listed using the Screening Population and will also be summarized for subjects in the Safety Population. All other safety data will be summarized using the Safety Population. The efficacy endpoints considered as secondary will be summarized using the ITT and PP Populations. CCI [REDACTED]

Continuous variables will be described using mean with the relevant 95% confidence intervals (CI); geometric mean and the relevant 90% CI; standard deviation; range; 25th, 50th (median), and 75th percentiles; geometric coefficient of variation expressed as a percentage (CCI [REDACTED]); and counts of missing and non-missing values.

Categorical values will be described using counts and percentages.

A complete description of the statistical analyses and methods will be available in 2 statistical analysis plans (1 for the original protocol and 1 for the Extension Period amendment), which will be finalized before the database is locked.

11.3.1 Subject Disposition and Characteristics

11.3.1.1 Subject Disposition

Treatment Period 1 and Treatment Period 2

At a minimum, the following will be presented in summary tables for the Screening Population by treatment and overall:

- The number of subjects who provide consent/assent (as appropriate).
- The number of subjects who undergo Screening.
- The number of subjects who continue directly from CSL830_3001 (ie, “CSL830-Continuation” Subjects).
- The number of subjects who have interrupted treatment between CSL830_3001 and CSL830_3002 (ie, “CSL830-Interrupted” Subjects).
- The number of subjects who are randomized to treatment with CSL830 (ie, the number of subjects who enter Treatment Period 1).

- The number of subjects who are randomized to treatment with 40 IU/kg CSL830.
- The number of subjects who are randomized to treatment with 60 IU/kg CSL830.
- The number of subjects who undergo 1 CSL830 dose increase in Treatment Period 1.
- The number of subjects who undergo 1 CSL830 dose increase in Treatment Period 2.
- The number of subjects who undergo 2 CSL830 dose increases in Treatment Period 1.
- The number of subjects who undergo 2 CSL830 dose increases in Treatment Period 2.
- The number of subjects who administer the same CSL830 dose over Treatment Period 1.
- The number of subjects who administer the same CSL830 dose over Treatment Period 2.
- The number of subjects who administer the same CSL830 dose over Treatment Periods 1 and 2.
- The number of subjects who complete Treatment Period 2.
- The number of subjects who discontinue participation in the study (including the reason for discontinuation).

Disposition data (including the reason for discontinuing use of CSL830 or withdrawing from the study) will be listed by site and subject. All Screen Failures will be listed.

The number of subjects in each analysis population will be summarized (by subjects who are randomized to 40 IU/kg CSL830; by subjects who are randomized to 60 IU/kg CSL830; and overall). The number of subjects in each analysis population will also be summarized (by subjects who are randomized to 40 IU/kg CSL830 and who have 1 dose increase; by subjects who are randomized to 40 IU/kg CSL830 and who have 2 dose increases; by subjects who are randomized to 60 IU/kg CSL830 and who have 1 dose increase; and overall) for both Treatment Period 1 (only) and for Treatment Periods 1 and 2 (together). A by-subject listing will be produced including the assignment of subjects to analysis populations.

Extension Period

The above described summaries for subject disposition will be performed for subjects who continued into the Extension Period by treatment and overall, except for the number of subjects who provide consent/assent (as appropriate) and the number of subjects who complete Treatment Period 2. In addition, the following will be presented by treatment and overall:

- The number of subjects who undergo no CSL830 dose increase in the extension Period

- The number of subjects who undergo 1 CSL830 dose increase in the extension period
- The number of subjects who undergo 2 CSL830 dose increases in the extension period
- The number of subjects who undergo no CSL830 dose increase in Treatment Period 1, Treatment Period 2, and the Extension Period

11.3.1.2 Subject Characteristics

Subject characteristics will be presented in summary tables for the ITT and Safety Populations.

Treatment Period 1 and Treatment Period 2

Subject characteristics will be presented in summary tables for all subjects in the ITT and Safety Populations. Demographic and baseline characteristics and medical history will be summarized (by subjects who are randomized to 40 IU/kg CSL830; by subjects who are randomized to 60 IU/kg CSL830; and overall). Demographic and baseline characteristics and medical history will also be summarized (by subjects who are randomized to 40 IU/kg CSL830 and who have 1 dose increase; by subjects who are randomized to 40 IU/kg CSL830 and who have 2 dose increases; by subjects who are randomized to 60 IU/kg CSL830 and who have 1 dose increase; and overall) for both Treatment Period 1 (only) and for Treatment Periods 1 and 2 (together). This will include age (years), sex, race, ethnicity, height, weight, and body mass index (BMI; calculated as kg/m²). Medical history will be presented by system organ class (SOC) and preferred term (PT), and will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequency counts and percentages. A by-subject listing of demographic characteristics, baseline characteristics, and medical history will also be presented.

Extension Period

The above described summaries for demographic and baseline characteristics and medical history will be also performed for subjects who participated in the Extension Period. The only difference is that data will also be summarized by treatment group and dose increase in the Extension Period.

11.3.2 Efficacy Analyses

11.3.2.1 Primary Efficacy Analysis

There is no primary efficacy analysis. The primary analysis for study CSL830_3002 is safety-based and can be found in [Section 11.3.3.1](#).

11.3.2.2 Secondary Efficacy Analyses

The ITT and PP Populations will be used as analysis populations for efficacy analyses.

Treatment Period 1 and Treatment Period 2

All subjects in the ITT and all subjects in the PP Population will be used as analysis populations for efficacy analyses. The number and percentage of subjects who are responders at the last visit in Treatment Period 1 and at the last visit in Treatment period 2, when “response” is defined as a $\geq 50\%$ relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks used to qualify for participation in the current study will be assessed. The number and percentage of subjects will be summarized (by subjects who are randomized to 40 IU/kg CSL830; and by subjects who are randomized to 60 IU/kg CSL830). Subjects who undergo a dose increase will be flagged in the listing.

The number and percentage of subjects who experience a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period will be summarized at the last visit in Treatment Period 1 and at the last visit in Treatment Period 2 (by subjects who are randomized to 40 IU/kg CSL830 and by subjects who are randomized to 60 IU/kg CSL830). Subjects who undergo a dose increase will be flagged in the listing.

A within-subject analysis will give the number and percentage of subjects who are responders or non-responders before a dose increase, after a first dose increase, and after a second dose increase (only applicable for subjects who are randomizes to the 40 IU/kg CSL830 treatment group) summarized by subjects who are randomized to the 40 IU/kg CSL830 and by subjects who are randomized to the 60 IU/kg CSL830 treatment group. Furthermore, a within-subject analysis will give the number and percentage of subjects who experience or who do not experience a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period before a dose increase, after a first dose increase, and after a second dose increase (only applicable for subjects who are randomizes to the 40IU/kg treatment group) summarized by

subjects who are randomized to the 40 IU/kg and by subjects who are randomized to the 60 IU/kg treatment group.

The secondary efficacy analyses will be done both for Treatment Period 1 (only) and for Treatment Periods 1 and 2 (together).

A descriptive subgroup analysis will be done for subjects who use oral agents for the treatment of HAE and for subjects who do not. A descriptive subgroup analysis will be done for subjects who previously used intravenously administered C1-INH for routine (long-term) prophylaxis. Additional subgroup analyses will be conducted for subjects who participated in study CSL830_3001 and for subjects who did not AND for subjects who are aged < 18 years and \geq 18 years. Subjects who use oral agents for the treatment of HAE will be flagged in the listings.

Extension Period

For the subjects who are in the Extension Period, the above described analyses of the number and percentage of subjects who are responders and the number and percentage of subjects who experience a time-normalized number of HAE attacks of < 1 HAE attack per 4-week period will be summarized for the Extension Period by treatment (40 IU/kg CSL830; 60 IU/kg CSL830) and for all treatment periods.

11.3.3 Safety Analyses

The Safety Population will be used for analyses of safety.

Treatment Period 1 and Treatment Period 2

All subjects in the Safety Population will be included in the safety analyses. The primary safety analysis will be performed by treatment group (ie, subjects who are randomized to 40 IU/kg CSL830 and by subjects who are randomized to 60 IU/kg CSL830). Data collected from those subjects will be included in the 40 IU/kg and 60 IU/kg CSL830 treatment groups, respectively, until the time they undergo the final study visit or they undergo a CSL830 dose increase, whichever comes first.

A secondary safety analysis will be performed by treatment group [ie, subjects who are randomized to 40 IU/kg CSL830 and by subjects who are randomized to 60 IU/kg CSL380, regardless of any dose increase(s)]. Data collected from those subjects will be included in the

40IU/kg and 60IU/kg CSL830 treatment groups, respectively, until the time they undergo the final study visit.

The analyses will be done both for Treatment Period 1 (only) and for Treatment Period 1 and 2 (together), unless otherwise noted.

Furthermore, safety analyses will be summarized by subjects who are randomized to 40 IU/kg CSL830 and who have 1 dose increase; by subjects who are randomized to 40 IU/kg CSL830 and who have 2 dose increases; by subjects who are randomized to 60 IU/kg CSL830 and who have 1 dose increase.

After the dose increase, data collected from subjects who undergo a 20 IU/kg dose increase from 40 IU/kg to 60 IU/kg or from 60 IU/kg to 80 IU/kg in Treatment Period 1 will be summarized separately for the 60 IU/kg and 80 IU/kg CSL830 doses. Furthermore, data collected from subjects who undergo a 20 IU/kg dose increase from 40 IU/kg to 60 IU/kg or from 60 IU/kg to 80 IU/kg in Treatment Period 2 will also be summarized separately for the 60 IU/kg and 80 IU/kg CSL830 doses.

After a second dose increase, data collected from subjects who undergo a 20 IU/kg x 2 dose increase from 60 IU/kg to 80 IU/kg in Treatment Period 1 will be summarized separately for the 80 IU/kg CSL830 dose. Furthermore, data collected from subjects undergo a 20 IU/kg x 2 dose increase from 60 IU/kg to 80 IU/kg in Treatment Period 2 will also be summarized separately for the 80 IU/kg CSL830 dose.

Subjects who undergo a CSL830 dose increase will be flagged in the listing

A descriptive subgroup analysis will be done for subjects who use oral agents for the treatment of HAE and for subjects who do not. A descriptive subgroup analysis will be done for subjects who previously used intravenously administered C1-INH for routine (long-term) prophylaxis. Additional subgroup analyses will be conducted for subjects who participated in study CSL830_3001 and for subjects who did not AND for subjects who are aged < 18 years and ≥ 18 years. Subjects who use oral agents for the treatment of HAE will be flagged in the listings.

Extension Period

Data collected from subjects in the Extension Period will be summarized as follows:

- For the Extension Period only (separate from data collected during Treatment Period 1 and Treatment Period 2)
- For Treatment Period 1, Treatment Period 2 and the Extension Period (combined)

Only data collected from subjects who are enrolled in the Extension Period will be included in these analyses.

11.3.3.1 Primary Safety Analysis

The person-time incidence rate of each primary endpoint safety event will be assessed as defined above in [Section 11.3.3](#) and overall. The person-time incidence rates are the number of subjects experiencing each primary endpoint safety event during the respective treatment duration with CSL830, divided by the sum of each subject's time at risk in the respective treatment. The person-time incidence rate of each primary endpoint safety event will be assessed for Treatment Period 1 and for the Treatment Periods 1 and 2 overall. For the subjects who are in the Extension Period, the person-time incidence rate of each primary endpoint safety event will also be assessed for the Extension Period and for the treatment periods overall.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA).

11.3.3.2 Secondary Safety Analyses

Adverse event data will be presented in individual listings and summary tables.

The number and percentage of subjects experiencing SAEs, temporally-related AEs, increased risk scores for DVT or PE, thromboembolic events, inhibitory anti-C1-INH antibodies, or clinically significant abnormalities in laboratory assessments during treatment will be summarized as defined above in [Section 11.3.3](#) and overall. The number and percentage of subjects who become seropositive for HIV-1, HIV-2, HBV, or HCV will be summarized as defined above in [Section 11.3.3](#) and overall. The number and percentage of subjects experiencing solicited local AEs, the number of solicited local AEs, and the number of solicited local AEs per administration will be summarized as defined above in [Section 11.3.3](#) and overall. The number and percentage of administrations of CSL830 resulting in solicited local AEs will be summarized as defined above in [Section 11.3.3](#) and overall. An overall summary of AEs will be given.

Temporally-related AEs will be defined as AEs which began within 24 hours of administration of CSL830. Note that temporally-related AEs are referenced as “suspected ADRs” in study CSL830_3001. Temporally-related AEs occurring during treatment will be summarized as defined above in [Section 11.3.3](#) and overall in the current study (CSL830_3002).

Summaries will include the number and percentage of subjects, the number of AEs, and the number of AEs per administration and per week (where applicable) and will also be summarized as defined above in [Section 11.3.3](#) and at study visits. Summaries by SOC and PT will also be presented.

Adverse events will also be described by intensity, relationship to CSL830, duration, and seriousness.

The safety analyses will be conducted for Treatment Period 1 (only), Treatment Period 2 (only), and for Treatment Period 1 and 2 (together). For the subjects who are in the Extension Period, the safety analyses will be conducted for the Extension Period and for the treatment periods overall.

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11.3.6 Interim Analysis

Interim analyses will be conducted on an as-needed basis in order to support regulatory activities. The results of interim analyses are not intended to be used to stop or adapt the study. Additional details will be provided in the SAP.

11.3.7 Missing Data

The primary safety endpoints are the person-time incidence rate of each primary endpoint safety event. Only if a subjects drops out directly after randomization this will lead to missing data for a subject, but the primary safety endpoints are still calculable. Therefore, no imputation is planned.

12 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, US Food and Drug Administration [FDA]). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will immediately notify the investigator of an 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.

13 Regulatory and Ethics Considerations

13.1 Regulatory Considerations

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

This study will be conducted under an a Clinical Trial Application, a Clinical Trial Notification or an FDA Investigational New Drug application, as appropriate, and 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.

13.2 Institutional Review Board / Independent Ethics Committee

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

13.3 Subject Information and Informed Consent

Informed consent/assent must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form

whenever possible and deemed appropriate by the IRB / IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

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), the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF/assent form indicating that they re-consent to participate in the study.

13.4 Subject Identification and 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.

13.5 Indemnity and Compensation

It is CSL policy that persons who participate in CSL's clinical studies should be no worse off for their having been involved in the study. These persons include the subjects / volunteers, the investigator, the hospital and the IRB / IEC.

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 14.1](#)).

14 Administrative Considerations

14.1 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.

14.2 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.

14.3 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 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.

14.4 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 subjects who have been entered in the study deviate from the IRB / IEC-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.

14.5 Documentation and Record Keeping

14.5.1 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 CSL830 or concomitant therapy, any AEs experienced, and other notes as appropriate. These records constitute source data.

An eCRF will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless there is prior agreement that the eCRF is the source data.

All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

The subject eDiary will be completed by the subject. At each clinic visit, the subject will present the completed diary to the investigator for review of entries and transfer of relevant information to the eCRF.

14.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. 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).

14.5.3 Record Retention

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 the 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.

14.6 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, all investigators and the relevant regulatory agencies will be immediately notified of the action and the reason for it. The investigator at each study site will advise the IRB / IEC overseeing the study at their site.

14.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). 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.

14.8 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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