

Statistical Analysis Plan

CSL Behring GmbH

Protocol: CSL830_3002

EUDRACT: 2014-001054-42

Treatment: CSL830

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

Author: PPD
Document Status: Version 2 Final
Version Dates: 12SEP2017

Pages: 60

STATEMENT OF CONFIDENTIALITY

The information contained herein is expressly subject to the terms and conditions of the Confidentiality Agreement by and between Chiltern and CSL Behring GmbH.

Contents

1	INTRODUCTION	8
2	STUDY OBJECTIVES	9
2.1	PRIMARY ENDPOINTS	9
2.2	SECONDARY ENDPOINTS	10
2.2.1	<i>Secondary safety endpoints</i>	10
2.2.2	<i>Secondary efficacy endpoints</i>	11
2.3	CCI [REDACTED]	11
2.2.3	CCI [REDACTED]	11
2.2.4	CCI [REDACTED]	12
3	STUDY DESIGN	13
3.1	DISCUSSION OF STUDY DESIGN	13
3.1.1	<i>Study Design</i>	13
3.1.2	<i>Screening Visit</i>	14
3.1.3	<i>Treatment Periods 1 and 2</i>	14
3.1.4	<i>Extension Period</i>	15
3.1.5	<i>Planned number of sites</i>	15
3.2	STUDY TREATMENT	15
3.3	STUDY SCHEDULE	17
3.3.1	<i>Planned study duration</i>	17
3.3.2	<i>Screening</i>	17
3.3.3	<i>Schedule of Events</i>	17
3.3.4	<i>Unscheduled Visits</i>	17
3.3.5	<i>Subject Assessments with the eDiary</i>	18
3.4	STUDY ANALYSIS POPULATIONS	18
3.4.1	<i>Intent to Treat Population</i>	19
3.4.2	<i>Safety Population</i>	19
3.4.3	<i>Per-Protocol Population</i>	19
3.4.4	CCI [REDACTED]	19
3.4.5	CCI [REDACTED]	19
3.4.6	CCI [REDACTED]	19
3.5	DISCONTINUED SUBJECTS	19
3.6	RANDOMIZATION	20
3.7	BLINDING	20
3.8	SAMPLE SIZE	20
4	STATISTICAL METHODOLOGY	21
4.1	PLANNED ANALYSES	21
4.2	INTERIM ANALYSIS	22
4.3	DISPOSITION OF SUBJECTS	22
4.4	BASELINE AND DEMOGRAPHIC CHARACTERISTICS	24
4.4.1	<i>Extent of exposure</i>	25
4.4.2	<i>Treatment compliance</i>	25
4.5	PRIOR AND CONCOMITANT MEDICATION	26
4.6	EFFICACY ANALYSIS	27
4.6.1	<i>Primary efficacy endpoints</i>	28
4.6.2	<i>Method of analysis for primary efficacy endpoint</i>	28
4.6.3	<i>Secondary efficacy endpoints</i>	28

4.6.3.1	The percentage of subjects who are responders.....	29
4.6.3.2	Time-normalized HAE attack frequency of < 1 HAE attack per 4-week Period	30
4.7	SAFETY ANALYSIS	31
4.7.1	Primary Safety Analysis.....	31
4.7.2	Safety Analysis of the Secondary Safety Endpoints	34
4.7.2.1	Method of analysis for secondary safety endpoints.....	34
4.7.2.2	Laboratory findings.....	38
4.7.2.3	Analysis of Laboratory Findings	39
4.7.3	Vital Signs and Body Weight.....	39
4.7.4	Physical examinations	40
4.7.5	Risk Assessment for Deep Vein Thrombosis and Pulmonary Embolism	40
4.8	CCI [REDACTED]	41
4.9	CCI [REDACTED]	41
4.9.1	CCI [REDACTED]	42
4.9.2	CCI [REDACTED]	42
4.9.3	CCI [REDACTED]	43
4.9.4	CCI [REDACTED]	44
4.9.5	CCI [REDACTED]	44
4.9.6	CCI [REDACTED]	47
4.9.7	CCI [REDACTED]	48
4.9.7.1	CCI [REDACTED]	48
4.9.8	CCI [REDACTED]	49
4.9.9	CCI [REDACTED]	49
4.9.9.1	CCI [REDACTED]	50
4.9.9.2	CCI [REDACTED]	51
4.9.9.3	CCI [REDACTED]	51
4.9.9.4	CCI [REDACTED]	52
4.9.9.5	CCI [REDACTED]	52
4.9.9.6	CCI [REDACTED]	54
4.10	ADJUSTMENT FOR COVARIATES.....	55
4.10.1	Center effects	55
4.11	ANALYSIS POPULATIONS, PROTOCOL DEVIATIONS.....	55
4.12	HANDLING OF MISSING DATA.....	56
4.13	DEVIATIONS FROM SAP.....	56
4.14	CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL	56
5	TABLES AND LISTINGS	59
5.1	TABLE FORMAT	59
5.2	CONVENTIONS	59
5.3	TABLES	59
5.4	LISTINGS	60
5.5	FIGURES.....	60
5.6	APPENDICES.....	60
5.7	REFERENCES	60

SIGNATURE PAGE

Approved by:

PPD [Redacted]
PPD [Redacted]

PPD [Redacted]
Date [Redacted]

PPD [Redacted]
PPD [Redacted]
PPD [Redacted]
PPD [Redacted]

PPD [Redacted]
Date [Redacted]

PPD [Redacted]
Date [Redacted]

REVISION HISTORY

Date	Version	Summary of Changes
31 May 2017	Version 1 Final [Original]	Not applicable
12 Sep 2017	Version 2 Final	<ol style="list-style-type: none"> 1. A subgroup analysis for age (≤ 17 years / >17 years) have been added for the secondary efficacy endpoints and the CCI [REDACTED] 2. For HAE attacks which are not treatment-emergent, the calculations of the length of a rest period and the time between the End of Study Visit and the Follow-up Visit were corrected. 3. For the endpoints “Time-Normalized Number of HAE Attacks” and “Percentage of Subjects who are Responders” the description of the different time windows during which HAE attacks are included in the analyses was corrected for subject who are participating in the Extension Period and who have a rest period. 4. In the calculations of the time from randomization (Week 1, Day 1) until first or second dose increase the “+1” has been deleted. 5. The description of the concomitant medications which are included in the calculation of the time-normalized number of uses of rescue medication have been clarified by making it clearer that the start date of the concomitant medication is only compared to the start/end date of treatment-emergent HAE attacks. 6. Minor corrections and clarifications have been made, including word modifications and administrative changes.

Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLA	Biologic License Application
BMI	Body Mass Index
C1-INH	C1-Esterase Inhibitor
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computer Tomographic
DVT	Deep vein thrombosis
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
CCI	
F1+2	Prothrombin Fragment 1+2
GGT	Gamma Glutamyl Transferase
CCI	
HAE	Hereditary Angioedema
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
CCI	
INR	International Normalized Ratio
IRT	Interactive Response Technology
ITT	Intent to Treat
IU	International Unit
IV	Intravenous
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

PE	Pulmonary embolism
PT	Preferred Term
CCI	
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
CCI	
SMQ	Standard MedDRA Query
SOC	System Organ Class
Suspected ADR	Suspected Adverse Drug Reaction (AEs within 24 hours of administration of the investigational product and/or at least possibly related to investigational product administration and/or with no causality rating)
TEE	Thromboembolic Event
CCI	
WHO	World Health Organization
CCI	

1 Introduction

This document presents the statistical analysis plan (SAP) for

CSL Behring GmbH, Protocol No. CSL830_3002, dated 28 July 2014: “An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous (SC) administration of human plasma-derived C1 esterase inhibitor in the prophylactic treatment of hereditary angioedema”

and for

CSL Behring GmbH, Country-Specific Protocol Amendment No.1 (United States) No. CSL830_3002, dated 10 July 2015: “An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous (SC) administration of human plasma-derived C1 esterase inhibitor in the prophylactic treatment of hereditary angioedema”.

The SAP bases on the electronic Case Report Form (eCRF) Version 6, dated 28Jul2016, and provides the description of the final analyses after all subjects have completed the study.

2 Study Objectives

The **primary objective** is

- To assess the clinical safety of subcutaneous (SC) administered CSL830 in the long-term prophylactic treatment of Hereditary Angioedema (HAE).

The **secondary objectives** are the following:

- To further characterize the clinical safety of SC administered CSL830 in the long-term (i.e., routine) prophylactic treatment of HAE.
- To characterize the clinical efficacy of SC administered CSL830 in the long-term (i.e., routine) prophylactic treatment of HAE.

CCI

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

2.1 Primary endpoints

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

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

For each primary endpoint safety event, the person-time incidence rates are calculated as:

- the number of subjects experiencing the primary endpoint safety event at least once during treatment with CSL830, divided by the sum of each subject's time at risk

and

- the total number of the primary endpoint safety events divided by the sum of each subject's time at risk.

Further details how the number of subjects experiencing the primary endpoint safety event, the number of the primary endpoint safety events and the time at risk will be calculated are outlined in [Section 4.7.1](#).

2.2 Secondary endpoints

2.2.1 Secondary safety endpoints

The secondary safety endpoints are the following:

- AEs,
- Solicited AEs,
- Unsolicited AEs,
- SAEs,
- Temporally-related AEs (AEs which start within 24 hours of administration of the investigational product),
- Suspected adverse drug reactions (ADRs) (AEs which start within 24 hours of administration of the investigational product or which are related to investigational product administration including AEs with missing causality rating),
- The CSL830 injections followed by at least one solicited AE,
- Subjects reporting CSL830 injections followed by at least one solicited AE,
- Risk scores for deep vein thrombosis (DVT) or pulmonary embolism (PE),
- TEEs,
- Hypersensitivity,
- Anaphylaxis,
- Clinical laboratory assessments:
 - Hematology.
 - Biochemistry.
 - Urinalysis.
 - Coagulation profile.
 - Anti-C1-INH antibodies.
 - Viral serology.
- Vital signs including body weight,
- Physical examination.

2.2.2 Secondary efficacy endpoints

Efficacy endpoints considered as secondary include the following:

- 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 of the protocol [inclusion criterion 5]).
- The percentage of subjects who experience a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.

2.3 CCI [redacted]

2.2.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI
[Redacted text block]

CCI
[Redacted text block]

CCI
[Redacted text block]

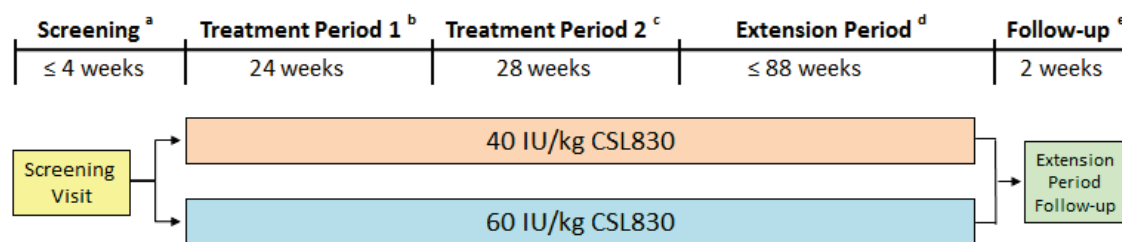
3 Study Design

3.1 Discussion of Study Design

3.1.1 Study Design

This is a multicenter, randomized, open-label, parallel-arm, phase 3b study designed to investigate the safety and efficacy of SC 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 of the Protocol.

^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 of the Protocol 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 of the Protocol 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.

3.1.2 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:

- “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 (i.e., the Day 1 Visit) may occur on the same day as the Screening Visit but after the End of Study Visit of CSL830_3001.

“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 [i.e., ≤ 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 of the protocol (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.

3.1.3 Treatment Periods 1 and 2

Treatment Period 1 will begin with the Day 1 Visit and will end with the Week 25 Visit, i.e. last until (excluding) the Week 25 Visit. Treatment Period 2 will begin immediately with the Week 25 Visit. Treatment Period 2 will end with completion of the Week 53 Visit (last visit of Treatment Period 2). 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.

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 SC injection twice weekly at home either independently (i.e., self-administered by the subject) or with assistance (i.e., 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 his or her HAE attacks. The rules for a dose increase are different during the “fixed dose” Treatment Period 1 and the “dose optimization” Treatment Period 2.

Dose increase rules are presented in [Section 3.2](#).

3.1.4 Extension Period

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.

The Extension Period will follow Treatment Period 2. The last visit (Week 53 Visit) of Treatment Period 2 will serve as the first visit of the Extension Period (Extension Period Week 0, 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. If the last visit of Treatment Period 2 and the first visit of the Extension Period are more than 14 days apart, subjects will attend a Follow-up Visit occurring 14 days (\pm 3 days) after the final visit in Treatment Period 2. The Extension Period will start with Extension Period Week 0 and will end with the Extension Period Week 88 Visit. Subjects will attend a Follow-up Visit (phone call) 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.

Of note, only AEs, HAE attacks and medications will be captured in the eDiary for the rest period. It will also be entered that there was no study treatment.

3.1.5 Planned number of sites

The study is planned to be conducted at approximately 50 study sites.

3.2 Study Treatment

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.

A subject will be randomized to one of 2 treatment groups (CSL830 40 IU/kg or CSL830 60 IU/kg) and will administer CSL830 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. The volume to be administered (planned volume) is based on treatment assignment, a subject's baseline body weight (Day 1, Treatment Period 1), and rounding (i.e., up to the nearest whole mL). For those subjects who experienced a body weight change of more than 10% relative to baseline, the dose is to be adjusted and subsequent weight measurements are to be compared to the new weight. For those subjects who experience a body weight change of more than 10% relative to the new weight, the dose is to be adjusted again. This is repeated throughout the study. To promote compliance, the twice weekly administration of CSL830 should be scheduled on fixed days of the week (e.g., 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.

Beyond the Week 53 Visit, the volume to be administered (planned volume) is based on treatment assignment, a subject's body weight, and rounding (i.e., the actual dose of CSL830 that is assigned will be rounded (i.e., 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 (i.e., rounded up to the nearest 500 IU, for further details please see Country-Specific Protocol Amendment No. 1 (United States), dated 10 July 2015).

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

CSL830 Dose Increase

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

During the fixed-dose Treatment Period 1, subjects who experience very frequent HAE attacks (i.e., ≥ 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 for a CSL830 dose increase, 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 for a CSL830 dose increase, 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, 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.

An evaluation period for any dose increase in either Treatment Period 1, Treatment Period 2, or the Extension Period will start after a dose-stable period which is defined:

- In Treatment Period 1 as the 2 weeks after the start of a CSL830 dose or a dose increase
- In Treatment Period 2 as the 2 weeks after a subject has a dose increase
- In the Extension Period as the 2 weeks after a subject has a dose increase or after a rest period prior to the Extension Period.

The evaluation period for a dose increase has no relevance for any statistical analyses.

CSL830 dose increases will 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.

3.3 Study Schedule

3.3.1 Planned study duration

The duration of the study for an individual subject who does not participate in the Extension Period 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 (i.e., 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.

US-subjects will have the opportunity beyond the Week 53 Visit to enter into an Extension Period of up to 90 weeks. The Extension Period will comprise a treatment period of 88 weeks and a follow-up period of 14 days \pm 3 days (see Country-Specific Protocol Amendment No. 1 (United States), dated 10 July 2015).

3.3.2 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.

For "CSL830-Naïve" Subjects and for "CSL830-Interrupted" Subjects, the first study visit of study CSL830_3002 is the Screening Visit of study CSL830_3002.

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

3.3.3 Schedule of Events

See Section 8 "Study Procedures and Visit Schedule" of the Country-Specific Protocol Amendment No. 1 (United States) for details of the schedule of procedures and assessments during the extension period.

3.3.4 Unscheduled Visits

Unscheduled visits can be arranged at any time point during the study (e.g., 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.

Measurements from unscheduled visits will be listed but not included in summary tables.

3.3.5 Subject Assessments with the eDiary

Following randomization, subjects will report the following information in the eDiary:

- Details of the administration of CSL830 (i.e., dose, date, start time of injection, location of injection, and needle type used).
- Local reactions at the site of CSL830 administration (discomfort [e.g., 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 HAE attacks is needed (yes/no).
- If medication for the treatment of 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).
- AEs (yes/no).
- Other concomitant medication (yes/no).

CCI



3.4 Study Analysis Populations

There will be six analysis populations defined for the study analyses:

3.4.1 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. Subjects in the ITT Population will be analyzed as randomized.

3.4.2 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. Subjects will be analyzed ‘as treated’, i.e., subjects in the Safety Population will be classified according to the actual treatment, regardless of the treatment assigned by randomization.

3.4.3 Per-Protocol Population

The Per-protocol (PP) Population will comprise all subjects in the ITT Population, excluding subjects who have a major protocol deviation. Protocol deviations will be reviewed and their impact assessed prior to database lock. See also [Section 4.11](#).

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

3.5 Discontinued Subjects

Subjects may withdraw from the study at any time at their own request, or they may be discontinued at any time at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (e.g., due to an AE, protocol violation, loss to follow-up, subject noncompliance, and study termination). If CSL terminates the study premature, all subjects who are still participating in the study are regarded as discontinued from the study and “Study Terminated by Sponsor” will be entered as the reason for discontinuation.

Subjects who discontinue from the study prematurely at any time are considered discontinued subjects. Subjects who participated in the entire study and complete the Week 53 Visit according to protocol and who do not participate in the Extension Period are considered study completers even if they do not attend the Follow-up Visit after Week 53. Subjects who have continued treatment in the Extension Period and discontinued early in the Extension Period

are regarded as discontinued subjects. Subjects who complete the Extension Study and attend Extension Period Week 88 visit are considered study completers even if they did not attend the Follow-up Visit of the Extension Period.

In the event that a subject discontinues from the study, the investigator should record the reason and date of discontinuation in the eCRF and in the subject's medical records.

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

3.6 Randomization

A block randomization with 1:1:1-stratification for “CSL830-Continuation” Subjects, “CSL830-Interrupted” Subjects, and “CSL830- Naïve” Subjects will be used to ensure that subjects are randomized in balanced manner to a starting dose of CSL830 of either 40 IU/kg or 60 IU/kg.

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) according to the above mentioned randomization scheme. The IRT will assign the appropriate study treatment to each subject.

3.7 Blinding

Not applicable.

3.8 Sample Size

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

4 Statistical Methodology

4.1 Planned Analyses

The data from Treatment Period 1, Treatment Period 2, and Extension Period will be analyzed and presented jointly, unless specified otherwise.

For subjects who are not participating in the Extension Period, the End of Study Visit will be at Week 53. For subjects who are participating in the Extension Period, the End of Study Visit will be at Week 88.

All summary tables will be presented by treatment groups 40 IU/kg CSL830, 60 IU/kg CSL830, and ≥ 40 IU/kg CSL830 unless specified differently. Events occurring under 80 IU/kg will be summarized in the ≥ 40 IU/kg CSL830 treatment group and otherwise listed only.

Subject disposition will be summarized for all subjects who provide informed consent/assent (as appropriate). Demographic and subject characteristics will be summarized using the ITT and Safety Populations.

All safety data will be summarized using the Safety Population. The analysis of the safety endpoints will be by actual CSL830 treatment (40 IU/kg CSL830, 60 IU/kg CSL830, or ≥ 40 IU/kg CSL830) the subject was taking when the event occurred, unless specified otherwise. In the analysis as treated, a subject contributes events or assessments to each treatment received, e.g. a subject randomized and treated with 40 IU/kg and up-titrated and treated with 60 IU/kg will be displayed in both treatments as well as displayed once in the ≥ 40 IU/kg treatment.

The efficacy endpoints considered as secondary will be summarized using the ITT and PP Populations. CCI

CCI

CCI

Continuous variables will be described by using the mean value with the respective 95% confidence intervals (CI) [only for efficacy variables]; standard deviation; range; 25th, 50th (median), and 75th percentiles; and counts of missing and non-missing values. The geometric coefficient of variation will be expressed as a percentage and the geometric mean and respective 90% CI will be calculated for CCI. The 90% CI for the geometric mean will be calculated by log transforming the data, calculating the lower and upper limits of the 90% CI of the mean of the log-transformed data and, subsequent back transforming the lower and upper limits. Categorical values will be described using counts and percentages. Time variables will be described by median, minimum and maximum and if applicable in addition by mean, standard deviation, 25th and 75th percentiles and graphically represented by Kaplan-Meier curves with the respective 95% CI.

All data will be displayed in by-subject listings. The listings will be sorted by treatment (40 IU/kg CSL830, 60 IU/kg CSL830, 80 IU/kg CSL830), site, subject, time point, and item number if applicable.

4.2 Interim Analysis

Interim analyses will be conducted on an as-needed basis in order to support regulatory activities. Two interim analyses were conducted. The first interim analysis supported the Biologic License Application (BLA) and the second interim analysis supported the 120 day safety update. The results of interim analyses were not intended to be used to stop or adapt the study.

The analysis for the first and the second interim analyses are described in two interim SAPs, dated 19Jan2016 and dated 21Jun2016, respectively.

4.3 Disposition of Subjects

The following will be presented in summary tables for all subjects who provide informed consent/assent (as appropriate) by treatment (40 IU/kg CSL830; 60 IU/kg CSL830 and ≥ 40 IU/kg CSL830 [i.e., combined treatment groups]) and overall:

- The number of subjects who provide consent/assent (as appropriate).
- The number of subjects who undergo Screening.
- The number of “CSL830- Continuation” Subjects.
- The number of “CSL830-Interrupted” Subjects.
- The number of “CSL830- Naïve” Subjects
- The number of subjects who are not allocated to a treatment.
- The number of subjects who are randomized.
- The number of subjects who participate in the Extension Period.
- The number of subjects who undergo no CSL830 dose increase in Treatment Period 1
- The number of subjects who undergo no CSL830 dose increase in Treatment Period 2
- The number of subjects who undergo no CSL830 dose increase in the Extension Period
- The number of subjects who undergo no CSL830 dose increase in Treatment Period 1 and Treatment Period 2
- The number of subjects who undergo no CSL830 dose increase in Treatment Period 2 and the Extension Period
- The number of subjects who undergo no CSL830 dose increase in in any Period
- 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 1 CSL830 dose increase in the Extension Period
- The number of subjects who undergo 1 CSL830 dose increase in Treatment Period 1 and Treatment Period 2
- The number of subjects who undergo 1 CSL830 dose increase in Treatment Period 2 and the Extension Period
- The number of subjects who undergo 1 CSL830 dose increase in any Period
- 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 undergo 2 CSL830 dose increase in the Extension Period
- The number of subjects who undergo 2 CSL830 dose increases in Treatment Period 1 and Treatment Period 2
- The number of subjects who undergo 2 CSL830 dose increases in Treatment Period 2 and the Extension Period
- The number of subjects who undergo 2 CSL830 dose increases in any period
- The number of subjects who completed the study
- The number of subjects who discontinued participation in the study (overall and for Period 1, 2 and the Extension Period; including the reason for discontinuation).

For detail of the definition of completers and non-completers see [Section 3.5](#).

Percentages are based on the number of subjects randomized/enrolled in each group. The percentages of subjects who underwent screening, "CSL830-Continuation", "CSL830-Interrupted" and "CSL830-Naive" Subjects as well as the percentage of the subjects randomized into the study are based on the number of subjects who provided informed consent/assent. Percentages for the reason for discontinuation are based on the number of subjects discontinued in each group.

The number of subjects in each analysis population will be summarized by treatment (40 IU/kg CSL830; 60 IU/kg CSL830; ≥ 40 IU/kg CSL830 and overall). Subjects in the ITT, the PP and the CCI will be assigned to treatment as randomized and subjects in the Safety Population, the CCI will be assigned to treatment as treated and will be assigned to all doses they have received during the study.

A by-subject listing will be produced including the assignment of subjects to analysis populations.

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.

4.4 Baseline and Demographic Characteristics

Subject characteristics and medical history will be presented in summary tables for the ITT and Safety Populations as described in [Section 4.1](#).

This will include:

- Demographics (age [years], sex, race, ethnicity, height, body weight, and body mass index [BMI; calculated as kg/m²]).
- Medical history (relevant medical history for the previous 6 months, contraception method [if relevant]) and the correspondent therapies which have an end date on or after the date of the first study treatment (current therapies). Medical history will be presented by system organ class (SOC) and preferred term (PT), and will be classified using version 18.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Current Therapies will be presented by Anatomical Therapeutic Chemical (ATC) class and PT.
- HAE history (including confirmation of HAE diagnosis, identification of HAE type, and number of HAE attacks in the 3 months before the Screening visit) and Medical HAE History (any prior prophylactic therapy relating to HAE during previous 3 months for “CSL830-Naïve” Subjects).

The relevant medical history for the previous 6 months will include all medical history of subjects during the previous 6 months before Screening. The confirmation of HAE diagnosis, identification of HAE type, and number of HAE attacks in the 3 months before Screening will be presented.

The number of HAE attacks in the 3 months before the Screening Visit will also be displayed as the rate of HAE attacks before the Screening Visit per month. Therefore, the number of HAE attacks in the 3 months before the Screening Visit will be divided by 3.

For “CSL830-Naïve” Subjects and “CSL830-Interrupted” Subjects screening is the Screening Visit of study CSL830_3002. For “CSL830-Continuation” Subjects, screening is the Screening Visit of study CSL830_3001. Information in the medical history will be updated if any changes occurred in the course of study CSL830_3001.

The label “Any Prior Prophylactic Therapy Related to HAE During Previous 3 Months” in the HAE history and medical HAE history table will only include therapies taken within 3 months prior to Screening of Study CSL830_3002. Prior therapies before Screening of study CSL830_3001 will not be included. Consequently, only “CSL830-Naïve” Subjects will have data in this part of the table.

Summaries of demographics, medical history, current therapies, HAE history, Medical HAE History will also be presented for the following subgroups:

- Roll over classification (“CSL830-Continuation” Subjects, “CSL830-Interrupted” Subjects, and “CSL830- Naïve” Subjects).

A by-subject listing of demographic characteristics, baseline characteristics, and medical history will also be presented.

Extent of exposure and treatment compliance will be calculated as described below and will be listed and summarized descriptively as described in [Section 4.1](#).

4.4.1 Extent of exposure

Exposure will be summarized using the Safety Population. The duration of exposure per subject (presented in years and weeks) will be summarized in 3 ways to support the 3 approaches to the analysis of the primary safety endpoint of person time incidence rates:

1. by treatment group, as treated, up to CSL830 dose increase or either CSL830 discontinuation or study completion – whichever comes first, i.e., the duration (years or weeks) of exposure per subject is equal to (the subject's first dose increase or discontinuation or completion visit [whichever comes first] – the subject's start date in this treatment + 1) / 365.25 [for weeks it will be divided by 7].
2. by treatment group, as treated at the time of randomization, up to CSL830 discontinuation or study completion – whichever comes first, i.e. the duration (years or weeks) of exposure per subject is equal to (the subject's study discontinuation date or study completion date – the subject's start date in the study + 1) / 365.25 [for weeks it will be divided by 7]. Subjects accrue exposure based upon their initial treatment until stopping CSL830; regardless of any dose increase.
3. by actual treatment. The duration (years or weeks) of exposure per subject is equal to (the subject's end date in the treatment – the subject's start date in this treatment + 1) / 365.25 [for weeks it will be divided by 7]. Subjects accrue exposure by treatment dose over the duration they receive each treatment dose while participating in the study, e.g. a subject randomized to 40 IU/kg and up-titrated to 60 IU/kg will be displayed in both treatments and in ≥ 40 IU/kg with their corresponding duration in that treatment.

Depending on the analysis approach, a subject's start date in a treatment will correspond to the first visit date or the date of dose increase. A subject's end date is the date of discontinuation, study completion, or the date of dose increase – 1. For subjects who are not taking part in the Extension Period, the date of study completion is the date of the Week 53 Visit and for subjects who are taking part in the Extension Period, the date of study completion is the date of the Week 88 Visit. If a subject discontinued from the study, the date the subject came back to site for a final study visit will be entered as the date of discontinuation (to be entered as Week 53 Visit for subjects not taking part in the Extension Period and entered as Week 88 Visit for subjects taking part in the Extension Period) or if no further study visit takes place, the date when the subject informed the investigator.

The time between the Week 53 Visit and the Follow-up Visit of Treatment Period 2 will not be included in the duration of exposure for subjects who are not taking part in the Extension Period. For subjects who are taking part in the Extension Period, a rest period will not be included in the duration of exposure. For subjects who are taking part in the Extension Period, the time between the Week 88 visit and the Follow-up Visit of the Extension Period will not be included in the duration of exposure.

A by-subject listing will be produced displaying all study drug injections.

4.4.2 Treatment compliance

Treatment compliance per subject will be assessed using the ITT Population.

The volume per dose recorded by subjects (mL) in the eDiary, the corresponding dose (IU/kg) per subject, the planned volume per dose per subject (mL), and the planned dose per subject (IU/kg) will be summarized by descriptive statistics.

Treatment compliance per subject based on subject reported volume in the eDiary will be assessed by treatment as follows:

For each dose of a subject the treatment compliance based on volume (%) will be calculated as

$$100 * (\text{volume (mL) of investigational product reported in the eDiary} / \text{planned volume (mL) of investigational drug}).$$

Then the mean of these compliance measures will be calculated per subject. Descriptive statistics will be presented.

A by-subject listing will be produced for all compliance variables.

4.5 Prior and Concomitant Medication

Medications that start and end before the date of the first administration of the corresponding study treatment will be classified as ‘prior’ medication for that study treatment. Medications that start before the date of the first administration of the corresponding study treatment, and end on or after the date of the first corresponding study treatment will be classified as ‘prior / concomitant’ medication for that study treatment. Medications that start on or after the date of the first administration of the corresponding study treatment and before the date of the last visit in the corresponding study treatment will be classified as ‘concomitant’ medication for that study treatment.

All drugs and/or procedures being administered before the time a subject signed informed consent/assent (as appropriate) will be included in the medical history for “CSL830- Naïve” Subjects. Prior medications include all medications taken within 3 months prior to screening day of study CSL830_3002. For “CSL830-Interrupted” Subjects and “CSL830-Continuation” Subjects drugs and/or procedures excluding HAE medications in study CSL830_3001 will be included in the medical history.

If medication start and/or stop dates are missing or partial, medications will be assumed to be ‘concomitant’, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the date of the first administration of the corresponding study treatment. If there is clear evidence to suggest that the medication started prior to the date of first administration of the corresponding study treatment, the medication will be assumed to be ‘prior / concomitant’, unless there is clear evidence to suggest that the medication stopped prior to the date of the first administration of the corresponding study treatment. If this is the case, the medication will be considered ‘prior’.

Medications which have a start date in the period from the completion visit in Period 2 to the Follow-up Visit or the first visit of the Extension Period will be assigned to Treatment Period 2. Medications which have a start date in the period from the completion visit of the Extension Period to the Follow-up Visit of the Extension Period will be assigned to the Extension Period.

The number and percentage of subjects with medication taken ‘prior / concomitant’ and/or ‘concomitant’ will be presented by ATC class and PT as described in [Section 4.1](#).

Note that a subject will only be counted once regardless of how many times they took medication reported under the same PT.

A by-subject listing will be produced for all ‘prior / concomitant’ and ‘concomitant’ medications.

Notes:

- Medications are coded using World Health Organization (WHO) Drug dictionary version B2 Enhanced March 2013.
- Therapeutic class will be the level 4 anatomical therapeutic chemical (ATC) name unless coding is not available at level 4. In these cases level 3 ATC name will be used. Similarly, if the level 3 ATC name is not available then the level 2 ATC name will be used and if the level 2 ATC name is not available then the level 1 ATC name will be used.

4.6 Efficacy Analysis

The secondary efficacy analyses will be carried out for the ITT and PP Populations. The ITT Population is used as the primary analysis and the Per Protocol Population will be used as secondary analysis.

The evaluation period for efficacy assessments will be from the start (Day 1) of Week 3 of a treatment in Treatment Period 1 until the End of Study Visit (Week 53 Visit) or the last administration of CSL830 + 4 days (whichever occurs first) for subjects who are not participating in the Extension Period. For subjects who are taking part in the Extension Period, the evaluation period will be from the start (Day 1) of Week 3 of the treatment in Treatment Period 1 until the End of Study Visit of the Extension Period (Week 88) or the last administration of CSL830 + 4 days (whichever occurs first). For subjects who are participating in the Extension Period and who have a rest period between Treatment Period 2 and the Extension Period, the evaluation period will exclude the rest period between the Week 53 Visit or the last administration of CSL830 + 4 days (whichever occurs first) of Treatment Period 2 and the first visit of the Extension Period.

CCI

Each day, subjects are to enter HAE symptoms (yes/no) into their eDiary and, if yes, the severity(s) and location(s) of the HAE symptom(s). Investigator-reported HAE attacks are based upon review of patient diaries and review of relevant interim medical history, including hospital/medical records and any information provided by the subject. Using medical judgment, the investigator is to determine the occurrence of an HAE attack and report its start and stop dates (generally from onset of the first symptom preceded by symptom-free day to the last symptom preceding symptom-free day), its severity (based upon maximal intensity of any symptom as judged by the investigator), and its location(s) (all involved locations as judged by the investigator are to be reported). Each HAE attack is to be preceded and followed by an attack-free day. For every visit, the Investigator is to report all HAE attacks that have occurred in the interim since the last visit the subject attended.

For the analyses, a HAE attack is defined on the basis of the HAE attacks reported by the investigator using the HAE attack eCRF and all HAE attacks reported by the investigator will be included in the analyses. The investigator reported HAE attacks that were not preceded and followed by an attack-free day are merged into one HAE attack, with the earliest start

date, the latest end date and the most severe severity of the individual HAE attacks. If the start date of a merged HAE attack is falling in the first two weeks of a treatment period, this merged HAE attack will not be included in the analyses. If the investigator entered the individual HAE attacks during the same time frame but in different attack locations, the corresponding merged HAE attack will be given the HAE attack location of “multiple”.

All secondary and exploratory efficacy endpoints which include HAE attacks will be analysed as described above as the primary analysis approach. In addition, a sensitivity analysis will be performed for all secondary and exploratory efficacy endpoints in which HAE attacks are analyzed as they are reported by the investigator in the attack eCRF. This sensitivity analysis will be regarded as secondary.

A by-subject listing will be produced for all HAE attacks of the primary analysis approach and an additional by-subject listing will be produced for all HAE attacks reported by the investigator in the eCRF.

4.6.1 Primary efficacy endpoints

There is no primary efficacy analysis. The primary analysis for study CSL830_3002 is safety-based and can be found in [Section 4.7.1](#).

4.6.2 Method of analysis for primary efficacy endpoint

Not applicable.

4.6.3 Secondary efficacy endpoints

Secondary efficacy endpoints are:

- a. The percentage of subjects who are responders. The “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 of the protocol [inclusion criterion 5]).
- b. The percentage of subjects who experience a time-normalized number of HAE attacks of < 1 HAE attack per 4-week period.

The time-normalized number of HAE attacks during treatment with CSL830 is calculated per subject as:

- The number of HAE attacks /length of stay of subject (days);

where the length of stay for subjects who are not participating in the Extension Period is calculated as:

- Date of End of Study Visit at Week 53, date of the 4th day post the last IMP administration or study discontinuation date (whichever occurs first) – date of Day 1 Week 3 + 1.

for HAE attacks with start date before (including) the Week 53 visit, the last administration of CSL830 + 4 days or study discontinuation date (whichever occurs first).

For subjects who are continuing into the Extension Period and have no rest period, the length of stay is calculated as:

- Date of End of Study Visit at Week 88, date of the 4th day post the last IMP administration or study discontinuation date (whichever occurs first) – date of Day 1 Week 3 + 1.

for HAE attacks with start date before (including) the Week 88 visit, the last administration of CSL830 + 4 days or study discontinuation date (whichever occurs first).

For subjects who are continuing into the Extension Period and have a rest period, the length of stay is calculated as:

- {Date of End of Study Visit at Week 53, date of the 4th day post the last IMP administration in Treatment Period 2 (whichever occurs first) – date of Day 1 Week 3 + 1} + {Date of End of Study Visit at Week 88, date of the 4th day post the last IMP administration in the Extension Period or study discontinuation date (whichever occurs first) – date of first visit of the Extension Period + 1}.

for HAE attacks with start date outside the rest period and before (including) the Week 88 Visit or the last administration of CSL830 + 4 days or study discontinuation date (whichever occurs first).

HAE attacks with start dates

- between one day after the End of Study Visit or 4th day post last IMP administration [whichever occurs first] and the Follow-up Visit of Treatment Period 2 (applicable for subjects not participating in the Extension Period)
- between one day after the End of Study Visit or 4th day post last IMP administration [whichever occurs first] and the Extension Follow-up Visit (applicable for subjects participating in the Extension Period)
- between one day after the Week 53 Visit or 4th day post last IMP administration [whichever is first] of Treatment Period 2 and the first visit of the Extension Period (applicable for subjects who are taking part in the Extension Period and who have a rest period)

will not be included in the analyses (ie the numerator “number of HAE attacks”).

4.6.3.1 The percentage of subjects who are responders

The percentage reduction in the time-normalized number of HAE attacks per subject is calculated as:

- $100\% * [1 - (\text{the time-normalized number of HAE attacks when treated with CSL830}) / (\text{the time-normalized number of HAE attacks used to qualify for participation in the current study})]$

The HAE attacks used to qualify for participation in the current study are derived from the subject medical records:

- “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 (e.g., 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 (i.e., the HAE attack frequency required for eligibility to participate in study CSL830_3001).

A subject is classified as a responder if the percentage reduction is $\geq 50\%$. A subject whose time-normalized number of attacks cannot be calculated in the treatment periods will be excluded from the calculation of the percentage of responder analysis.

The number and percentage of responders and non-responders and the difference in the percentage of responder between the 60IU/kg CSL830 and 40IU/kg CSL830 treatments will be summarized. 95% Wilson Confidence Intervals will be calculated for all percentages.

The analyses will be repeated including only subjects who have no dose increase.

Subgroup analyses will be performed for age (≤ 17 years / >17 years) and subjects' completion status (completed study / discontinued early). The number and percentage of responders and non-responders will also be calculated and presented descriptively for each of the following time windows:

- 1) For all subjects: every 6 months excluding the first 2 weeks in Period 1 (for subject who are participating in the Extension Period and who have a rest period: the rest period will also be excluded),
- 2) For subjects who are not participating in the Extension Period: first 6 months and first 12 months excluding the first 2 weeks in Period 1,
- 3) For subjects who are participating in the Extension Period: first 6 months, first 12 months, first 18 months and first 22 months excluding the first 2 weeks in Period 1 (for subject who have a rest period: the rest period will also be excluded).

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

4.6.3.2 Time-normalized HAE attack frequency of < 1 HAE attack per 4-week Period

The number and percentage of subjects who experience less than 1 HAE attack per 4 week period (i.e. 28 days) and those who experience at least 1 HAE attack per 4 week period will be summarized. For the calculation of the HAE attacks per 4 week period the time-normalized number of HAE attacks as described in [Section 4.6.3](#) will be multiplied by 28. 95% Wilson Confidence Intervals will be calculated for all percentages.

The number of HAE attacks as well as the difference in the number of attacks experienced following treatment with CSL830 as compared to number of attacks pre-study will also be summarized.

A subgroup analysis will be performed for age (≤ 17 years / >17 years).

Subjects who have less than 1 HAE attack per 4-week period will be flagged.

4.7 Safety Analysis

Safety endpoints will be analyzed using the Safety Population as described in [Section 4.1](#).

AE will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.

AEs which have a start date and time on or after the first injection date and time of CSL830 in study CSL830_3002 are considered treatment-emergent AEs. AEs with missing or partial start date or time will also be considered treatment-emergent following the worst case principle unless the partial date clearly indicates that the AE started before first injection date and time.

Only treatment-emergent AEs will be summarized in tables as described in [Section 4.1](#). AEs occurring after the Week 53 Visit and before the Follow-up Visit of Treatment Period 2 or the first visit of the Extension Period will be assigned to Treatment Period 2. AEs occurring between the Extension Period completion visit and the Extension Period Follow-up Visit will be assigned to the preceding treatment of the Extension Period.

Subgroup analyses will be performed for

- Use of any oral Prophylaxis for Treatment of HAE during the study
- Subject roll-over classification (“CSL830-Continuation” Subjects, “CSL830-Interrupted” Subjects, and “CSL830-Naïve” Subjects)

The subgroup “Subjects who use oral agents for the prophylactic treatment of HAE during the study” will only include subjects who are taking their prophylaxis according to protocol.

Notes:

- The above described subgroup analyses will only be done for
 - the overall AE tables for summary measures of safety
 - the primary safety endpoints by actual treatment
- Categories of subgroups will be presented in tables only if there are a minimum number of subjects in the subgroup ($n \geq 5$).
- If a causality assessment is not provided for an AE, that AE will be considered related to the investigational product. A subject having related and unrelated AEs will be counted once in each category, related and unrelated.
- Missing severity or outcome will be classified as “severe” or “not recovered”, respectively.
- A subject having AEs with different severities will be counted once in each severity category.
- A subject with more than one occurrence of the same AE PT will be counted once in the total count for that AEs PT. Similarly, a subject with one or more AEs in a particular SOC will be counted once in the total for that SOC.

4.7.1 Primary Safety Analysis

Primary safety endpoints are listed in [Section 2.1](#).

The date of study completion is defined for the safety analyses as the (latest) Follow-up Visit. If a subject discontinued from the study, the date the subject came back to site for a final

study visit will be entered as the date of study discontinuation (to be entered as Week 53 Visit for subjects not taking part in the Extension Period and to be entered as Week 88 Visit for subjects taking part in the Extension Period) or if no further study visit takes place, the date when the subject informed the investigator. The study completion or study discontinuation (whichever applies for the individual subject) is considered as the end of treatment date.

The person-time incidence rates will be calculated in two different ways:

- For the number of subjects experiencing a particular event (bullet points i. below),
- For the number of experienced events (bullet points ii. below).

These 2 analyses approaches for the primary safety endpoints are conducted using 3 different approaches for the selection of the treatment groups which are included in the respective analyses. The following treatment groups will be regarded:

- 1) Treatment, as treated, up until CSL830 dose increase, or either CSL830 discontinuation or study completion – whichever comes first.
- 2) Treatment, as treated at the time of randomization, up to CSL830 discontinuation or study completion – whichever comes first.
- 3) Actual treatment.

In total, six analyses will result and the person-time incidence rates will be calculated

for 1) as

- i. the number of subjects experiencing a given primary endpoint safety event during the treatment duration with CSL830 up until the time of CSL830 dose increase or either CSL830 discontinuation or study completion (whichever is first), divided by the sum of each subject's time at risk. The "time at risk" (in years) is calculated per subject as:

(Date the subject experiences the first event or a CSL830 dose increase or either CSL830 discontinuation or study completion (whichever is first) – date of the subject's first injection of CSL830 in treatment + 1) / 365.25.

- ii. the sum of each subject's total number of events of a given primary endpoint safety event during the treatment duration with CSL830 up until the time of CSL830 dose increase or either CSL830 discontinuation or study completion (whichever is first), divided by the sum of each subject's time at risk. The "time at risk" (in years) is calculated per subject as:

(Date the subject undergoes CSL830 dose increase or either CSL830 discontinuation or study completion (whichever is first) – date of the subject's first injection of CSL830 in treatment + 1) / 365.25.

A subject accrues events from the subject's first CSL830 dose until the subject's first CSL830 dose change (i.e., CSL830 dose increase or either CSL830 discontinuation or study completion, whichever is first). If a subject undergoes a dose increase and such subject experiences events after the dose increase, such events are not included in this analysis. Only events which start under the dose as assigned at the time of randomization are included.

for 2) as

- i. the number of subjects experiencing a given primary endpoint safety event up until the time of CSL830 discontinuation or study completion (whichever is first), divided by the sum of each subject's time at risk in the study. The "time at risk" (in years) is calculated per subject as:

(Date the subject experiences the first event or either CSL830 discontinuation or study completion (whichever is first) – date of the subject's first injection of CSL830 in treatment + 1) / 365.25

- ii. the sum of each subject's total number of events of a given primary endpoint safety event up until the time of CSL830 discontinuation or study completion, divided by the sum of each subject's time at risk. The "time at risk" (in years) is calculated per subject as:

(Date the subject undergoes CSL830 discontinuation or study completion (whichever is first) – date of the subject's first injection of CSL830 in treatment + 1) / 365.25

A subject accrues events by treatment group, as treated at time of randomization, from the subject's first CSL830 dose until the subject undergoes CSL830 discontinuation or study completion. If a subject undergoes a dose increase and such subject experiences events after the dose increase, such events are included and attributed to the CSL830 treatment at time of randomization.

for 3) as

- i. the number of subjects experiencing a given primary endpoint safety event during treatment with an actual dose of CSL830 divided by the sum of each subject's time at risk while receiving that actual dose of CSL830. The "time at risk" (in years) is calculated per subject as:

(Date the subject experiences the first event, a CSL830 dose increase, or either CSL830 discontinuation or study completion (whichever is first) while taking a given, actual dose of CSL830 – date of the subject's first injection of the given, actual dose of CSL830 + 1)] / 365.25.

- ii. the sum of each subject's total number of events of a given primary endpoint safety event during treatment with an actual dose of CSL830 divided by the sum of each subject's time at risk while receiving that actual dose. The "time at risk" (in years) is calculated per subject as:

(Date the subject undergoes CSL830 dose increase or either CSL830 discontinuation or study completion (whichever is first) while taking the given, actual dose of CSL830 – date of the subject's first injection of the given, actual dose of CSL830 + 1)] / 365.25.

A subject accrues events over the time during which that subject receives a given actual CSL830 dose while participating in the study. If a subject undergoes a dose increase during the study and that subject experiences events during treatment with each respective dose of CSL830, such a subject contributes events in each treatment received. A subject randomized to 40 IU/kg and up-titrated to 60 IU/kg will be displayed in both treatments as well as in the ≥ 40 IU/kg treatment based upon their corresponding duration in that treatment.

The 95% CI will be calculated for each of the above described person-time incidence rates using the following formula:

$$\text{Lower CI} = \frac{k}{T} \chi^2(2 * Y, 0.025)/2$$

$$\text{Upper CI} = \frac{k}{T} \chi^2(2 * Y + 2, 0.975)/2$$

with

k = factor to normalize for annual rate which is equal to 1

T = sum of time at risk [years] over subjects calculated as described in the bullet points above.

For the person-time incidence rates described above in i.:

Y = number of subjects who experienced the safety event

For the person-time incidence rate described above in ii.:

Y = number of safety events

A by-subject listing will be produced showing the information if a subject has each primary endpoint safety event.

4.7.2 Safety Analysis of the Secondary Safety Endpoints

Secondary safety endpoints are listed in [Section 2.2.1](#).

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

The analysis of the secondary safety endpoints will be by actual CSL830 treatment (40 IU/kg or 60 IU/kg and ≥ 40 IU/kg) the subject was taking when the event occurred. In this analysis, a subject contributes events in each treatment received, e.g. a subject randomized and treated with 40 IU/kg and up-titrated and treated with 60 IU/kg will be displayed in both treatments as well as displayed once in the ≥ 40 IU/kg treatment.

4.7.2.1 Method of analysis for secondary safety endpoints

The AE tables will comprise two type of tables, one for number of subjects experiencing a particular AE, percentage of subjects based on the Safety Population, and number of events and the other type of tables for number of events per subject-injections and number of events per subject-years, the latter giving exposure-adjusted rates (per injection and per year).

All AEs

A summary of all AEs will be given presenting: number and percentage of subjects with AEs, with temporally-related AEs, with suspected ADRs, with SAEs, with related AEs, AE leading to discontinuation based on AE start date with subcategories for “related” and “not related”, with each severity and with each outcome of AEs. Analogue summaries will be provided for only SAEs and for only non-serious AEs.

The following tables will be generated for all AEs (including unsolicited AEs and solicited AEs):

- Incidence of subjects with AEs by SOC and PT.
- Incidence of subjects with SAEs by SOC and PT.
- Incidence of subjects with AEs by severity, SOC, and PT.
- Incidence of subjects with AEs by relationship to investigational product, SOC, and PT.
- Incidence of subjects with AE leading to discontinuation based on adverse event start date by SOC and PT.
- Incidence of subjects temporally-related AEs by SOC and PT.
- Incidence of subjects with suspected ADRs by SOC and PT

- Incidence of subjects with AE matching the PT ‘Embolic and Thrombotic Events’ (SMQ) by SOC and PT overall and split by subjects with versus without indwelling venous catheter. Events identified by this SMQ PT are reviewed by CSL Behring to assist in identification of cases of TEEs.

- Incidence of subjects with AE High Level Term ‘Sepsis, Bacteraemia, Viraemia and Fungaemia NEC’ (by SOC and PT, overall and split by subjects with vs. without venous catheter). Events identified by this High Level Term are reviewed by CSL Behring to assist in identification of cases of sepsis and/or bacteremia events.

- Incidence of subjects with SMQs to identify anaphylaxis defined as severe and clinically relevant systemic allergic reaction with sudden onset and rapid progression by SOC and PT. AE terms screened to assist in identification of cases of anaphylaxis were selected for review using the following SMQs:
 - SMQ = ‘Anaphylactic reaction (SMQ)’ and selection = ‘Broad’.
 - SMQ = ‘Anaphylactic/anaphylactoid shock conditions (SMQ)’ and selected = ‘Broad’.

- Summary of AEs that are included in one of the following SMQs that will be used to screen for hypersensitivity (number of subjects with AEs, with SAEs, with events occurring within 24 hours of investigational product administration, with temporally-related AEs, related events, events leading to study discontinuation, with each severity and with each outcome). Potential events of hypersensitivity are identified using the following SMQs:
 - SMQ = ‘Hypersensitivity (SMQ)’ and selected = ‘Broad’.
 - SMQ = ‘Anaphylactic reaction (SMQ)’ and selected = ‘Broad’.
 - SMQ = ‘Anaphylactic/anaphylactoid shock conditions (SMQ)’ and selected = ‘Broad’.

Incidence of subjects with AEs that are included in one of the above defined SMQs that will be used to screen for hypersensitivity by SOC and PT.

Anaphylactic events will be classified as an AE of special interest (AESI)

The number of subjects experiencing non-serious AEs, non-serious unsolicited AEs and non-serious solicited AEs which occur in at least one treatment in at least 1, 2, 3, 4 and 5% of events will also be presented.

A summary table for AEs occurring within 24 hours after administration of rescue medication for the treatment of HAE attacks will be presented by SOC and PT. Rescue medications are defined as Firazyr, Cinryze, Berinert, Kalbitor, Ruconest, Fresh Frozen Plasma, others.

By-subject listings will be produced for all AEs, related AEs, SAEs, AEs Leading to Study Discontinuation, AE PT ‘Embolic and Thrombotic Events’, AE High Level Term ‘Sepsis, Bacteraemia, Viraemia and Fungaemia NEC’ and for AE PT ‘Anaphylactic Reaction’ (SMQ) and ‘Anaphylactic / Anaphylactoid Shock Conditions’ (SMQ).

Solicited AEs

Solicited AEs are investigational product injection site reactions (i.e., local reactions, including pain, swelling, bruising, itching, erythema or other) selected using the MedDRA high level term (HLT) = “injection site reactions” but excluding those reactions which have been determined to be injection site reactions following an injection of a non-investigational product. All solicited AEs will be reviewed for their AE term verbatim. If the AE verbatim term contains the name of a non-investigational product (i.e. Firazyr, Cinryze, Berinert, Kalbitor, Ruconest, Fresh Frozen Plasma, others), the AE will be excluded from the solicited AE tables.

The following summaries of solicited AEs will be produced:

- Summary of subject with solicited AEs (number with solicited AEs, solicited AEs occurring within 24 hours of investigational product administration, with suspected solicited ADR, solicited SAEs, related solicited AEs, AE leading to discontinuation based on adverse event start date, with subcategories for “related” and “not related”, with each severity and outcome of AEs,).
- Incidence of subjects with solicited AEs by SOC and PT.
- Incidence of subjects with solicited SAEs by SOC and PT.
- Incidence of subjects with solicited AEs by severity and SOC and PT.
- Incidence of subjects with solicited AEs by relationship to investigational product and SOC and PT.
- Incidence of subjects with AE leading to discontinuation based on adverse event start date by SOC and PT
- Incidence of subjects with temporally-related solicited AEs by SOC and PT.
- Incidence of solicited suspected ADRs by SOC and PT
- Incidence of injections followed by
 - at least one solicited AE,
 - no solicited AE,
 - 1, 2, 3, 4, 5, 6, 7 solicited AEs, respectively,
 - > 1 solicited AE,

- 1, 2, 3, 4, 5, 6, 7 solicited AEs within 24h after start of injection and no solicited AE after 24 hours,
- by ≥ 1 solicited AE within 24h after start of injection and no solicited AE after 24 hours,
- by > 1 solicited AE within 24h after start of injection and no solicited AE after 24 hours,
- ≥ 1 solicited AE after 24h after start of injection.

The start dates of the solicited AEs will be compared with the start dates of the injections. If there is at least one start date of a solicited AE after the start date of an injection and before the start date of the subsequent injection, the preceding injection will be counted as an injection followed by at least one solicited AE.

The analyses will be repeated for the subgroup of causal relation (related / not related solicited AEs).

- Incidence of subjects reporting
 - injections followed by at least one solicited AE
 - no injection followed by at least one solicited AE,
 - injections followed by 1, 2, 3, 4, 5, 6, 7, > 1 solicited AE,
 - only at least 1 solicited AE within 24 hours after the injection and no solicited AE after 24 hours,
 - injections only followed by 1, 2, 3, 4, 5, 6, 7, > 1 solicited AE within 24 hours after the injection and no solicited AE after 24 hours,
 - only at least 1 solicited AE after 24 hours and before the next subsequent injection,

The overview summary table of solicited AEs will be presented by solicited AE category (Pain, Swelling, Bruising, Itching, Erythema, or Other), as well as overall across categories.

All solicited AEs will also be summarized by duration and PT. Duration in days is calculated as AE end date – AE start date + 1. Durations will be grouped into the following categories for the summary:

- 1 day,
- 2 days,
- 3 days,
- > 3 days (ongoing events will be included here).

A by-subject listing will be produced for all solicited AEs. In addition, a by-subject listing will be produced including the information to which CSL830 treatment the subject is randomized, the CSL830 dose(s) to which the subject is up-titrated (if applicable) and the number of solicited AEs the subjects experience at each treatment received and overall.

Unsolicited AEs

All AEs which are not considered solicited, are considered unsolicited AEs. The following tables will be generated for unsolicited AEs:

- Summary of subjects with unsolicited AEs (number with unsolicited AE, with unsolicited AEs occurring within 24 hours of investigational product administration, with suspected unsolicited ADR, with unsolicited SAE, related unsolicited AE, AE leading to discontinuation based on adverse event start date with subcategories for “related” and “not related”, with each severity and with each outcome of AEs and overall).
- Incidence of subjects with unsolicited AEs by SOC and PT.
- Incidence of subjects with unsolicited SAEs by SOC and PT.
- Incidence of subjects with unsolicited AEs by severity and SOC and PT.
- Incidence of subjects with unsolicited AEs by relationship to investigational product and SOC and PT.
- Incidence of subjects with AE leading to discontinuation based on adverse event start date by SOC and PT
- Incidence of subjects with temporally-related unsolicited AEs by SOC and PT.
- Incidence of unsolicited suspected ADRs by SOC and PT

4.7.2.2 Laboratory findings

The following laboratory parameters will be collected:

Hematology:

Hemoglobin, hematocrit, basophils, eosinophils, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, platelets.

Biochemistry:

Alanine aminotransferase (ALT), chloride, gamma glutamyl transferase (GGT), creatinine, lactate dehydrogenase (LDH), glucose, protein, total bilirubin, potassium, albumin, aspartate aminotransferase (AST), urea, calcium, sodium.

Urinalysis:

Bilirubin, blood, erythrocytes, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen.

Coagulation:

International normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, D-dimer, F1+2.

Immunogenicity:

Inhibitory and non-inhibitory antibodies specific to C1-INH.

Viral serology:

HIV types 1 and 2, HBV, HCV.

Dipstick Pregnancy testing:

Dipstick Pregnancy tests will be performed.

4.7.2.3 Analysis of Laboratory Findings

Normal ranges will be provided for laboratory tests. Values outside the normal range will be judged as clinically significant or non-clinically significant by the investigator. All abnormal laboratory data considered as clinically significant will be presented as AE.

All continuous laboratory parameters will be plotted against their scheduled assessments visits.

Analyses of haematology, biochemistry, and coagulation parameters will consist of the following:

- Descriptive statistics for baseline and each treatment visit, including changes from baseline to each treatment visit
- Mean values and the SD of the continuous laboratory parameters at each scheduled visit will be plotted against scheduled visits.

Baseline will be the assessment before the first injection (Week 1 Day 1) for 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. For “CSL830-Continuation” Subjects who complete the assessments at the CSL830_3001 End of Study Visit, these assessments will be the baseline. If the baseline value for a subject is missing, no change from baseline will be calculated for the subject.

The number and percentage of subjects without anti-C1-INH antibodies and with anti-C1-INH antibodies (inhibitory, non-inhibitory and inhibitory and non-inhibitory combined) during the study will be summarized overall and for each study visit

Urinalysis, viral serology and pregnancy testing results will be listed only.

Notes:

- All results outside predefined normal ranges will be flagged as high or low in the data listings.
- Clinically significant laboratory values will be flagged in the listings.
- Unscheduled results will be listed only and not included in summary tables.

4.7.3 Vital Signs and Body Weight

Results of vital signs and body weight will be summarized by visit. Descriptive statistics for baseline and each treatment visit will be displayed. Descriptive subgroup analysis will be done for subjects who use any oral Prophylaxis for Treatment of HAE during the study.

Baseline will be Week 1 Day 1 for 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. For “CSL830-Continuation” Subjects who complete the assessments at the CSL830_3001 End of Study Visit, these assessments will be the baseline. All vital signs and body weight data will be listed and abnormal results will be flagged.

4.7.4 Physical examinations

Abnormal physical examination results will be recorded as either medical history (if prior to first study drug administration) or AEs (if after first study drug administration). Normal results will not be recorded. As such, physical examination results will be summarized through medical history and AEs only and there will be no summary of individual examination results.

All physical examinations dates will be listed.

4.7.5 Risk Assessment for Deep Vein Thrombosis and Pulmonary Embolism

The clinical model scoring system will be used for the risk assessment of deep vein thrombosis:

Clinical Feature	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

Note: In subjects with symptoms in both legs, the more symptomatic leg is used.

Individual clinical feature scores and calculated risk scores will be recorded in the eCRF.

If a subject has a risk score of ≥ 1 , a lower extremity ultrasound examination will be arranged by the investigator to exclude deep vein thrombosis. If a deep vein thrombosis is confirmed on ultrasound examination, the event will be classified as an AESI and will be reported as a SAE.

The following clinical model scoring system will be used for the risk assessment of pulmonary embolism:

Clinical Feature	Score
Previous pulmonary embolism or deep vein thrombosis	+1.5
Heart rate >100 beats per minute	+1.5
Immobilization or surgery in the previous four 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

Individual clinical feature scores and calculated risk scores will be recorded in the eCRF.

If a subject has a risk score of ≥ 2 , a computerized tomographic (CT) angiogram or appropriate investigation will be arranged by the investigator to exclude pulmonary embolism. If pulmonary embolism is confirmed on investigation, the event will be classified as an AESI and will be reported as a SAE.

The number and percentage of subjects with a risk score for deep vein thrombosis and pulmonary embolism of ≥ 1 or ≥ 2 (respectively) will be summarized at each visit.

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [Redacted]

CCI [Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI
[Redacted text block]

- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]

[Redacted text block]

CCI [Redacted]

[Redacted text block]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

CCI [Redacted]

CCI [Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [redacted]
[redacted]
[redacted]
[redacted]

[redacted]
[redacted]

[redacted]
[redacted]
[redacted]

[redacted]
[redacted]
[redacted]

CCI [redacted]

CCI [redacted]
[redacted]
[redacted]
[redacted]

- | [redacted]
- | [redacted]
- | [redacted]

[redacted]
[redacted]

CCI [redacted]

CCI [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

CCI [Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

4.10 Adjustment for Covariates

Not applicable.

4.10.1 Center effects

The study is planned to be conducted at approximately 50 sites in North America, Europe, and other regions. Subjects from all centers will be pooled. No adjustment for center will be carried out.

4.11 Analysis Populations, Protocol Deviations

Prior to the database lock, any recorded deviations plus the following outputs will be reviewed to assess the impact on the efficacy, safety and QoL endpoints and to make decisions about the analysis populations:

- Listing of informed consent/assent (as appropriate) dates/times, screening evaluation dates and randomization dates/time
- Listing of eligibility and visit dates.
- Listing of any failed inclusion/exclusion criteria.
- Listing of subjects who discontinued the study.
- Listing of medical history.
- Listing of study drug injections showing any incomplete, missed injections and delayed injections.
- Listing of extent of exposure and treatment compliance.
- Listing of treatment compliance below 80% or above 120%.
- Listing of concomitant medications
- Listing of potentially prohibited concomitant medications with an indication including HAE prophylaxis (eg, IV C1-INH for prophylaxis, androgens, antifibrinolytics). Indication will be checked for other terms with the same meaning.
- List of oral medications for HAE prophylaxis (eg, androgens, progestins, antifibrinolytics) and if they were used at a stable dose for 3 months before Screening and at the same dose throughout the study.
- Listing of hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen / progesterone containing product).
- Listing of subjects not treated.
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

- Listing of any subjects with one or two dose increases, with reason for dose increase and dates.

If needed, additional listings will be added.

If protocol deviations occur as outlined in the criteria above, then the data from complete individual subjects, individual visits or individual evaluations may be excluded from analysis populations.

The finalization of protocol violations and the final decision about excluded data will be made prior to the Database Lock and will be documented in the Data Review Meeting Minutes.

4.12 Handling of Missing Data

No imputation is planned. The primary safety endpoints are the person-time incidence rates of each primary endpoint safety event which are already taking into account that subjects' observation times can differ between subjects. Subjects receiving study drug will always have a certain amount of observation time and so will always contribute data/information to the primary safety endpoint independent if they discontinue early from the study or not. Only if a subject drops out before receiving any study drug this will lead to missing data for this subject, but this subject would not be included in the Safety Population anyway.

4.13 Deviations from SAP

Any deviations from the statistical analysis plan will be described and justified in the final Clinical Study Report (CSR).

4.14 Changes in Conduct or Planned Analyses from the Protocol

The statistical analysis for the original protocol and the Extension Period amendment are described in the one SAP to be on hand and not in two different statistical analysis plans.

The data from Treatment Period 1, Treatment Period 2, and Extension Period will be analyzed and presented jointly. Data collected from subjects who are enrolled in the Extension Period will be analyzed together with the data of subjects who are not participating in the Extension Period.

Because of the assumption that a minority (e.g., less than 20%) of subjects will undergo a CSL830 dose increase during the study, the first and second approaches as specified in 11.3.3 of the protocol will not be performed for the secondary safety endpoints. Rather, the approach to safety analysis based upon the actual treatment (40 IU/kg CSL830, 60 IU/kg CSL830 and ≥ 40 IU/kg CSL830) at the time of the event will be performed for the safety analyses.

The analyses 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 will not be done.

A treatment group ≥ 40 IU/kg CSL830 has been added in the analyses by treatment and overall group has been deleted.

If an event or evaluation occurred while a subject was receiving 80 IU/kg, these data will be listed and summarized in the ≥ 40 IU/kg CSL830 treatment group.

Adverse events that occur during the Screening will not be summarized for subjects in the Safety Population and will only be listed.

Safety and some efficacy analyses will not be performed for age group. No subgroups of subjects who previously used intravenously administered C1-INH for routine (long-term) prophylaxis will be assessed.

The additional calculation of the primary safety endpoint to divide the number of experienced safety events of the correspondent primary endpoint safety event from all subjects during the treatment duration with the CSL830 dose by the sum of each subject's time at risk in the same CSL830 dose was added and the analyses of the primary safety endpoint will also be performed by actual treatment. Subjects accrue events by dose over the duration(s) they receive each treatment dose while participating in the study, e.g. a subject randomized to 40 IU/kg and up-titrated to 60 IU/kg will be displayed in both treatments as well as in the ≥ 40 IU/kg treatment based upon their corresponding duration in that treatment.

CCI

The evaluation period for efficacy assessments was modified to be from the start (Day 1) of Week 3 of a treatment in Treatment Period 1 until the End of Study Visit (Week 53 Visit) or the last administration of CSL830 + 4 days (whichever occurs first) for subjects who are not participating in the Extension Period. For subjects who are taking part in the Extension Period, the evaluation period will be from the start (Day 1) of Week 3 of the treatment in Treatment Period 1 until the End of Study Visit of the Extension Period (Week 88) or the last administration of CSL830 + 4 days (whichever occurs first).

The analyses of merged HAE attacks (please see for details [Section 4.6](#)) were added as the primary analysis approach. The analyses of the HAE attacks reported by the investigator in the eCRF are kept as secondary analysis approach.

HAE attacks which start between the End of Study Visit or 4th day post last IMP administration [whichever occurs first] and the Follow-up Visit of Treatment Period 2 (applicable for subjects not participating in the Extension Period) or the Extension Follow-up Visit (applicable for subjects participating in the Extension Period) will not be included in the analyses of the secondary efficacy endpoints. For subjects who are taking part in the Extension Period and who have a rest period, HAE attacks with a start date in the rest period will also not be included in the analyses. CCI

The within-subject analyses of subjects who are responders or non-responders before and after a dose increase were deleted.

Different analyses of treated HAE attacks (for details see [Section 4.9.3](#)) have been added. The rescue medications which are included in the calculation of the time-normalized number of uses of rescue medication have been changed to include rescue medications and concomitant medications entered by the investigator in the eCRF which are administered during a merged HAE attack. As a sensitivity analysis, the analyses will be repeated including only rescue medications and concomitant medications which have a date of administration identical to the start date of a merged HAE attack.

The Screening Population was deleted.

CCI

Various subgroup analyses have been added for the efficacy and safety endpoints.

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.3 or a later version.

In the top left portion of each table/listing, a table/listing number followed by the title of the table/listing will be presented. After the title line, optional sub-title or population information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be put under the tables.

The sponsor name, protocol number, and SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

All tables, listings and figures will be displayed in landscape format on US letter size.

The left and right margins of all tables and listings will be a minimum of 2.54 cm/1.00 inches from the left and from the right. The top and bottom margins will be a minimum 2.87 cm/1.13 inches and 2.82cm/1.11 inches. Header and footer will be both 1.27 cm/0.5 inches.

There is no special requirement of font type and size, but a 9-point font size for tables and listings is proposed using Courier New font. In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (eg, the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean, median and the quartiles will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. The maximum number of decimal places will be four. Wherever possible, data will be aligned at the decimal point.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

Any date information in the listing will use the SAS *date9.* format, for example, 07MAY2002. In the listings, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, subject and visit and have the source data received by data management referenced in a footnote. All tables, listings and figures will be converted into Microsoft Word documents and PDF documents and collated into three complete documents. A hyperlinked Table of Content will be provided at the beginning of each file. PDF documents will be bookmarked, displayed as panel and page.

5.3 Tables

List of tables will be provided in the separate document of the Shell TFLs.

5.4 Listings

List of listings will be provided in the separate document of the Shell TFLs.

5.5 Figures

List of figures will be provided in the separate document of the Shell TFLs.

5.6 Appendices

Not applicable.

5.7 References

Zbynek Skidak. Rectangular Confidence Regions for the Means of Multivariate Normal Distributions. American Statistical Association Journal. 1967; 623 -633.

Signature Page

CSL830_3002 - Statistical Analysis Plan - 16.1.9 - 12Sept2017 - Final

Signed By	Date (GMT)
PPD	10-Nov-2017 16:48:52
Approved-Technical Approval	

--- Do Not Detach This Signature Page ---