BLA Clinical Review Memorandum

Application Type	Original Application
STN	125606/0
CBER Received Date	30 June 2016
PDUFA Goal Date	30 June 2017
Division / Office	DHCR
Priority Review (Yes/No)	No
Reviewer Name(s)	Laurence Landow
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	CSL Behring
Established Name	C1 esterase inhibitor subcutaneous (Human)
(Proposed) Trade Name	HAEGARDA
Pharmacologic Class	C1 esterase inhibitor
Formulation(s), including Adjuvants, etc.	Lyophilized powder to be reconstituted with Sterile Water
Dosage Form(s) and Route(s) of Administration	60 IU/kg body weight by subcutaneous injection
Dosing Regimen	Twice weekly
Indication(s) and Intended Population(s)	Routine prophylaxis to prevent hereditary angioedema attacks in adolescent and adult patients
Orphan Designated (Yes/No)	No

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GLOSSARY

Adverse Reaction	An adverse event at least possibly related to study medication
Combined active treatments	Combination of 40 IU/kg and 60 IU/kg CSL830 (≥ 40 IU/kg CSL830) administered during Study 3001
Combined placebo	Combination of the high- and low-volume placebo administered during Study 3001
"CSL830-Continuation" Subjects	Study 3002 subjects who completed participation in Study 3001 and started Study 3002 ≤ 1 week after the End of Study Visit of Study 3001.
"CSL830-Interrupted" Subjects	Study 3002 subjects who completed participation in Study 3001 and started Study 3002 > 1 week after the End of Study Visit of Study 3001.
"CSL830-Naïve" Subjects	Study 3002 subjects who did not participate in Study 3001, or Study 3002 subjects who participated in Study 3001 but did not receive blinded investigational product as a part of Study 3001.
Study 1001	Study number CSL830_1001; A randomized, double-blind, single-center, crossover study to evaluate the safety, bioavailability and pharmacokinetics of two formulations of C1-esterase inhibitor administered intravenously.
Study 2001	Study number CSL830_2001; An open-label, crossover, dose-ranging study to evaluate the pharmacokinetics, pharmacodynamics and safety of the subcutaneous administration of a human plasma-derived C1-esterase inhibitor in subjects with hereditary angioedema.
Study 3001	Study number CSL830_3001; A double-blind, randomized, placebo-controlled, crossover study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.
Study 3002	Study number CSL830_3002; 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.
PTIR	Person-time incidence rate
TP1	Treatment Period 1
TP2	Treatment Period 2

1. Executive Summary

CSL830, CSL Behring's investigational C1-esterase inhibitor (C1-INH) product for **prophylaxis** of hereditary angioedema (HAE) by subcutaneous (SC) administration, is a (b) (4) . The manufacturing steps of CSL830 are (b) (4) . CSL830 will be marketed as a single-use vial available in two sizes: 2000 International Units (IU) with 4mL water for injection and 3000 International Units (IU) with 6 mL water for injection each containing 500 IU/ml C1-esterase inhibitor after reconstitution.

Four clinical study reports (CSR) are included in the submission.

Study 3001

Study 3001 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete-crossover **safety, efficacy and pharmacokinetic (PK)** study for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent and adult subjects[1] with HAE type I or II. A placebo solution consisting of reconstituted human albumin solution with CSL830 excipients was used to match the protein-based C1-INH solution. The primary endpoint was time-normalized **number of HAE attacks**, identical to the indication granted for IV C1-INH (Berinert). Secondary efficacy endpoints included the percentage of responders and time-normalized number of uses of rescue medication[2]. Table 1 summarizes dosing of investigational product and placebo during the two treatment periods, Treatment Period 1 (TP1)and Treatment Period 2 (TP2).

Table 1: Overview of Dosing in Study 3001

Randomized Dose Cohort		Treatment Period 1	Treatment Period 2
40 IU/kg CSL830			
	Treatment sequence 1	40 IU/kg	High-volume placebo
	Treatment sequence 2	High-volume placebo	40 IU/kg
60 IU/kg CSL830			
	Treatment sequence 3	60 IU/kg	Low-volume placebo
	Treatment sequence 4	Low-volume placebo	60 IU/kg

Adapted from Figure 9-1, CSR, page 20 of 3005, May 2, 2016

Figure 1 is a study schematic that shows TP1 and TP2 were preceded by a Screening Period (4 weeks) and a Run-in Period (8 weeks).

1 Throughout this memo, N=number of subjects receiving treatment and n=number of subjects experiencing ≥1 event.

2 The type of rescue medication used was determined by the investigator and not mandated per protocol. However, in countries where Berinert is licensed, Berinert was offered and provided as needed to subjects who elected to use C1-INH as rescue medication for the acute treatment of HAE attacks. The use of IV Berinert as a rescue medication for the acute treatment of HAE attacks was permitted at any time during the Run-in Period, TP1, and TP2. Subjects were also permitted to use other plasma-derived or recombinant C1-INH, icatibant (a bradykinin antagonist), ecallantide (a kallikrein inhibitor), and fresh frozen plasma as rescue medications.

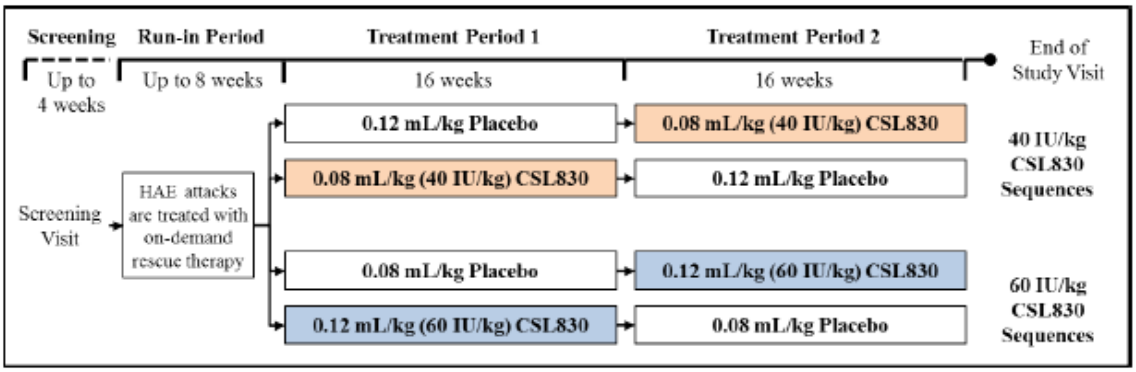


Figure 1: Study 3001 design schematic. *Source: Figure 9-1, CSR, page 20 of 3005, May 2, 2016*

Study duration for individual subjects was up to 45 weeks. To maintain the study blind, subjects randomized to receive 40 IU/kg (0.08 mL/kg) CSL830 in one treatment period were administered placebo at the higher volume (0.12 mL/kg) in the other treatment period. Similarly, subjects randomized to receive 60 IU/kg (0.12 mL/kg) CSL830 in one treatment period were administered placebo at the lower volume (0.08 mL/kg) in the other treatment period. Treatment allocation was in a 1:1:1:1 sequence. The dosing schedule is outlined in Table 1 and the overall study design is presented in Figure 1.

Study 3002
Study 3002 is an ongoing phase 3, open-label, randomized, long-term **safety** study in subjects with HAE. Primary endpoints include AEs leading to premature study discontinuation, TEEs, anaphylaxis, HAE attacks resulting in hospitalization, local injection site AEs, related SAEs (SAR), and anti-C1-INH antibodies. Time-normalized number of HAE attacks is an exploratory efficacy endpoint. Upon completion, this study will provide 2-year safety and tolerability data.

Study 2001
Study 2001 was a phase 2, multicenter, open-label, crossover, dose-ranging **PK, pharmacodynamic (PD), safety and tolerability** study using 3 dosing regimens (1500 IU, 3000 IU and 6000 IU twice per week for 4 weeks) in subjects with HAE.

Study 1001
Study 1001 was a phase 1, single center, randomized, double blind, double-dummy crossover, dose-ranging **PK, PD and safety** study that compared a single IV dose of 1500 IU CSL830 with a single IV dose of 1500 IU Berinert in healthy volunteers.

EFFICACY
Study 3001
Twice per week SC doses of 40 IU/kg and 60 IU/kg CSL830 significantly reduced mean time-normalized number of HAE attacks from 0.12 to 0.04 attacks/day (3.61 to 1.19 attacks/month) using 40 IU/kg compared with high-volume placebo ($p < 0.001$) and from 0.13 to 0.02 attacks/day (4.03 to 0.52 attacks/month) using 60 IU/kg compared with low-volume placebo ($p < 0.001$).

Secondary endpoint outcomes were supportive.

- Number of subjects with HAE attacks (CSL830 *vs.* placebo)
  - 40 IU/kg cohort: 26/45 (57.7%) *vs.* 40/45 (88.9%)
  - 60 IU/kg cohort: 25/45 (55.6%) *vs.* 42/45 (93.3%)
- Number of HAE attacks (CSL830 *vs.* placebo)
  - 40 IU/kg cohort: 145 attacks *vs.* 503 attacks
  - 60 IU/kg cohort: 71 attacks *vs.* 472 attacks
- Number of Laryngeal HAE attacks (CSL830 *vs.* placebo)
  - 40 IU/kg cohort: 5/45 *vs.* 16/45 subjects
  - 60 IU/kg cohort: 0/45 *vs.* 9/45 subjects
- Rate of rescue use (placebo *vs.* CSL830)
  - 40 IU/kg cohort: From 5.6 uses to 1.1 uses per month
  - 60 IU/kg cohort: From 3.9 to 0.3 uses per month
- Number of subjects with a severe HAE attack (placebo *vs.* CSL830)
  - 40 IU/kg cohort: From 33/45 (73.3%) subjects to 9/45 (20.0%) subjects
  - 60 IU/kg cohort: From 31/45 (68.9%) subjects to 4/45 (8.9%) subjects

Study 3002

Interim safety analysis (mean duration of exposure: 49 weeks; maximum duration of exposure: ≥70 weeks)

- Number of HAE attacks/month (60 IU/kg *vs.* 40 IU/kg CSL830)
  - 0.51 (0.916) *vs.* 0.43 (0.647)
- Number of subjects HAE attack-free (60 IU/kg *vs.* 40 IU/kg CSL830)
  - 34.9% *vs.*46.0%

SAFETY

Serious Adverse Events (SAE)

Three subjects in Study 3001 experienced 4 unrelated SAEs: a TEE (**pulmonary embolism**) in one placebo subject, **angioedema and syncope** in another placebo subject, and **urosepsis** in a 40 IU/kg CSL830 subject. No cases of anaphylaxis were reported.

Nine subjects in Study 3002 experienced 11 unrelated SAEs: 5 SAEs (**bronchitis**, **contusion**, **dehydration**, hypokalemia and **lymphoma**) in four 40 IU/kg subjects and 6 SAEs (**myocardial infarction**, **diplopia**, **cholelithiasis**, **pneumonia**, **chest pain** and **dizziness**) in five 60 IU/kg subjects.

Two subjects in Study 2001 experienced 2 unrelated SAEs: **syncope** (before initiation of CSL830) and **hypovolemic shock**.

Adverse Reactions (AR)[3]
The most frequent safety events reported in >4% of CSL subjects were **injection site reaction** (27/86 or 31.4% *vs.* 21/86 or 24.4%, CSL830 *vs.* placebo, respectively), **nasopharyngitis** (9/86 or 10.5% *vs.* 6/86 or 7.0%), **hypersensitivity** (5/86 or 5.8% *vs.* 1/86 or 1.2%) and **dizziness** (4/86 or 4.7% *vs.* 1/86 or 1.2%).

More CSL830 subjects in Study 3001 experienced systemic AEs than injection site ARs.

- Systemic AEs were experienced by 55.8% *vs.* 55.8% of subjects, CSL830 *vs.* placebo, respectively; the incidence was higher in 60 IU/kg CSL830 subjects than in 40 IU/kg CSL830 subjects (58.1% and 53.5%, respectively). Most cases were mild (44.2% *vs.* 41.9%, 60 IU/kg *vs.* 40 IU/kg, respectively), with fewer subjects experiencing moderate (27.9% *vs.* 20.9%) intensity ARs and far fewer experiencing severe (4.7% *vs.* 4.7%) intensity ARs.

- Local ARs were experienced by 31.4% *vs.* 24.4% of subjects, CSL830 *vs.* placebo, respectively). The most common reactions were **pain** and **erythema**, with a higher incidence reported in the 60 IU/kg cohort than in the 40 IU/kg cohort (34.9% *vs.* 27.9%). These events typically occurred within 24 hours after injection and resolved within 24 hours after onset. Most cases were of mild (34.9% *vs.* 25.6%) or moderate (11.6% *vs.* 4.7%) intensity and none was graded as severe or resulted in discontinuation of product administration.

Three cases of rash were reported in 3 subjects (40 IU/kg, 60 IU/kg and placebo), 9 cases of urticaria in 2 subjects (60 IU/kg, 40 IU/kg), and 2 cases of conjunctivitis (40 IU/kg). No case of transmission of viral infections (i.e., HIV, HBV, or HCV) was reported. No inhibitory antibodies to C1-INH were observed.

ASSESSMENT
Twice per week SC administration of 40 IU/kg or 60 IU/kg CSL830 is safe and effective for routine prophylaxis to prevent HAE attacks in adolescent and adult patients. SC administration offers a convenient option for patients who wish to avoid intravenous injections. Of the 2 doses evaluated in phase 3 studies, 60 IU/kg has the best benefit / risk profile, providing better efficacy and more favorable outcomes than the 40 IU/kg dose, with no evidence of dose-dependent safety concerns.

RECOMMENTATION
I recommend approval of HAEGARDA at the 60 IU/kg dose for routine prophylaxis.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographic and baseline characteristics of subjects are similar in Studies 3001 and 3002 because half of the 3002 subjects participated in Study 3001 (64/126, 50.8%).

3 For the purposes of this review, the difference between an adverse event (AE) *vs.* adverse reaction (AR) is based on the hierarchy presented in FDA's "*Guidance: Safety Reporting Requirements for INDs and BA/BE Studies*", in which an AR is defined as an "untoward medical occurrence associated with use of a drug" (=AE) where there is a reasonable possibility that the drug *caused* the AE. Nonserious AEs that lacked sufficient information in the application to make a causality determination were classified as ARs.

Table 2 shows that a majority of the population consisted of middle-aged females, almost all of whom were White.

Table 2: Demographics of the Study 3001 and 3002 Study Population

Parameter		Study 3001 N (%)	Study 3002 N (%)
Sample size		90	126
Age (years)			
	Median	40	41
	Min; Max	12; 72	8; 72
Gender			
	Male [N (%)]	30 (33.3)	50 (39.7)
	Female [N (%)]	60 (67.7)	76 (60.3)
Race			
	White [N (%)]	84 (93.3)	121 (96.0)
	Black/African American [N (%)]	4 (4.4)	2 (1.6)
	Asian [N (%)]	1 (1.1)	1 (0.8)
	Other [N (%)]	1 (1.1)	2 (1.6)

Adapted from Table 11-1, page 90 of 3005, 3001 CSR 3001, 2 May 2016 and Table 11-1, page 80 of 1155, 3002 Interim CSR 3002, 1 June 2016

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

HAE is characterized clinically by unpredictable and recurrent attacks of edema affecting the SC tissues of the face, trunk, or limbs, or the submucosal tissues of the respiratory, gastrointestinal, or genitourinary tracts. Attacks can be painful, disfiguring, and disabling. Laryngeal attacks are the most serious concern in HAE and can be fatal.

HAE is an autosomal dominant disease caused by a gene mutation on chromosome 11 that affects the production of C1-INH protein. There are two main types of HAE. HAE type I (approximately 85% of patients) is characterized by low concentrations of functional C1-INH protein. HAE type II (approximately 15% of patients) is characterized by "normal" concentrations of functionally deficient C1-INH protein.

C1-INH is a serine protease inhibitor (serpin) that regulates activation of the complement, contact (kallikrein/kinin)[4] and coagulation systems by binding to and inactivating target serine proteases. Dysregulation of these systems because of C1-INH deficiency results in the uncontrolled production of vasoactive peptides (e.g., bradykinin) that promote inflammation through increased vascular permeability and excessive fluid accumulation in body tissues.

The diagnosis of HAE is confirmed by low complement component 4 (C4) antigen and

4 The contact system consists of four components: factor XI, factor XII, plasma kallikrein and the cofactor, high molecular weight kininogen. Activation of the contact system, also known as the kallikrein/kinin system, leads to the release of the highly potent proinflammatory peptide bradykinin (*J Mol Med* 2010; 88:121-126

absent or greatly reduced C1-INH antigen (protein) or C1-INH functional activity. C4 is a component of the classical complement pathway that is digested by active complement component 1 (C1) when C1 is not inhibited by C1-INH. Typical C1-INH functional activity in untreated HAE patients is between 5% and 30% of normal. Enhanced activation of the complement system has been observed with C1-INH functional activity of < 38% of normal, suggesting a minimum threshold of C1-INH function to protect against HAE symptoms.

HAE is estimated to affect approximately 1 in 50,000 individuals, with no ethnic predominance, suggesting that more than 6000 individuals are affected in the U.S.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Therapeutic approaches to HAE include

- Acute or "on-demand" treatment administered after an HAE attack begins
- Long-term prophylaxis to prevent or minimize attacks
- Short-term prophylaxis to prevent attacks caused by known triggers such as medical, dental, or surgical procedures

Unrelated products approved for **treatment** of HAE attacks include

- SC: Kalbitor (kallikrein inhibitor)
- SC: Firazyr (bradykinin receptor antagonist)

Unrelated products approved for **prophylaxis** of HAE attacks include

- PO: danazol, stanozolol (attenuated androgens)

2.3 Safety and Efficacy of Pharmacologically Related Products

CINRYZE is a human plasma-derived C1-inhibitor indicated for routine intravenous **prophylaxis** of adult and adolescent patients with HAE. The safety and efficacy of CINRYZE prophylaxis therapy to reduce the incidence, severity, and duration of HAE attacks was demonstrated in a single randomized, double-blind, placebo-controlled multi-center cross-over study of 24 subjects. The only serious adverse reaction observed was cerebrovascular accident. The most common adverse reactions observed (≥8% of subjects) were headache, nausea, rash, and vomiting.

RUCONEST is a C1 esterase inhibitor [recombinant] indicated for intravenous **treatment** of acute attacks in adult and adolescent patients with HAE. The efficacy of RUCONEST was demonstrated in a placebo-controlled, double-blind, randomized study, supported by two double-blind, randomized, placebo-controlled studies. Adverse reactions (≥ 2% of subjects) reported in clinical trials were headache, nausea, and diarrhea.

Berinert (plasma-derived C1-inhibitor) was approved in 2009 for intravenous **treatment** of HAE attacks. In clinical trials, the most serious adverse reaction associated with its use was an increase in the severity of pain associated with HAE; the most common

adverse reactions (>4% of subjects) were nausea, dysgeusia (distorted sense of taste), abdominal pain and vomiting (Berinert Prescribing Information).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Amendment 1 (20 February 2014) introduced several features found in the original protocol (7 June 2013). The amended protocol

- Allowed use of documented historical values for C1-INH functional activity and C4 antigen concentration as biochemical confirmation of HAE diagnosis
- No longer stated that intravenous Berinert was the suggested rescue medication for this study
- Did not require subjects to discontinue use of their medications for HAE prophylaxis at entry into the Run-in Period
- Permitted inclusion of subjects who used a stable regimen of oral medication for prophylaxis against HAE attacks (i.e., androgens, tranexamic acid, progestins) within 3 months of the Screening Visit and who did not plan to change that regimen during the study
- Excluded subjects with the following characteristics
    - Body weight < 40 kilograms
    - Subject has used intravenous C1-esterase inhibitor (C1-INH) for routine prophylaxis against HAE attacks (i.e., administered every 3 or 4 days) within 3 months of the Screening Visit or who planned to use intravenous C1-INH for routine prophylaxis against HAE attacks during the study
    - Subjects is unable to have their HAE adequately managed pharmacologically with on-demand treatment, administered either independently or with assistance
- Permitted the use of medications (e.g., intravenous C1-INH) for the pre-procedure prevention of acute HAE attacks during the study
- Revised the statistical analysis to include
    - New sub-group analyses
    - A description of missing data handling
    - The lower bound of the 95% confidence interval for the responder rate of the combined active treatment group

Amendment 2 (11 Dec 2014) revised the protocol by clarifying the joint intent of the Steering Committee, the Data Safety Monitoring Board, and CSL Behring regarding study conduct pertaining to the stopping, restarting, and termination rules.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was complete and of acceptable quality.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant stated the studies complied with GCP. Data integrity was acceptable.

3.3 Financial Disclosures

Covered clinical study (name and/or number): **Study 3001**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 41		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): **Study 3002**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		applicant)
Total number of investigators identified: 32		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): **2001**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 8		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize	Yes ☒	No ☐ (Request information

potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

See the CMC reviewer's memo.

4.2 Assay Validation

See the CMC reviewer's memo.

4.3 Nonclinical Pharmacology/Toxicology

See the pharmacology/toxicology reviewer's memo.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action
C1-INH is a normal constituent of human plasma that inhibits the complement, contact (kallikrein/kinin) and coagulation systems. Suppression of contact system activation by C1-INH and inactivation of plasma kallikrein and factor XIIa is thought to modulate vascular permeability by preventing generation of bradykinin.[4] Since HAE patients have absent or low levels of functional C1-INH, administration of HAEGARDA is designed to replace the missing or malfunctioning C1-INH protein.

4.4.2 Human Pharmacodynamics (PD)
In untreated patients, insufficient levels of functional C1-INH lead to increased activation of C1, which results in decreased levels of complement component 4 (C4). The administration of HAEGARDA increases plasma levels of C1-INH in a dose-dependent manner and subsequently increases plasma concentrations of C4. The C4 plasma concentrations after S.C. administration of 60 IU/kg HAEGARDA were in the normal range (16 to 38 mg/dL).

4.4.3 Human Pharmacokinetics (PK)
See the pharmacokineticist's review memo.

4.5 Statistical

See the statistical reviewer's memo.

4.6 Pharmacovigilance

See the epidemiologist's review memo.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

After reviewing the draft package insert, the following CSRs were reviewed in depth.

- Study 3001, the pivotal study of safety and efficacy. Study 3001 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover **efficacy and safety** study for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent and adult subjects with HAE type I or II.
- Study 3002 (interim), which is an ongoing, phase 3b, open-label, randomized, long-term **safety** study in subjects with HAE. Upon completion, it will provide additional, long-term safety and tolerability data; efficacy is an exploratory endpoint.
- Study 2001, a phase 2, open-label, crossover, dose-ranging **PK, PD, safety and tolerability** study in subjects with HAE. Three subcutaneous treatment regimens were investigated: 1500 IU administered 2 times weekly for 4 weeks; 3000 IU administered 2 times weekly for 4 weeks; and 6000 IU administered 2 times weekly for 4 weeks.
- Study 1001, a phase 1, single center, randomized, double blind, double-dummy crossover, dose-ranging **PK, PD and safety** study that compared a single IV dose of 1500 IU CSL830 with a single IV dose of 1500 IU Berinert in healthy volunteers.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

CSR 3001: Abnormal lab results, adverse event listings, compliance and drug concentration data, concomitant medications, CSR report-body, CSR report-body erratum, Deaths, demographic data, discontinued patients, documentation of hand calculated data points, efficacy response, individual efficacy response data, individual laboratory measurements listed by patient, patient list by batch, patients excluded from efficacy analysis listing, original protocol, protocol amendments, randomization scheme and subject reported outcome measures.

CSR 3002 (interim): 4-month safety update, abnormal clinical lab results, adverse event listings, CSR report-body, demographic data, description of investigators and sites, discontinued patients, individual efficacy response data, patient list by batch, patients excluded from the efficacy analysis, original protocol, protocol amendment 1, protocol deviations and randomization scheme.

CSR 2001: Adverse event listings, CSR report-body, demographic data listing, discontinued patient listings, individual efficacy response data listing, individual laboratory measurements listing, list of investigators, listing of patients receiving test drugs, patients excluded from efficacy analysis, original protocol, protocol amendment 1 and protocol deviation listings.

CSR 1001: CSR report-body and description of investigators and sites.

5.3 Table of Studies/Clinical Trials

Study Identifier Status; Report Location	Type of Study	Location of Study Centers (N)	Phase; Study Design	Primary Objective(s)	Subject Population; Median Age (Range)	Treatment; Route; Dose; Duration
CSL830_1001 Completed Module 5.3.3.1 (Final CSR)	PK and safety	Germany (1)	Phase 1, single-center, randomized, double-blind, crossover study	Assess the safety of IV CSL830, a volume-reduced presentation of Berinert	16 healthy subjects (5 females / 11 males) 35 years (24 to 45 years)	Single IV bolus dose of 1500 IU CSL830 (500 IU/mL) and a single IV infused dose of 1500 IU Berinert (50 IU/mL), administered in a randomized order using a double-dummy approach.
CSL830_2001 Completed Module 5.3.3.2 (Final CSR)	PK, PD, and safety	Germany (3) US (5)	Phase 1/2, multicenter, open-label, dose-ranging, crossover study	Characterize the PK and PD of 3 different dosing regimens of SC CSL830	18 subjects with HAE type I or II (11 females / 7 males) 34 years (19 to 69 years)	Single IV dose of 20 IU/kg Berinert (50 IU/mL) followed by 2 treatment periods with CSL830 (500 IU/mL) administered SC twice per week for 4 weeks according to 1 of 6 treatment sequences: • 1500 IU in TP1 and 3000 IU in TP2 • 3000 IU in TP1 and 1500 IU in TP2 • 3000 IU in TP1 and 6000 IU in TP2 • 1500 IU in TP1 and 6000 IU in TP2 • 6000 IU in TP1 and 1500 IU in TP2 • 6000 IU in TP1 and 3000 IU in TP2

Study Identifier Status; Report Location	Type of Study	Location of Study Centers (N)	Phase; Study Design	Primary Objective(s)	Subject Population; Median Age (Range)	Treatment; Route; Dose; Duration
CSL830_3001 Completed Module 5.3.5.1 (Final CSR)	Efficacy, safety, PK, PD, and QoL	Australia (1) Canada (6) Czech Republic (2) Hungary (1) Israel (2) Italy (2) Romania (2) Spain (4) UK (2) US (19)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover study	Demonstrate the clinical efficacy of SC CSL830 in the prophylactic treatment of HAE, and compare the clinical efficacy of 2 doses of SC CSL830	90 subjects with HAE type I or II (60 females / 30 males) 40 years (12 to 72 years)	Single SC injection of CSL830 or placebo twice per week for 16 weeks in 2 consecutive treatment periods (according to 1 of 4 treatment sequences): • High-volume placebo (0.12 mL/kg) in TP1 and 40 IU/kg CSL830 (0.08 mL/kg) in TP2 • 40 IU/kg CSL830 (0.08 mL/kg) in TP1 and high-volume placebo (0.12 mL/kg) in TP2 • Low-volume placebo (0.08 mL/kg) in TP1 and 60 IU/kg CSL830 (0.12 mL/kg) in TP2 • 60 IU/kg CSL830 (0.12 mL/kg) in TP1 and low-volume placebo (0.08 mL/kg) in TP2
CSL830_3002 Ongoing Module 5.3.5.2 (Interim CSR, data cut-off: 11 February 2016)	Safety, efficacy, PK, PD, and QoL	Australia (1) Canada (4) Czech Republic (1) Germany (4) Hungary (1) Israel (2) Italy (2) Romania (1) Spain (3) UK (1) US (12)	Phase 3b, multicenter, randomized, open-label, parallel-group study	Assess the safety of SC CSL830 in the long term prophylactic treatment of HAE	126 subjects with HAE type I or II (76 females / 50 males) 41 years (8 to 72 years)	Single SC injection of 40 IU/kg or 60 IU/kg CSL830 twice per week for up to 140 weeks: • TP1 (fixed-dose period): 24 weeks • TP2 (dose-adjustment period): 28 weeks • Extension Period (US subjects only): 88 weeks

CSR = clinical study report; HAE = hereditary angioedema; IU = international units; IV = intravenous; N = number of study centers; PK = pharmacokinetics; PD = pharmacodynamics; QoL = quality of life; SC = subcutaneous; UK = United Kingdom; US = United States; TP1 = Treatment Period 1; TP2 = Treatment Period 2.

Source: Table 1, Clinical Overview, page 11 of 47,June 9, 2016

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 TRIAL #1: CLS830-3001

A double-blind, randomized, placebo-controlled, crossover study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.

6.1.1 Objectives

1. Primary:
    a. To demonstrate the clinical efficacy of subcutaneous (SC) CSL830 in the prophylactic treatment of hereditary angioedema (HAE).
    b. To compare the clinical efficacy of 2 doses of SC CSL830
2. Secondary
    a. To further characterize the clinical efficacy of 2 doses of SC CSL830.
    b. To demonstrate the safety and tolerability of SC CSL830.

6.1.2 Design Overview

Phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover study comprising 4 distinct parts as depicted in Figure 1: Screening Period (4 weeks), Run-in Period (8 weeks) Treatment Period 1 [TP1], and Treatment Period 2 [TP2]). Study duration for individual subjects was up to 45 weeks.

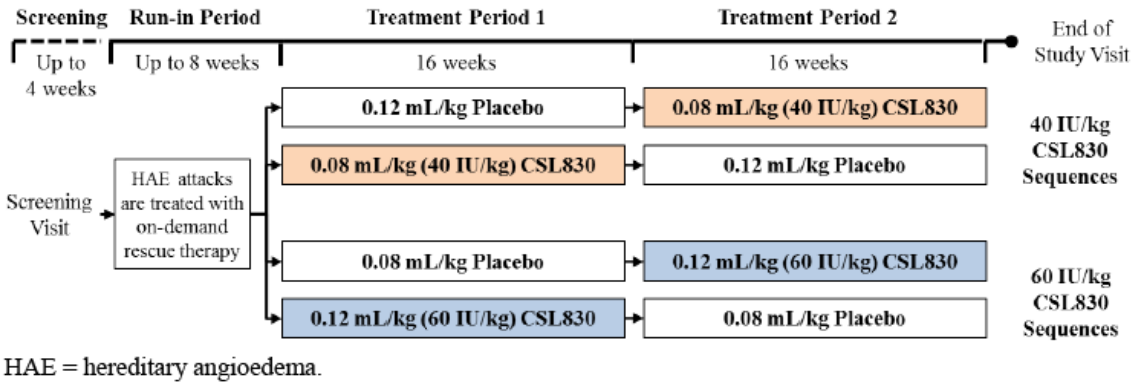


Figure 2: Study design schematic
Source: Figure 9-1, page 20 of 3005, CSR 3001, May 2, 2016

In both TP 1 and TP 2, subjects received CSL830 or placebo (a reconstituted human albumin-based solution with CSL830 excipients) as a single SC injection (preferably in the abdomen) twice per week for 16 weeks. Two doses of CSL830 were evaluated: 40 IU/kg (0.08 mL/kg) and 60 IU/kg (0.12 mL/kg). Subjects randomized to receive 40 IU/kg CSL830 in one TP received high-volume placebo (0.12 mL/kg) in the other treatment period. Alternatively, subjects randomized to receive 60 IU/kg CSL830 in one treatment period received low-volume placebo (0.08 mL/kg) in the other treatment period. Investigators, study center staff, and subjects were blinded to subject treatment allocation and the order of active treatment and placebo within sequences.

6.1.3 Population

1. Male and female subjects aged ≥12 years.
2. Diagnosis of HAE type I or II confirmed by central laboratory testing.
3. Experienced at least 4 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period within the 3 months before the Screening Visit, as documented in the subject's medical records.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study product: CSL830; comparator: placebo ((a reconstituted human albumin-based solution with CSL830 excipients).

CSL 830 batch numbers: (b) (4)

Placebo batch numbers: (b) (4)

6.1.5 Directions for Use

Before use, each vial was reconstituted with 3 mL of water for injection, yielding a CSL830 concentration of 500 IU/mL C1-esterase inhibitor (C1-INH).

6.1.6 Sites and Centers

Site No.	Study Location	Investigator
Active Sites		
0360024	Campbelltown Hospital Therry Rd 2560 Campbelltown, NSW Australia	Dr. Constance Helen Katelaris
1240023	Gordon Sussman Clinical Research Inc. 202 St. Clair Avenue West Toronto, Ontario M4V 1R2 Canada	Gordon L. Sussman, MD FRCPC FACP FAAAAI
1240025	Hamilton Health Sciences, McMaster University Medical Center Site 1200 Main Street West Hamilton, Ontario L8N3Z5 Canada	Paul Keith, MD
1240027	Ottawa Allergy Research Corporation 1081 Carling Avenue Suite 800 Ottawa, Ontario K1Y4G2 Canada	Dr. William H. Yang, MD FRCPC FAAAAI

Site No.	Study Location	Investigator
Active Sites		
1240028	Effective as of 27 October 2015: Centre de recherche appliquée en allergie de Québec 2600 boul Laurier, bureau 880 Québec, Québec G1V4W2 Canada Prior to October 2015: Centre de recherche appliquée en allergie de Québec 2590 boul Laurier, bureau 225 Tour Belle Cour Québec, Québec G1V 4M6 Canada	Jacques Hébert, MD
1240029	Research Transition Facility 8308 114 Street Room 4-016 Edmonton, Alberta T6G 2V2 Canada	Bruce Ritchie, MD, FRCPC
2030012	Fakultni nemocnice Hradec Kralove Ustav klinicke Imunologie a Alergologie Sokolska 581 50005 Hradec Kralove Czech Republic	Pavlina Kralickova, MD
2030014	Allergology and Clin. Immunology Charles University Hospital in Pilsen Alej Svobody 80 30460 Pilsen Czech Republic	Jana Hanzlikova, MD

Site No.	Study Location	Investigator
Active Sites		
3480001	Semmelweis University 3rd Department of Internal Medicine Kútvölgyi út 4 1125 Budapest Hungary	Prof. Henriette Farkas
3760008	The Chaim Sheba Medical Center Allergy and Clinical Immunology Unit 52621 Tel Hashomer Israel	Dr. Avner Reshef
3760009	Pulmonology, Allergy and Immunology Unit Tel Aviv Sourasky Medical Center 6, Weitzman St. Tel Aviv 64239 Israel	Prof. Shmuel Kivity
3800044	Università degli Studi di Milano, Dipartimento di Scienze Biochimiche e Cliniche L. Sacco–Ospedale L. Sacco Unità Operativa di Medicina Generale Via G.B. Grassi 74, 20157 Milano Italy	Prof. Marco Cicardi
3800046	Azienda Ospedaliero - Universitaria "Policlinico - Vittorio Emanuele", Presidio G. Rodolico, Dipartimento di Medicina Interna Via S.Sofia 86 95123 Catania Italy	Sergio Neri, MD

Site No.	Study Location	Investigator
Active Sites		
8260025	Brighton and Sussex University Hospitals NHS Trust Royal Sussex County Hospital Eastern Road Brighton, BN2 5BE United Kingdom	Dr. Michael Tarzi, BA MBBS MRCP MD FRCPATH
8260027	Barts Health NHS Trust Immunopathology, Division of Blood Sciences, 2nd Floor, Pathology and Pharmacy Building Royal London Hospital 80 Newark Street Whitechapel London, E1 2ES United Kingdom	Dr. Hilary Longhurst, BA (HONS) MBBS MRCP (UK) FRCP PhD MRCPATH FRCPATH

Site No.	Study Location	Investigator
Active Sites		
8400147	Baker Allergy, Asthma and Dermatology Research Center, LLC Effective as of 10/11 July 2015: 9495 SW Locust Street Suites A & E Portland, Oregon 97223 USA Prior to July 2015: 3975 SW Mercantile Drive Suite 165 Lake Oswego, Oregon 97035 USA	James W. Baker, MD
8400151	AARA Research Center 10100 N. Central Expressway, Suite 125 Dallas, Texas 75231 USA	William R. Lumry, MD

Site No.	Study Location	Investigator
Active Sites		
8400001	Penn State Milton S. Hershey Medical Center 500 University Drive, Hershey, PA 17033 USA	Timothy Craig, DO
8400143	Institute for Asthma and Allergy, MD 5454 Wisconsin Ave, Suite 700 Chevy Chase, MD 20815 USA	H. Henry Li, MD, PhD

Site No.	Study Location	Investigator
Active Sites		
8400227	Marycliff Allergy Specialists 823 West 7th Avenue Spokane, WA 99204 USA	Richard G. Gower, MD
8400228	Effective as of 12Jan2014: Allergy & Asthma Clinical Research 370 N. Wiget Lane, Suite #210 Walnut Creek, CA 94598 USA Prior to Jan 2014: Allergy & Asthma Clinical Research 130 La Casa Via, Bldg. #2 Suite 110 Walnut Creek, CA 94598 USA	Joshua S. Jacobs, MD
8400229	Optimed Research, LTD 8080 Ravines Edge Court Suite 200 Columbus, OH 43235 USA	Donald L. McNeil, MD

Site No.	Study Location	Investigator
Active Sites		
8400219	Effective as of 25Mar2014: Vital Prospects Clinical Research Institute, P.C. 7307 S. Yale Ave. Suite 201 Tulsa, OK 74136-3808 USA Prior to Mar 2014: Vital Prospects Clinical Research Institute, P.C. 6565 S. Yale Ave. Suite 209 Tulsa, OK 74136-3808 USA	Iftikhar Hussain, MD
8400223	Clinical Research Center of Alabama 504 Brookwood Boulevard Suite 250 Birmingham, AL 35209 USA	James Bonner, MD
8400225	Clinical Research Services Unit-Virginia Commonwealth University North Hospital 8th Floor, 1300 E. Marshall Street Richmond, VA 23298 USA	Lawrence Barry Schwartz, MD, PhD

Site No.	Study Location	Investigator
Active Sites		
8400185	Effective as of 02 April 2015: Bernstein Clinical Research Center, LLC 8444 Winton Road Cincinnati, Ohio 45231 USA Prior to April 2015: UC Physicians Company, LLC (Department of Internal Medicine Division of Immunology, Allergy & Rheumatology) 3255 Eden Avenue Suite 250 (pt visit) suite 350 (admin & Del) Cincinnati, Ohio 45267 USA	Jonathan A. Bernstein, MD
8400187	Toledo Institute of Clinical Research 7247 W. Central Ave. Suite A Toledo, Ohio 43617 USA	Syed M. Maseehur Rehman, MD
8400205	Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 USA	Aleena Banerji, MD

Site No.	Study Location	Investigator
Non-active Sites		
1240024	Gordon Sussman Clinical Research Inc. 202 St. Clair Avenue West Toronto, Ontario M4V 1R2 Canada	Dr. Stephen Betschel, BSc (HONS) MD FRCPC
6420026	Spitalul Clinic Judetean Mures, Compartimentul de Alergologie-Imunologie, Str. Gheorghe Marinescu nr.1 Targu Mures 540103 Jud. Mures Romania	Dr. Dumitru Moldovan
8400246	3386 Holland Road, Suite 202 Virginia Beach, VA 23452 USA	Robert C. Radin, MD

Site No.	Study Location	Investigator
Active Sites		
8400231	Asthma & Allergy Associates, P.C. 2709 North Tejon Street Colorado Springs, CO 80907 USA	Robert A. Nathan, MD
8400232	SRCR, Inc 5985 Florence Ave, Suite N Bell Gardens, CA 90201 USA	Galal Salem, MD
8400243	Medical Research of Arizona 7514 E. Monterey Way, Suite1A Scottsdale, Arizona 85251 USA	Michael E. Manning, MD
8400248	705 W. La Veta Ave, Suite 101 Orange, CA 92868 USA	Donald S. Levy, MD
8400250	University of California, San Diego School of Medicine 9500 Gilman Dr., MC 0732 La Jolla, CA 92093 USA	Marc A. Riedl, MD, MS

Source: Appendix 16.1.4, CSR 3001, May 2, 2016

6.1.7 Surveillance/Monitoring

The safety and tolerability of CSL830 for the prophylactic treatment of HAE was assessed based on the following:

- Overall AEs
- SAEs
- Injection site reactions
- Systemic AEs
- AEs that began within 24 hours after investigational product administration
- Suspected adverse drug reactions (ADRs), including related AEs (ARs), AEs that started within 24 hours after the administration of investigational product, and AEs with no causality assessment (ARs)
- AEs of special interest
    - TEEs
    - Anaphylaxis events
    - Sepsis and / or bacteremia events
    - Coagulation profile
    - Thrombotic screen
    - Viral serology
    - Anti-C1-INH antibodies
    - Clinical score of risk assessment for deep vein thrombosis (DVT) and pulmonary embolism

Electronic diaries were used to capture "real time" subject recorded data, including the daily recording of HAE symptoms (e.g., anatomic location and severity), the use of rescue medication, details of the administration of investigational product, and the occurrence of injection site reactions. Subjects rated the severity of their HAE symptoms using the following definitions:

- Mild: A symptom that does not generally interfere with usual activities of daily living
- Moderate: A symptom that interferes with usual activities of daily living
- Severe: A symptom that interrupts usual activities of daily living

HAE attacks were reported by investigators. At each study visit, the investigator was to review the subject electronic diary, relevant interim medical history, including hospital / medical records, and any other information provided by the subject. Using medical judgment, and in consideration of the HAE attack reporting guidelines, the investigator reported the start / stop dates, all involved anatomic locations, and the maximum symptom severity of HAE attacks on the HAE Attacks electronic case report form. Each HAE attack was to be preceded by and followed by an attack-free day.

6.1.8 Endpoints and Criteria for Study Success

1. Primary endpoint: time-normalized number of HAE attacks.
2. Secondary endpoints

a. Percentage of "responders" defined as a ≥ 50% relative reduction in the time-normalized number of HAE attacks during infusion of CSL830 compared with placebo (within individual subjects). "Success" was defined as a responder rate of > 33% (lower 95% confidence interval).
b. Time-normalized number of uses of rescue medication.
c. Adverse events (AEs) that began within 24 hours after the administration of investigational product.
d. AEs, serious adverse events (SAEs), systemic AEs, suspected adverse drug reactions, thromboembolic events (TEEs), anaphylaxis events, sepsis and / or bacteremia events, increased risk scores for deep vein thrombosis and pulmonary embolism, inhibitory anti C1-INH antibodies, or clinically significant abnormalities in laboratory assessments.
e. Injection-site AEs: pain, swelling, bruising, itching, or erythema at the investigational product injection site.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- Screening Population: All subjects who provided informed consent / assent and had a Screening Visit.
- ITT Population: All subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.
- Safety Population: All subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product. Subjects in the Safety Population were analyzed "as treated" (i.e., subjects were classified according to the treatment actually received, regardless of the treatment assigned by randomization).
- Per-protocol (PP) Population: All subjects in the ITT Population, excluding subjects who had a significant protocol violation. Protocol violations that led to exclusion from the PP Population were determined before unblinding.

Primary endpoint

A total of 72 subjects was calculated to provide approximately 99% power to detect a difference between 60 IU/kg CSL830 and low-volume placebo and between 40 IU/kg CSL830 and high-volume placebo at an alpha of 5%, and more than 80% power to detect an assumed 30% difference in the primary efficacy endpoint between the two CSL830 doses at an alpha of 5%.

Secondary endpoints

Assuming a response rate of 0.50 for both active treatments, a sample size of 72 subjects (both groups combined) yielded 80% power for the lower bound of a 95% confidence interval to exceed 33% for the secondary percentage of responders endpoint.
Continuous variables were summarized using mean, standard deviation (SD), median, range, the 25th and 75th percentiles, and counts of missing and non-missing values. Categorical values were summarized using counts and percentages.
The primary endpoint analysis was analyzed following a hierarchical testing procedure: 60 IU/kg CSL830 tested against 0.08 mL/kg placebo, followed by 40 IU/kg CSL830

tested against 0.12 mL/kg placebo and subsequently 60 IU/kg CSL830 tested against 40 IU/kg CSL830) by using mixed effect models. Least squares means for the treatment effect and the treatment differences were estimated with 2-sided 95% confidence intervals (the corresponding p-value was presented).

Safety analysis
Analyses were performed on all subjects who received investigational product. AEs, local injection AEs, and systemic AEs were also described by intensity, relationship to investigational product, outcome, and seriousness by treatment. The duration of all local injection AEs were also summarized by treatment. The percentage of subjects with AEs beginning during or within 24 hours of administration was summarized by treatment. Risk scores for deep vein thrombosis and pulmonary embolism, TEE, potential cases of anaphylaxis and suspected adverse drug reactions were also assessed.

6.1.10 Study Population and Disposition

Of the 90 randomized subjects (N=90), 45 were randomized to a 40 IU/kg CSL830 treatment sequence, and 45 were randomized to a 60 IU/kg CSL830 treatment sequence.

Eleven subjects discontinued from the study and 79 subjects completed the study. Reasons for discontinuation included AEs (3 subjects), lack of efficacy (2 subjects), withdrawal by subject (3 subjects), non-compliance (2 subjects), and physician decision (1 subject).

6.1.10.1 Populations Enrolled/Analyzed

The percentage of subjects with HAE type I and type II were similar in the 40 IU/kg CSL830 and 60 IU/kg CSL830 treatment sequences and consistent with the general HAE population. The mean (SD) reported historic number of HAE attacks per subject in the 3 months before Screening was 10.8 (6.73) attacks in the 40 IU/kg CSL830 treatment sequences and 8.8 (6.40) attacks in the 60 IU/kg CSL830 treatment sequences. The percentages of subjects who received HAE prophylaxis (i.e., intravenous C1-INH and/or oral androgens) in the 3 months before Screening was higher in the 60 IU/kg CSL830 treatment sequences (46.7%) than in the 40 IU/kg CSL830 treatment sequences (35.6%).

6.1.10.1.1 Demographics

Table 3 shows that the study population was predominantly White and middle-aged (median age: 40 years) in which females represented the majority (67%).

Table 3: Demographics of the Study 3001 Population

Parameter		Study 3001 N (%)
Sample size		90
Age (years)		
	Median	40
	Min; Max	12; 72
Sex		
	Male [N (%)]	30 (33.3)
	Female [N (%)]	60 (67.7)
Race		
	White [N (%)]	84 (93.3)
	Black/African American [N (%)]	4 (4.4)
	Asian [N (%)]	1 (1.1)
	Other [N (%)]	1 (1.1)

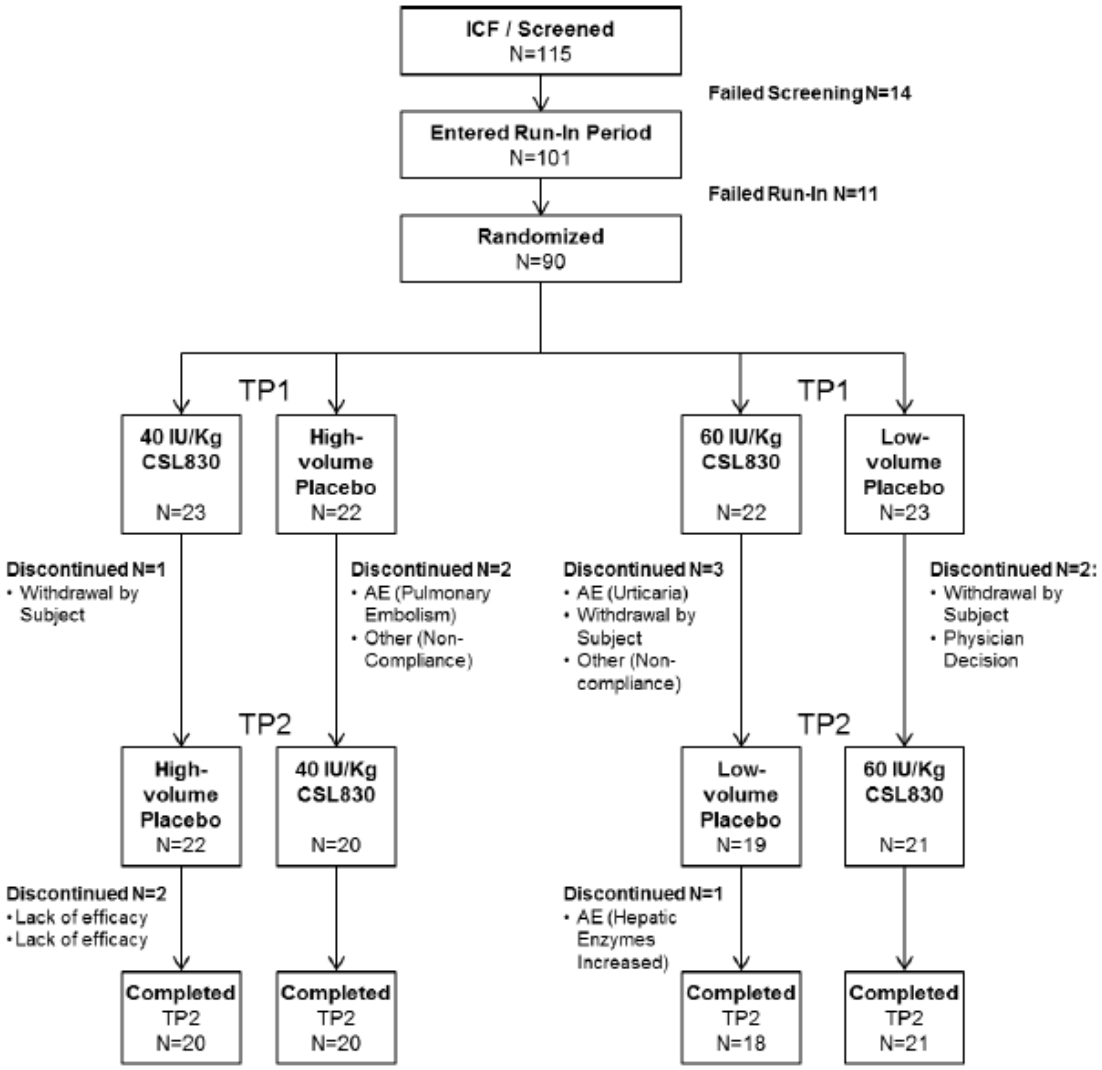
Adapted from Table 11-1, page 90 of 3005, 3001 CSR 3001, 2 May 2016

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Median treatment compliance was 100% for all treatments. For subjects in the 40 IU/kg CSL830 treatment sequences, mean (SD) duration of exposure to active treatment and placebo was 16.3 (1.56) weeks and 15.5 (3.33) weeks, respectively. For subjects in the 60 IU/kg CSL830 treatment sequences, mean duration of exposure to active treatment and placebo was 16.0 (2.11) weeks and 15.1 (3.27) weeks, respectively.

6.1.10.1.3 Subject Disposition
Figure 2 depicts subject disposition. Subjects (N=115) provided informed consent / assent and were screened. A total of 14/115 failed Screening and were not eligible for entry into the Run-in Period. Of the 101 subjects who entered the Run-in Period, 11 subjects failed Run-in and were not eligible for randomization into the study. Thus, a total of 90 subjects completed the Run-in Period and were randomized to 1 of the 4 treatment sequences (ITT Population) (Figure 10-1).

Overall, 45 subjects were randomized to a 40 IU/kg CSL830 treatment sequence and 45 subjects were randomized to a 60 IU/kg CSL830 treatment sequence. All 90 subjects in the ITT Population were treated (Safety Population) and were included in the QoL, PK, and PD Populations.

One subject in the ITT Population was excluded from the PP Population. A total of 11/90 subjects discontinued from the study and 79 subjects completed the study. Eight subjects discontinued in TP1 and did not cross over to TP2: 4 subjects during treatment with CSL830 and 4 subjects during treatment with placebo. Three subjects discontinued in TP2 (all during treatment with placebo).



AE = Adverse event; ICF = Informed consent form; N = Number of subjects; TP1 = Treatment Period 1; TP2 = Treatment Period 2;

Figure 3: Subject disposition
Source: Table 14.1.1, page 195 of 3005, CSR, May 2, 2016

6.1.11 Efficacy Analyses

6.1.11.1 Analysis of Primary Endpoint

Twice per week SC doses of 40 IU/kg CSL830 and 60 IU/kg CSL830 significantly reduced time-normalized number of HAE attacks relative to placebo.

Reviewer Comment

Changes in hormonal contraceptive regimens have the potential to influence the frequency of HAE attacks. Thus, the ITT population (N=90) was used for the primary analysis, supported by the Per Protocol population (N=89), where one subject was excluded because she stopped her dose of oral contraceptive use.

Table 4 shows a significant reduction (p<0.001) in HAE attacks (number/day) using CSL830 compared with placebo. Mean number of HAE attacks/day was lower in the 40 and 60 IU/kg dose cohorts compared with their respective placebo cohorts (p=0.11).

Corresponding values expressed in terms of HAE attacks (number/month) are as follows:

- **40 IU/kg treatment cohort (N=45)**: CSL830 reduced the mean rate of attacks from 0.12 to 0.04 attacks/day (equivalent to a reduction from 3.61 to 1.19 attacks/month based on 30 days/month and computed by this reviewer) compared with high-volume placebo ($p < 0.001$). Overall, 26 CSL830 subjects (57.7%) experienced 145 attacks *vs.* 40 placebo subjects (88.9%) who experienced 503 attacks.
- **60 IU/kg treatment cohort (N=45)**: CSL830 reduced the mean rate of attacks from 0.13 to 0.02 attacks/day (equivalent to a reduction from 4.03 to 0.52 attacks/month) compared with placebo ($p < 0.001$). Overall, 25 CSL830 subjects (55.6%) experienced 71 attacks *vs.* 42 placebo subjects (93.3%) who experienced 472 attacks.

Table 4: Time-Normalized Number of HAE Attacks (Number/Day) by Treatment

	40 IU/kg High-volume Placebo N=45		**60 IU/kg Low-volume Placebo N=45**	
	CSL830	**Placebo**	**CSL830**	**Placebo**
No. of subjects	43	44	43	42
Mean (SD)	0.04 (0.08)	0.12 (0.07)	0.02 (0.03)	0.13 (0.08)
Min, Max	0.0, 0.4	0.0, 0.3	0.0, 0.1	0.0, 0.4
Median	0.01	0.13	0.01	0.12
LS Mean (SE)[a]	0.04 (0.01)	0.12 (0.01)	0.02 (0.01)	0.13 (0.01)
95% CI for LS Mean[a]	(0.02, 0.06)	(0.10, 0.14)	(0.00, 0.03)	(0.12, 0.15)
Treatment difference (within subjects)	40 IU/kg – High-volume placebo		60 IU/kg – Low-volume placebo	
Least Square Mean (95% CI)	-0.08 (-0.11, -0.05)		-0.12 (-0.14, -0.09)	
p-value	<0.001		<0.001	
Treatment difference (between subjects)	60 IU/kg – 40 IU/kg			
Least Square Mean (95% CI)	-0.02 (-0.05, 0.01)			
p-value	0.11			

[a] From a mixed model

Adapted from Table 14.2.1.1, CSR 3001, page 453 of 3005, May 2, 2016

Reviewer Comment

The primary efficacy analysis showed that although both doses of CSL830 confer a clinically important treatment effect when compared with placebo, the effect size of the 60 IU/kg dose was greater than the 40 IU/kg dose.

6.1.11.2 Analyses of Secondary Endpoints

CSL830 consistently reduced the following endpoints when compared with placebo.

- **Number of subjects with HAE attacks** (CSL830 vs. placebo)
  - 40 IU/kg cohort: 26/45 (57.7%) *vs.* 40/45 (88.9%)

- 60 IU/kg cohort: 25/45 (55.6%) *vs.* 42/45 (93.3%)

- **Number of HAE attacks** (CSL830 vs. placebo)
  - 40 IU/kg cohort: 145 attacks *vs.* 503 attacks
  - 60 IU/kg cohort: 71 attacks *vs.* 472 attacks
- **Number of Laryngeal HAE attacks** (CSL830 vs. placebo)
  - 40 IU/kg cohort: 5/45 *vs.* 16/45 subjects
  - 60 IU/kg cohort: 0/45 *vs.* 9/45 subjects
- **Rate of rescue use** (placebo vs. CSL830)
  - 40 IU/kg cohort: From 5.6 uses to 1.1 uses per month
  - 60 IU/kg cohort: From 3.9 to 0.3 uses per month
- **Number of subjects with a severe HAE attack** (placebo vs. CSL830)
  - 40 IU/kg cohort: From 33/45 (73.3%) subjects to 9/45 (20.0%) subjects
  - 60 IU/kg cohort: From 31/45 (68.9%) subjects to 4/45 (8.9%) subjects

Reviewer Comment

Results of the secondary endpoint analyses are consistent with a clinically meaningful treatment effect , with a greater effect size apparent in the higher dose cohort.

6.1.11.3 Subpopulation Analyses

Responder Analysis

Subgroup analyses of responders were conducted for the primary endpoint in the ITT population. A responder was defined as a subject with a ≥ 50% reduction in the time-normalized number of HAE attacks on CSL830 relative to placebo. The percentage reduction (%) in time-normalized number of HAE attacks per subject was calculated as:

100 x [1 – (the time-normalized number of HAE attacks when treated with CSL830) / (the time-normalized number of HAE attacks when treated with placebo)]

a) Table 5 shows that 68/90 (82.9%) of subjects in the CSL830 treatment cohort experienced a ≥50% reduction in number of HAE attacks compared with placebo.

Table 5: Percent Reduction of ≥50% in Number of HAE Attacks

	40 IU/kg CSL830 N=45 N (%)	**60 IU/kg CSL830 N=45 N (%)**	**≥40 IU/kg CSL830 N=90 N (%)**
Number of subjects	42	40	82
Responder[s]	32 (76.2)	36 (90.0)	68 (82.9)
95% Wilson CI	(61.5, 86.5)	(76.9, 96.0)	(73.4, 89.5)
Difference in % of Responders			
60 IU/kg – 40 IU/kg		13.8%	-
95% Wilson CI		(-2.8, 29.7)	-

a Percentages are based on the number of subjects (N) included in the analysis. Subjects whose time-normalized number of HAE attacks could not be calculated in 1 or both treatment periods were excluded from the analysis. Subjects with 0 attacks on high-volume placebo (N=4) were classified as non-responders because a percentage reduction could not be calculated for these subjects.
b The difference between CSL830 doses is assessed using Wilson asymptotic confidence limits for the difference in percentages.
Adapted from Table 14.2.2.1, CSR 3001, page 556 of 3005, May 2, 2016

b) Table 6 shows that 74.4% and 50.0% of subjects experienced a ≥70% and ≥90% reduction in HAE attacks, respectively.

Table 6: Percent Reduction of ≥70% and ≥90% in Number of HAE Attacks

	40 IU/kg CSL830 N=45 N (%)	60 IU/kg CSL830 N=45 N (%)	≥40 IU/kg CSL830 N=90 N (%)
Number of subjects	42	40	82
Reduction of ≥70% Responder, % (N)[a]	66.7 (28)	82.5 (33)	74.4 (61)
95% Wilson CI	(51.6, 79.0)	(68.1, 91.3)	(64.0, 82.6)
Reduction of ≥90% Responder, % (N)[a]	42.9 (18)	57.5 (23)	50.0 (41)
95% Wilson CI	(29.1, 57.8)	42.2, 71.5)	(39.4, 60.6)
Difference in % of Responders[b]			
60 IU/kg – 40 IU/kg		14.6%	-
95% Wilson CI		(-6.7, 34.3)	-

a Percentages are based on the number of subjects (N) included in the analysis. Subjects whose time-normalized number of HAE attacks could not be calculated in 1 or both treatment periods were excluded from the analysis. Subjects with 0 attacks on high-volume placebo (N=4) were classified as non-responders because a percentage reduction could not be calculated for these subjects.
b The difference between CSL830 doses is assessed using Wilson asymptotic confidence limits for the difference in percentages.
Adapted from Table 14.2.2.7, CSR 3001, page 592 of 3005, May 2, 2016

Subgroup results for time-normalized number of HAE attacks were similar to the overall analysis results (i.e., rate of attack was lower on CSL830 than placebo, and 60 IU/kg exerted a stronger treatment effect than 40 IU/kg CSL830). Subgroup results for the percentage of responders were similar to the overall analysis results (i.e., the proportion of responders was higher using 60 IU/kg than 40 IU/kg CSL830. Meaningful assessment by race was precluded because the majority of subjects were White (84/90, 93.3%). No subjects were included in the oral prophylaxis and oral antifibrinolytics use subgroups.

Rescue Medication Analysis

The selection of the type of rescue medication used was determined by the investigator and not mandated per protocol. However, in countries where Berinert is licensed, Berinert was offered and provided as needed to subjects who elected to use C1-INH as rescue medication for the acute treatment of HAE attacks. The use of IV Berinert as a rescue medication for the acute treatment of HAE attacks was permitted at any time during the Run-in Period, TP1, and TP2. Subjects were also permitted to use other plasma-derived or recombinant C1-INH, icatibant, ecallantide, and fresh frozen plasma as rescue medications.

Table 7 shows that both doses of CSL830 reduced the number of uses of rescue medication relative to placebo, with 60 IU/kg having a greater treatment effect than 40 IU/kg.

Table 7: Time-normalized Number of Uses of Rescue Medication (Number/Day)

	40 IU/kg High-volume Placebo Treatment (N=45)		60 IU/kg Low-volume Placebo Treatment (N=45)	
	CSL830	Placebo	CSL830	Placebo
Number of subjects	43	44	43	42
Mean (SD)	0.04 (0.08)	0.18 (0.36)	0.01 (0.02)	0.13 (0.10)
Median	0.01	0.13	0.00	0.10
Treatment difference (within subjects)				
LS Mean (95% CI)[a]	-0.15 (-0.26, -0.03)		-0.12 (-0.15, -0.09)	
Nominal p-value[a,b]	0.02		<0.001	
Treatment difference (between-subjects0				
LS Mean (95% CI)[a]	-0.03 (-0.07, 0.02)			
Nominal p-value[a,b]	0.31			

a From a mixed model
b Exploratory analysis
Adapted from Table 14.2.3.1, CSR, page 673 of 3005, May 2, 2016

6.1.11.4 Dropouts and/or Discontinuations

- AEs
  - 60 IU/kg, Treatment Period 1: urticaria (b) (6)
  - 60 IU/kg, Treatment Period 1: elevated liver enzymes (b) (6)
  - Placebo, Treatment Period 1: pulmonary embolism (Subject (b) (6)
- Lack of efficacy
  - 40 IU/kg ((b) (6))
- Withdrawal by subject
  - 40 IU/kg: relocated (b) (6))
  - 60 IU/kg: found a new job ((b) (6))
  - Placebo: length of travel to site ((b) (6))
- Non-compliance
  - Placebo: refused to remain in study ((b) (6))
  - Placebo: no reason listed (b) (6))
- Physician decision
  - Placebo: subject non-compliance (b) (6)

6.1.11.5 Exploratory and Post Hoc Analyses

Table 8 shows that across multiple exploratory endpoints, treatment with CSL830 consistently showed benefit relative to treatment with placebo.

- Duration of HAE attacks
  The duration of HAE attacks per subject was generally shorter on CSL830 relative to placebo.

Table 8: Duration of HAE Attacks as Reported by the Investigator (ITT Population)

	40 IU/kg N=45 (%)	60 IU/kg N=45 (%)	≥40 IU/kg N=90 (%)	Placebo High Volume N=45 (%)	Placebo Low Volume N=45 (%)	Placebo Combined N=90 (%)
Duration of attacks per Subject (Days)						
Without attacks	17 (38)	18 (40)	35 (39)	4 (9)	0	4 (4)
No. of subjects	26 (58)	25 (56)	51 (57)	40 (89)	42 (93)	82 (91)
No. missing	2	2	4	1	3	4
Mean	1.80	1.58	1.69	2.08	1.64	1.85
Median	1.57	1.00	1.29	1.71	1.45	1.58
Duration of attacks per attack (Days)						
No. of attacks	145	71	216	503	472	975
No. missing	0	0	0	0	0	0
Mean	1.67	1.61	1.65	1.92	1.61	1.77
Median	1.00	1.00	1.00	2.00	1.00	1.00

Adapted from Listing 16.2.6.3, CSR 3001 Appendix, page 361 of 1041, March 18, 2016

Reviewer Comment

Use of rescue medication is a potential confounder for analysis of HAE attack duration.

Severity of HAE attacks

Investigators graded the intensity of each HAE attack as Mild = 1, Moderate = 2, or Severe = 3 in a blinded manner based on the intensity of the most severe symptom. The average severity of HAE attacks was lower on CSL830 relative to placebo.

Table 9: Severity of HAE Attacks by Treatment (ITT Population)

	40 IU/kg N=45 (%)	60 IU/kg N=45 (%)	≥40 IU/kg N=90 (%)	Placebo High Volume N=45 (%)	Placebo Low Volume N=45 (%)	Placebo Combined N=90 (%)
Mild	5 (11.1)	8 (17.8)	13 (14.4)	1 (2.2)	1 (2.2)	2 (2.2)
Moderate	12 (26.7)	13 (28.9)	25 (27.8)	6 (13.3)	10 (22.2)	16 (17.8)
Severe	9 (20.0	4 (8.9)	13 (14.4)	33 (73.3)	31 (68.9)	64 (71.1)

Adapted from Table 14.2.6.1, CSR, page 681 of 3005, May 2, 2016

Table 9 shows that of the 45 subjects randomized to a 40 IU/kg CSL830 treatment sequence, 9 (20.0%) subjects had at least 1 severe HAE attack compared with 33 (73.3%) subjects on high-volume placebo. Conversely, 17 (37.8%) subjects on 40 IU/kg CSL830 had only mild or moderate HAE attacks compared with 7 (15.6%) subjects on high-volume placebo. Of the 45 subjects randomized to a 60 IU/kg CSL830 treatment sequence, 4 (8.9%) subjects had at least 1 severe HAE attack compared with 31 (68.9%) subjects on low-volume placebo. Conversely, 21 (46.7%) subjects on 60 IU/kg CSL830 had only mild or moderate HAE attacks compared with 11 (24.4%) subjects on low-volume placebo.

6.1.12 Safety Analyses

6.1.12.1 Methods

All AEs, SAEs, local injection AEs, TEEs, anaphylaxis events, sepsis and / or bacteremia events, AEs leading to study discontinuation, and non-treatment emergent AEs were summarized using the Safety Population. Subjects who experienced 1 or more AEs in a particular system organ class (SOC) were counted only once in the total number of subjects who experienced AEs in that SOC. Similarly, a subject who experienced more than 1 occurrence of the same AE was counted only once in the total number of subjects who experienced that AE.

6.1.12.2 Overview of Adverse Reactions

In terms of **subjects**: The same number of CSL830 and placebo **subjects** (N=48/86 or 56%) experienced systemic AEs, whereas more CSL830 (N=27/86 or 31%) than placebo (N=21/86 or 24%) **subjects** experienced local injection site ARs.

In terms of **events**:
The number of local injection site **events** was higher in CSL830 than placebo subjects (n=377 *vs.* 212) whereas the number of systemic **events** was lower in CSL830 subjects than placebo subjects (n=122 *vs.*132). Overall, CSL830 subjects experienced more local injection site events and systemic events.

Anaphylaxis

- No cases of anaphylaxis were identified. No potential hypersensitivity events were classified as SAEs. The majority of potential hypersensitivity events were mild, were reported as not related, and had an outcome of recovered / resolved The most commonly reported hypersensitivity type events identified were Rash (3 subjects, 3 events), Urticaria (2 subjects, 9 events), and Conjunctivitis (2 subjects, 2 events). No other reports of hypersensitivity were identified in more than 1 subject.

Thromboembolic Events

- No cases of TEE were reported in HAEGARDA cohorts.

Local ARs

- Local ARs in the CSL830 cohorts (n=377) occurred more frequently in CSL830 (N=27/86 or 31%) than placebo subjects (21/86 or 24%)
    - The majority of local ARs were mild and resolved within 1 day (247/274 events in 40 IU/kg subjects and 64/103 events in 60 IU/kg subjects)
    - No severe ARs occurred in the CSL830 cohort but a single severe event of injection site pain occurred in a placebo subject. All injection site ARs recovered / resolved. The most common local ARs were injection site pain and injection site erythema

Systemic AEs

- Systemic AEs in the CSL830 cohorts (n=122) occurred at the same rate in CSL830 (N=48/86 or 56%) and placebo (48/56 or 56%) subjects less frequently than local ARs (n=377).

- CSL830 dose-proportion was evident as more systemic AEs were experienced by a smaller percentage of 40 IU/kg subjects (n=68; N=53.5% of subjects) than 60 IU/kg subjects IU/kg (n=54; N=58.1%)
- Most systemic AEs were of mild intensity

6.1.12.3 Deaths

No subject died during the study.

6.1.12.4 Nonfatal SAEs

Table 10 shows that no SAEs were reported during treatment with 60 IU/kg CSL830. However, two placebo subjects and one 40 IU/kg CSL830 subject experienced nonfatal SAEs.

- Subject (b) (6) was a 66 year old female who experienced a severe intensity, product-unrelated urosepsis SAE on TP2, Day 4 necessitating hospitalization after receiving 40 IU/kg in TP1
- Subject (b) (6) was 50 year old female who experienced a severe intensity pulmonary embolus SAE after receiving High volume placebo in TP1
- Subject (b) (6) was a 19 year old female who experienced two SAEs, an abdominal-genital HAE attack and syncope, after receiving placebo low-volume in TP2.

All SAEs had an outcome of recovered / resolved.

Table 10: Summary of SAEs by Subject

	40 IU/kg CSL830 N=43 N (%)	**60 IU/kg CSL830 N=43 N (%)**	**≥40 IU/kg CSL830 N=86 N (%)**	**Combined Placebo (N=86) N (%)**
SAEs	1 (2.3)	0	1 (1.2)	2 (2.3)
Local SAEs	0	0	0	0
Systemic SAEs	1 (2.3)	0	1 (1.2)	2 (2.3)
SAEs within 24 h after administration	1 (2.3)	0	1 (1.2)	0
SAEs leading to study discontinuation	0	0	0	1 (1.2)
Causality				
Related	0	0	0	1 (1.2)
Not related	1 (2.3)	0	1 (1.2)	1 (1.2)
Severity				
Mild	0	0	0	0
Moderate	0	0	0	1 (1.2)
Severe	1 (2.3)	0	1 (1.2)	1 (1.2)
Outcome				
Recovered / resolved	1 (2.3)	0	1 (1.2)	2 (2.3)
Not recovered / not resolved	0	0	0	0

Adapted from Table 14.3.1.1.3.1, Table 14.3.1.2.1.1, Table 14.3.1.1.1 and Table14.3.1.3.1.1, CSR 3001, page 861 of 3005

NARRATIVES

Subject (b) (6) (**Urticaria**) was a 47-year-old white, non-Hispanic female who experienced a related urticaria adverse event while on CSL830 and prematurely dropped out of the study. Prior to her participation in the study, IV C1-INH (Berinert) was administered for acute treatment of HAE attacks. No medical / surgical history for the preceding 6 month before screening was reported. Relevant medical history was remarkable for a reported but probably untested childhood allergy to penicillin. In adulthood, there was a history of an allergy to local anesthetics used in a dental procedure that was associated with facial, tongue, and upper airway edema. Skin prick testing, performed in 1999 was positive to local anesthetics. The subject was not reported to have a history of asthma, allergic rhinitis, eczema, or urticaria. There were no recent changes in laundry soap, bathing soap, sunscreen, or lotions.

On 18 August 2014, she was randomized to receive 60 IU/kg CSL830 subcutaneously twice weekly over a 4 week period. Following randomization, the subject experienced no additional HAE attacks through 24 September 2014. With the fifth administration of 60 IU/kg CSL830, the first urticarial reaction was reported (mild severity). The following 3 administrations were followed by urticarial reactions at additional locations (arms, legs, abdomen) with increasing intensity (severe) and itching. These symptoms developed the day after each 60 IU/kg CSL830 injection and lasted approximately 1 to less than 3 days. These were isolated symptoms without accompanying gastrointestinal distress or respiratory distress / wheezing. The subject did not have any injection site reaction.

The investigator reported that these AEs were probably related to 60 IU/kg CSL830, and the subject's participation was discontinued. The investigator's assessment was based on the facts that symptoms occurred after 60 IU/kg CSL830 administration and increased in severity with subsequent dosing. Following the discontinuation of 60 IU/kg CSL830 (last administered on 11 September 2014), the subject experienced 2 additional episodes of Urticaria (on 17 September 2014 and on 22 September 2014). The additional AEs were reported as related and had an outcome of resolved. The End of Study Visit was on 29 September 2014 (TP1 / Day 42). The subject also received C1-INH products to treat HAE attacks at a later date with no urticaria.

Reviewer Comment

I concur with the investigator's assessment of causality.

Subject (b) (6) (**Urosepsis**) was a 66-year-old white, non-Hispanic female with a BMI of 37 kg/m who experienced an unrelated urosepsis SAE a few days after exposure to low-dose CSL830. Relevant medical history included Type 1 HAE, chronic urinary tract infection, insomnia, Type 2 diabetes mellitus, hypertension, hypercholesterolemia, hypothyroidism, gastroesophageal reflux disease, irritable bowel syndrome, depression, sleep apnea, restless leg syndrome, intermittent shortness of breath, lupus, diastolic dysfunction, congestive heart failure, antiphospholipid syndrome, chronic urinary tract infections, edema, and numerous allergies / sensitivities to medications.

Prior to her participation in the study, she used danazol (100 mg once daily) in addition to Berinert (2000 IU twice weekly) for IV HAE prophylaxis. Kalbitor (30 mg as needed) was administered SC as needed to treat HAE attacks. Numerous medications were taken to treat co-morbid conditions including insulin lispro, insulin glargine, glipizide, omeprazole, levothyroxine, sertraline hydrochloride, pramipexole, ramelteon, furosemide, atenolol, carisoprodol, vicodin, loperamide hydrochloride, ondansetron, hydroxychloroquine, lisinopril, pramipexole, canagliflozin, ropinirole hydrochloride, temazepam, gabapentin, and metolazone.

She was randomized to high-volume placebo followed by 40 IU/kg CSL830 on 26 March 2014 (TP1, Day 1). On 27 May 2014 she began TP2. Three days later she was admitted to the hospital (TP2, Day 4) with a diagnosis of Urosepsis. She received IV antibiotics and was discharged on 1 June 2014.

The investigator considered her Urosepsis as serious (inpatient hospitalization), severe, and unrelated to CSL830. The investigator referenced her history of lupus and bacterial infection, proposing that concomitant medication taken by the subject for her type 2 diabetes (Invokana) may have caused / contributed to this condition as it is known to increase the risk of urinary tract infections or cause urinary tract infections. The subject completed the study on 15 September 2014 (End of Study Visit, Day 173).

Reviewer Comment
I concur with the investigator's assessment.

6.1.12.5 Adverse Reactions of Special Interest (AESI)

Table 11 presents AESIs and shows 1 related pulmonary embolism SAE was reported in a female placebo subject aged 50 years. All other AESIs were mild or moderate in intensity.

Table 11: Adverse Reactions of Special Interest

Subject No.	Age (yr)	Sex	AE	Intensity	Dose (IU/kg)	Treatment Period
(b) (6)	60	Female	Cough	Mild	60	2
	23	Female	Back skin rash	Moderate	60	2
	47	Female	Urticaria	Mild	60	1
	41	Female	Conjunctivitis	Mild	40	1
	43	Female	Facial rash with pruritus	Mild	40	2
	61	Male	Upper extremity urticaria	Mild	40	2
	26	Female	Injection site urticaria	Mild	40	2
	33	Male	Eosinophilia	Mild	placebo*	1
	14	Male	Excessive sneezing		placebo*	2
	43	Female	Excessive sneezing, asthma exacerbation	Moderate	placebo*	2
	72	Male	Blisters on toes and feet		placebo*	2
	32	Female	Rash, dyspnea	Mild	placebo**	2
	47	Female	Conjunctivitis	Mild	placebo**	2
	50	Female	Related pulmonary embolus	Serious	placebo**	1

(b) (6)	32	Female	Back rash, dyspnea	Mild	placebo**	2
	38	Female	Seasonal allergy	Mild	placebo**	2

* = low-volume placebo
** = high-volume placebo
Adapted from Listing 16.2.759, CSR, page 429 of 449, March 18, 2016

6.1.12.6 Clinical Test Results

No inhibitory antibodies to C1-INH, cases of anaphylaxis, or seroconversions for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus were identified during the study. Although non-inhibitory antibodies to C1-INH were detected during the study, no association between outcomes and the detection of these antibodies was apparent.

6.1.12.7 Dropouts and/or Discontinuations

See 6.1.11.4.

6.1.13 Study Summary and Conclusions

Of the 90 subjects randomized in this double-blind, placebo-controlled, cross-over study, 86 subjects received at least 1 dose of CSL830 and 86 subjects received at least 1 dose of placebo. A total of 5081 injections of CSL830 and placebo were administered over a range of 3 to 19 weeks (median of 16.6 weeks for CSL830; median of 16.3 weeks for placebo). Results demonstrate the efficacy of SC CSL830 for routine prophylaxis to prevent HAE attacks in adolescent and adult patients. A dose-response was observed across the primary, secondary, and exploratory endpoints, with 60 IU/kg consistently demonstrating better efficacy than 40 IU/kg.

6.2 TRIAL #2: CSL830-3002

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.

6.2.1 Objectives (Primary, Secondary, etc)

Primary Interim Objective
To assess the safety of subcutaneously (SC) administered CSL830 in the long-term (i.e., routine) prophylactic treatment of hereditary angioedema (HAE).

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

Exploratory Interim Objective
To characterize the efficacy of SC administered CSL830 in the long-term (i.e., routine) prophylactic treatment of HAE.

6.2.2 Design Overview

Multicenter, randomized, open-label, parallel-arm, phase 3b study comprising 4 distinct parts (Screening Period, Treatment Period 1 [TP1], Treatment Period 2 [TP2], and Follow-up Period) as depicted in Figure 2.

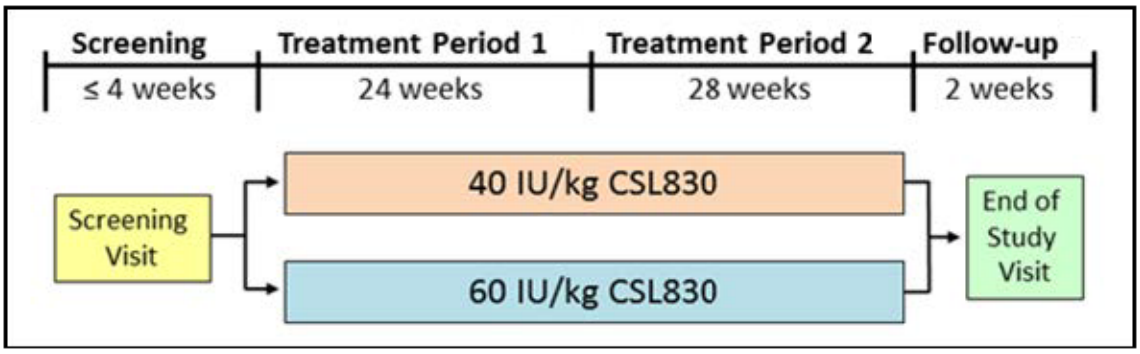


Figure 4: Study schematic.
Source: Figure 9-1, CSR 3002, page 21 of 1155, June 1, 2016

The study duration for an individual subject participating in TP1 and TP2 was up to 58 weeks (including assessment of eligibility and follow-up). The study duration for an individual subject participating in TP1, TP2, and the Extension Period was up to 146 weeks (including assessment of eligibility and follow-up).

6.2.3 Population

As of 17 May 2016, 126 subjects had been randomized, 63 each in the 40 IU/kg CSL830 and 60 IU/kg CSL830 treatment arms.

Inclusion Criteria

1. Male or female, ≥ 6 years of age.
2. Clinical diagnosis of HAE type I or II, as determined by clinical history and C1-esterase inhibitor (C1-INH) functional activity < 50%, concurrent with C4 antigen concentrations below normal limits.
3. Experienced at least 4 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period before treatment with CSL830 or IV C1-INH prophylaxis (for "*CSL830-Naïve*" Subjects using IV C1-INH prophylaxis).
4. Subjects who used oral medication for prophylaxis against HAE attacks (i.e., androgens, tranexamic acid, progestins): use of a *stable* regimen of oral prophylactic medication during the 3 months before their first study visit and willingness to continue the stable regimen for at least 25 weeks.

Three cohorts were enrolled depending on their prior exposure to the product.

- "*CSL830-Naïve*": Subjects who did not participate in the preceding Study 3001 or subjects who participated in Study 3001 but did not receive investigational product as a part of Study 3001

- "*CSL830-Interrupted*": Subjects who completed participation in Study 3001, but who delayed entry into the current study i.e., > 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 TP1]
- "*CSL830-Continuation*": Subjects who completed participation in Study 3001 and who continued directly on to participate in the current study [i.e., ≤ 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 TP1].

Prior Prophylaxis Therapy
As depicted in Table 12, only 21 / 126 (16.7%) subjects in the ITT Population received prior prophylaxis therapy related to HAE in the 3 months before Screening. The percent of "CSL830-Naïve" Subjects who used any prior HAE prophylaxis was similar in the 40 IU/kg dosing cohort (7 [22.6%] subjects) and the 60 IU/kg dosing cohort (8 [25.8%] subjects). In the 40 IU/kg treatment arm, 6 (19.4%) subjects used IV C1-INH and 1 (3.2%) subject used Danazol as prior HAE prophylaxis. In the 60 IU/kg treatment arm, 5 (16.1%) subjects used IV C1-INH and 3 (9.7%) subjects used Danazol as prior HAE prophylaxis.

Table 12: Prior Prophylaxis Therapy Related to HAE (ITT Population)

Cohort	40 IU/kg CSL830	60 IU/kg CSL830	≥40 IU/kg CSL830
All subjects	N=63	N=63	N=126
Prior HAE therapy in previous 3 months (N [%])	10 (15.9)	11 (17.5)	21 (16.7)
CSL830 continuation subjects	N=6	N=6	N=12
Prior HAE therapy in previous 3 months (N [%])	0	0	0
CSL830 interrupted subjects	N=26	N=26	N=52
Prior HAE therapy in previous 3 months (N [%])	3 (11.5)	3 (11.5)	6 (11.5)
CSL830 Naïve subjects	N=31	N=31	N=62
Prior HAE therapy in previous 3 months (N [%])	7 (22.6)	8 (25.8)	15 (24.2)

Adapted from Table 14.1.3.2.1 and Table 14.1.3.2.2, page 277 of 1155, interim CSR 3002, April 15, 2016

Reviewer Comment
Since only a small number of subjects received HAE therapy prior to enrollment in Study 3002, treatment bias due to prior HAE therapy (carry-over effect) is unlikely.

6.2.4 Study Treatments or Agents Mandated by the Protocol

During both treatment periods, subjects administered their randomized dose of CSL830 (40 IU/kg or 60 IU/kg) via a single SC injection, twice per week. The randomized dose of CSL830 could be increased in increments of 20 IU/kg up to a maximum dose of 80 IU/kg in subjects meeting the pre-specified criteria for up-titration of their dose.

Frequent attacks were defined as ≥ 12 attacks within a 4-week evaluation period in TP1, and as ≥ 3 HAE attacks within an 8-week evaluation period in TP2 and the Extension Period.

The batch numbers of CSL830 used in the study thus far are: (b) (4)

6.2.5 Directions for Use

Before use, each vial of CSL830 was reconstituted with 3 mL of water for injection for a concentration of 500 IU C1-INH/mL.

6.2.6 Sites and Centers

Site No.	Study Location	Investigator
Active Sites		
0360024	Campbelltown Hospital Therry Rd 2560 Campbelltown, NSW Australia	Dr. Constance Helen Katelaris
1240023	Gordon Sussman Clinical Research Inc. 202 Saint Clair Avenue West Toronto, Ontario M4V 1R2 Canada	Gordon L. Sussman, MD, FRCPC, FACP, FAAAAI
1240025	Hamilton Health Sciences, McMaster University Medical Center Site HSC-3H1G, 1200 Main Street West Hamilton, Ontario L8N 3Z5 Canada	Paul Keith, MD
1240027	Ottawa Allergy Research Corporation 1081 Carling Avenue Suite 800 Ottawa, Ontario K1Y 4G2 Canada	William H. Yang, MD, FRCPC, FAAAAI

Site No.	Study Location	Investigator
1240028	Effective as of November 2015: Centre de recherche appliquée en allergie de Québec 2600 boul Laurier, bureau 880 Québec, Québec G1V 4W2 Canada Prior to November 2015: Centre de recherche appliquée en allergie de Québec 2590 boul Laurier, bureau 225 Tour Belle Cour Québec, Québec G1V 4M6 Canada	Jacques Hébert, MD
2030014	Fakultni nemocnice Plzen Ustav imunologie a alergologie Alej Svobody 80 304 60 Plzen Czech Republic	Jana Hanzlikova, MD
2760059	Universitätsmedizin der Johannes Gutenberg-Universität Mainz Hautklinik / Clinical Research Center (Geb.401/1. Etg. links) Langenbeckstr. 1 55131 Mainz Germany	Dr. med. Petra Staubach
2760082	HZRM Hämophilie Zentrum Rhein Main GmbH, Hessenring 13a, Geb. G. 64546 Mörfelden-Walldorf Germany	Inmaculada Martinez-Saguer, PhD, MD

Site No.	Study Location	Investigator
2760083	Charité-Universitätsmedizin Allergologie und Venerologie Allergie-Centrum-Charité Charitéplatz 1 10117 Berlin Germany	Prof. Dr. med. Markus Magerl
2760088	Universitätsklinikum Frankfurt Klinik für Kinder- und Jugendmedizin Angioödem-Ambulanz Theodor-Stern-Kai 7 60596 Frankfurt Germany Klinisches Studienzentrum Rhein-Main (KSRM) Schleusenweg 22 60528 Frankfurt am Main Germany	Dr. med. Emel Aygören-Pürsün
3480001	Semmelweis Egyetem III. Számú Belgyógyászati Klinika Kútvölgyi ÚT 4. 1125 Budapest Magyarorszag	Prof. Dr. Henriette Farkas
3760008	Chaim Sheba Medical Center Allergy and Clinical Immunology unit 52621 Tel-Hashomer Israel	Dr. Avner Reshef
3760009	Pulmonology, Allergy and Immunology Unit Tel Aviv Sourasky Medical Center 6, Weizman St. Tel Aviv 64239 Israel	Prof. Shmuel Kivity

Site No.	Study Location	Investigator
3800044	Ospedale L. Sacco Unità Operativa di Medicina Generale Via G.B. Grassi 74 20157 Milano Italy	Prof. Marco Cicardi
3800046	Azienda Ospedaliero - Universitaria "Policlinico - Vittorio Emanuele", Presidio G. Rodolico, Dipartimento di Medicina Interna Via S. Sofia 86 95123 Catania Italy	Prof. Sergio Neri
6420028	Spitalul Clinic Municipal Cluj Napoca, Str. Tabacarilor nr. 11 400139, Cluj Napoca Romania	Dr. Ioana Gabriela Crisan
7240018	Hospital Universitario La Paz Paseo de la Castellana 261 28046 Madrid Spain	Dr. Teresa Caballero
7240020	Hospital Universitario Gregorio Marañón Doctor Esquerdo 46 28007 Madrid Spain	Dr. Maria Luisa Baeza
7240022	Hospital Universitario La Fe Bulevar del Sur, s/n 46026 Valencia Spain	Dr. Maria Dolores Hernández

Site No.	Study Location	Investigator
8260027	Administrative address: Barts Health NHS Trust Royal London Hospital 80 Newark Street Whitechapel London, E1 2ES United Kingdom Research address: Barts Health NHS Trust Royal London Hospital Clinical Research Centre 2 Newark Street London, E1 2AT United Kingdom	Dr. Hilary Longhurst BA (HONS) MBBS MRCP (UK) FRCP PHD MRCPATH FRCPATH
8400001	Penn State Hershey Medical Center 500 University Drive, Hershey, PA 17033 USA	Timothy Craig, DO

Site No.	Study Location	Investigator
8400143	Effective as of 20May2015: Institute for Asthma and Allergy, PC 2 Wisconsin Circle, Suite 250 Chevy Chase, MD 20815 USA Prior to 20May2015: Institute for Asthma & Allergy, PC5454 Wisconsin Ave, Suite 700Chevy Chase, MD 20815 USA	H. Henry Li, MD, PhD
8400147	Baker Allergy, Asthma and Dermatology Research Center, LLC 3975 SW Mercantile Drive Suite 165 Lake Oswego, OR, 97035 USA	James W. Baker, MD
8400151	AARA Research Center 10100 N. Central Expressway, Suite 125 Dallas, Texas 75231 USA	William R. Lumry, MD
8400185	Bernstein Clinical Research Center, LLC 8444 Winton Road Cincinnati, OH 45231 USA	Jonathan A. Bernstein, MD

Site No.	Study Location	Investigator
8400219	Vital Prospects Clinical Research Institute, P.C. 7307 S. Yale Ave. Suite 200 Tulsa, OK 74136 USA	Iftikhar Hussain, MD
8400223	Clinical Research Center of Alabama 504 Brookwood Blvd., Suite 250 Birmingham, AL 35209 USA	James Bonner, MD
8400225	Clinical Research Services Unit-Virginia Commonwealth University North Hospital 8th Floor, 1300 E. Marshall Street Richmond, VA 23298 USA	Lawrence Barry Schwartz, MD, PhD
8400228	Effective as of Dec2014: Allergy & Asthma Clinical Research 370 N. Wiget Lane, Suite #210 Walnut Creek, CA 94598 USA Prior to Dec2014: Allergy & Asthma Clinical Research 130 La Casa Via, Bldg #2, Suite 110 Walnut Creek, CA 94598 USA	Joshua S. Jacobs, MD
8400243	Medical Research of Arizona, A Division of Allergy, Asthma, & Immunology Associates, Ltd. 7514 E. Monterey Way, Suite1-A Scottsdale, Arizona 85251 USA	Michael E. Manning, MD
8400248	705 W. La Veta Ave, Suite 101 Orange, CA 92868 USA	Donald S. Levy, MD
8400250	UC San Diego School of Medicine 9500 Gilman Drive, Mailcode 0732 Stein Clinical Research Building, Room 205 La Jolla, CA 92093 USA	Marc Andrew Riedl, MD, MS

Source: 16.1.4, CSR 3002, June 1, 2016

6.2.7 Surveillance/Monitoring

A CSL830 program-level Steering Committee provided scientific advice and safety monitoring for the study on an as needed basis. No formal meeting schedule was maintained by the Steering Committee. Due to the open-label design, there was no data safety monitoring board for this study.

6.2.8 Endpoints and Criteria for Study Success

Primary Interim Endpoints
Person-time incidence rates (PTIRs) of each of the following:

- AEs leading to premature study discontinuation
- Thromboembolic event (TEEs)
- Anaphylaxis
- HAE attacks resulting in in-patient hospitalization (where hospitalization is the consequence of the need for emergent medical care)
- Injection site reactions at the CSL830 injection site graded as severe by the investigator
- Related serious adverse reactions (SARs), other than events specified above.

Secondary Interim Safety Endpoints

- AEs, SAEs, injection site reactions, systemic AEs, AEs that began within 24 hours after CSL830 administration, and suspected adverse drug reactions (suspected ADRs, defined as AEs that began within 24 hours after CSL830 administration, AEs at least possibly related to CSL830 administration (ARs), and AEs with no causality assessment (ARs)
- AEs of special interest (TEEs, anaphylaxis events), sepsis and bacteremia events
- Clinical laboratory assessments, including hematology, biochemistry, urinalysis, coagulation profile, viral serology, and anti-C1-INH antibodies
- Vital signs (including body weight) and physical examination
- Risk scores for deep vein thrombosis (DVT) and pulmonary embolism

Exploratory Interim Efficacy Endpoint

- Time-normalized number of HAE attacks, as reported by the investigator

Primary Safety Analyses

Primary safety analyses were performed on all subjects who received CSL830 (safety population). The PTIRs for each primary endpoint safety event were calculated as follows:

- Subject-based analysis for PTIR = (the total number of subjects who experienced the event during the respective treatment) / (the sum of the date each subject experienced the event – the subject's start date + 1 day) / (365.25 days). Subjects without the respective event were not included in the numerator, but were included in the time at risk with their entire study participation time.

- Event-based analysis for PTIR = (the total number of events documented during the respective treatment) / (the sum of each subject's end date – the subject's start date + 1 day) / (365.25 days). Subjects with or without the respective event were included in the time at risk with their entire study participation time.

Secondary Safety Analyses

AEs, local injection site ARs and systemic AEs were described by intensity, relationship to investigational product, outcome, and seriousness by treatment. All local injection site ARs were in addition summarized by duration. The percent of subjects with AEs beginning, during or within 24 hours of administration was summarized by treatment. Risk scores for DVT and pulmonary embolism, TEE events, events of sepsis or bacteremia, potential cases of anaphylaxis, and suspected ADRs were also assessed.

Exploratory Efficacy Analysis

The time-normalized number of HAE attacks, as reported by the investigator, was summarized descriptively by treatment, and was calculated as the number of HAE attacks reported by the investigator per subject in the actual treatment divided by the length of stay of the subject in the actual treatment.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- Intent to Treat (ITT) Population: All subjects who provided informed consent / assent and were randomized, regardless of whether or not they received CSL830.

- Safety Population: All subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.

Primary Safety Analyses

See 6.2.8.

Secondary Safety Analyses

The secondary safety analyses were performed on data from all subjects who received CSL830. AEs, local injection site ARs and systemic AEs were described by intensity, relationship to investigational product, outcome, and seriousness by treatment. All local injection site ARs were also summarized by duration. The percent of subjects with ARs beginning, during or within 24 hours of administration, was summarized by treatment. Risk scores for DVT and pulmonary embolism, TEE events, events of sepsis or bacteremia, potential cases of anaphylaxis, and suspected ADRs also were assessed.

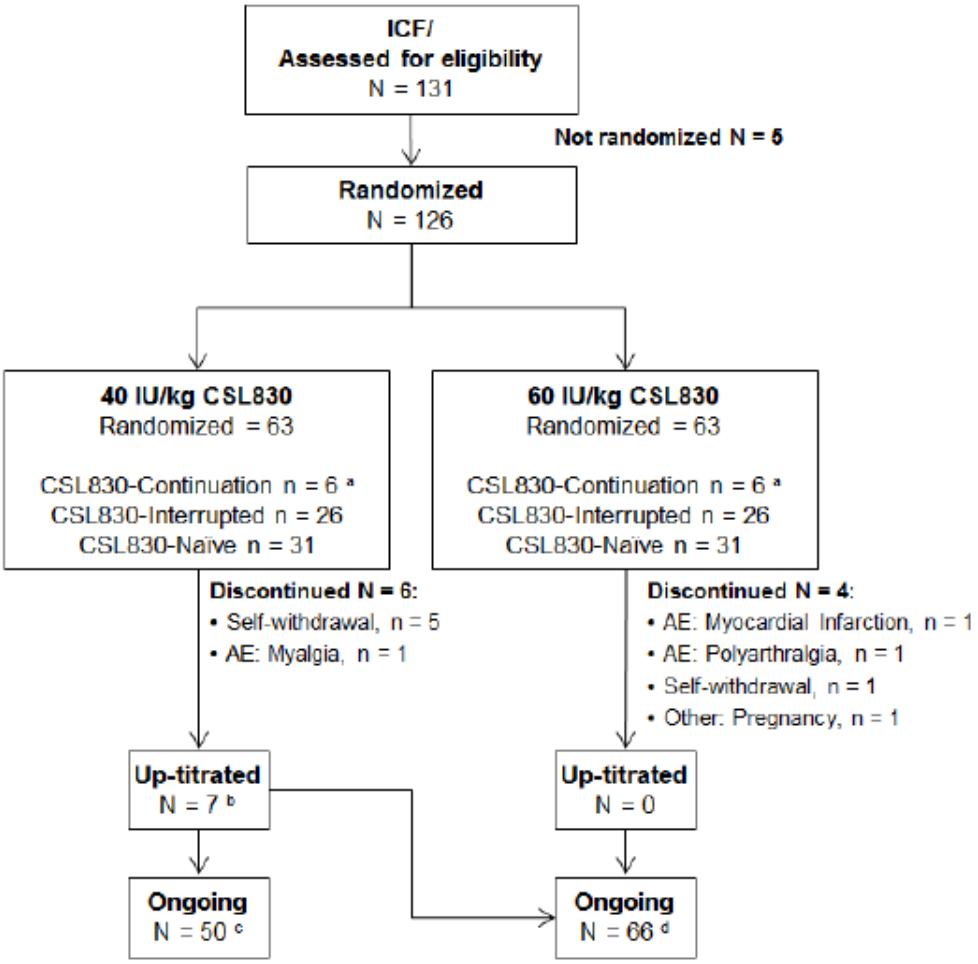
Exploratory Efficacy Analysis

The time-normalized number of HAE attacks, as reported by the investigator, was summarized descriptively by treatment, and was calculated as the number of HAE attacks reported by the investigator per subject reported by the investigator per subject.

Reviewer Comment
Enrollment of 100 subjects allows detection (95% confidence limit) of AEs that occur at ≥3% ("Rule of 3s").

6.2.10 Study Population and Disposition

- A total of 131 subjects provided Informed Consent/ Assent. Overall, 67 subjects (51.1%) were CSL830-Naïve, 52 subjects (39.7%) were CSL830-Interrupted, 12 subjects (9.2%) and 5 subjects (3.8%) were CSL830-Interrupted + Continuation subjects. A total of 126/131 subjects were randomized (63 to the 40 IU/kg dose and 63 to the 60 IU/kg dose).
- Of the 126 randomized subjects, 76 (60.3%) were female and 121 (96.0%) were White. Mean age of the study population was 40.5 years. The 40 IU/kg and 60 IU/kg treatment arms were similar in terms of age, sex, race, weight, and body mass index.
- As of 17 May 2016, 116 subjects remained in the study and 10/126 subjects had discontinued: 9 subjects in TP1 (5 subjects in the 40 IU/kg treatment arm and 4 subjects in the 60 IU/kg treatment arm), and 1 subject in TP2 (40 IU/kg treatment arm). Reasons for study discontinuation included AEs (3 subjects), withdrawal by subject (6 subjects), and pregnancy (1 subject).
- The percent of subjects with HAE type I and type II were similar in the 40 IU/kg and 60 IU/kg treatment arms and consistent with what is seen in the general HAE population. The mean (SD) reported historic number of HAE attacks per subject in the 3 months before Screening was 12.2 (8.99) attacks in the 40 IU/kg treatment arm and 13.3 (10.12) attacks in the 60 IU/kg treatment arm. The percentages of "CSL830-Naïve" Subjects who used any prior HAE prophylaxis (i.e., intravenous C1-INH and / or oral androgens) in the 3 months before Screening was similar in the 40 IU/kg treatment arm (7 [22.6%] subjects) and the 60 IU/kg treatment arm (8 [25.8%] subjects).



AE = adverse event; ICF = informed consent form; N = number of subjects; TP1 = Treatment Period 1; TP2 = Treatment Period 2.

[a] Four "CSL830-Continuation" Subjects received CSL830 in TP2 of Study 3001 (ie, subjects were treated with CSL830 across Studies 3001 and 3002 without interruption). The remaining 8 "CSL830-Continuation" Subjects received treatment with placebo in TP2 of Study 3001.

[b] 1 subject up-titrated from 40 IU/kg to 60 IU/kg CSL830 in TP1; 6 subjects up-titrated from 40 IU/kg to 60 IU/kg CSL830 in TP2; no subjects up-titrated from 60 IU/kg to 80 IU/kg in either TP1 or TP2.

[c] At the time of the data cut-off, 50 subjects were receiving treatment with 40 IU/kg (ie, 63 subjects randomized to 40 IU/kg minus 6 discontinued subjects minus 7 subjects who up-titrated from 40 IU/kg to 60 IU/kg).

[d] At the time of the data cut-off, 66 subjects were receiving treatment with 60 IU/kg (ie, 63 subjects randomized to 60 IU/kg minus 4 discontinued subjects plus 7 subjects who up-titrated from 40 IU/kg to 60 IU/kg).

Figure 5: Subject disposition.
Source: Table 14.1.1.1, interim CSR 3002, page 77 of 1155, June 1, 2016

6.2.10.1 Populations Enrolled/Analyzed

All 126 subjects randomized and treated with CSL830 were included in both the ITT and Safety populations.

ITT population: Subjects who were enrolled in the study according to their randomized treatment arm (i.e., 63 subjects in the 40 IU/kg treatment arm and 63 subjects in the 60 IU/kg treatment arm).

Safety population: Subjects who were exposed to the product. The 7 subjects who were up-titrated from 40 IU/kg to 60 IU/kg were included in both treatment arms in the Safety Population. Therefore, the Safety Population included 63 subjects in the 40 IU/kg treatment arm and 70 subjects in the 60 IU/kg treatment arm.

6.2.10.1.1 Demographics
As depicted in Table 13, the study population consisted primarily of White subjects with a mean age of 41 years.

Table 13: Demographics of the Study 3002 Population

Parameter		40 IU/kg CSL830 N (%)	60 IU/kg CSL830 N (%)	≥40 IU/kg CSL830 N (%)
Sample size		63	70	126
Age (years)		41	41	40.5
	Median	43.0	41.5	41.0
Min; Max		8, 67	10,72	8, 72
Gender				
	Male [N (%)]	40 (63.5)	41 (58.6)	76 (60.3)
	Female [N (%)]	23 (36.5)	29 (41.4)	50 (39.7)
Race				
	White [N (%)]	60 (95.2)	67 (95.7)	121 (96.0)
	Black/African American [N (%)]	1 (1.6)	1 (1.4)	2 (1.6)
	Asian [N (%)]	0	1 (1.4)	1 (0.8)
	Other [N (%)]	2 (3.2)	1 (1.4)	2 (1.6)

Adapted from Table 14.1.2.3, page 156 of 1155, CSR, June 1, 2016

Reviewer Comment
In contrast to the 3001 population, where females outnumbered females 2:1, males outnumbered females 3:2 in 3002.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

- Treatment compliance was high in both treatment arms: 99.9% (range: 81% to 109%) in the 40 IU/kg treatment arm and 100.3% (range: 94% to 112%) in the 60 IU/kg treatment arm.
- Mean duration of exposure (regardless of any dose increase) was 37.3 weeks in the 40 IU/kg treatment arm and 37.1 weeks in the 60 IU/kg treatment arm.
- Maximum duration of exposure was 58 weeks in the 40 IU/kg treatment arm and 57 weeks in the 60 IU/kg treatment arm.

6.2.10.1.3 Subject Disposition
See 6.2.10.

6.2.11 Efficacy Analyses (Exploratory)

Duration of exposure to 40 IU/kg and 60 IU/kg CSL830 was similar: 35.7 weeks (0.68 years) and 34.9 weeks (0.67 years), respectively. As shown in Tables 13 and 14, there was little difference between dose cohorts in the rate of time-normalized number of HAE attacks per day and per month, respectively.

Table 14: Time-Normalized Number of HAE Attacks (Number/Day) Reported by the Investigator (ITT Population)

	40 IU/kg CSL830 N=63	60 IU/kg CSL830 N=63	≥40 IU/kg CSL830 N=126
No. of subjects	63	63	126
Mean (SD)	0.01 (0.02)	0.02 (0.03)	0.01 (0.02)
Min, Max	0,00, 0.10	0.00, 0.12	0.00, 0.12
Median	0.004	0.000	0.003

Adapted from Table 14.2.1.1, interim CSR, page 321 of 1155, June 1, 2016

Table 15: Time-Normalized Number of HAE Attacks (Number/Month) Reported by the Investigator (ITT Population)

	40 IU/kg CSL830 N=63	60 IU/kg CSL830 N=63	≥40 IU/kg CSL830 N=126
No. of subjects	63	63	126
Mean (SD)*	0.4 (0.6)	0.5 (0.8)	0.4
Min, Max	0.0, 3.0	0.0, 3.6	0.0, 3.6
Median	0.1	0.0	0.1

*Based on 1 month = 30 days (computed by this reviewer)
Adapted from Table 14.2.1.1, interim CSR 3002, page 321 of 1155, June 1, 2016

Reviewer Comment
The FDA biostatistician was asked by this reviewer to compute p-values and 95% confidence intervals for the 40 and 60 IU/kg treatment cohorts in terms of attacks per day, which were not included in the submission. A two sample t-test yielded a p-value of 0.7 (-0.010, 0.006), indicating no difference.

As shown in Table 15, more than half (54.0%) of subjects randomized to 60 IU/kg were HAE attack-free during the reporting period, compared with 44.4% of subjects randomized to 40 IU/kg.

Table 16: Number and Percent of Subjects with No HAE Attacks During Treatment (ITT Population)

	40 IU/kg CSL830 N=63	60 IU/kg CSL830 N=63
No. of subjects	28	34
Percent of subjects	44.4	54.0

Adapted from Documentation of Hand-calculated Data Points, interim CSR 3002, page 1146 of 1155, June 1, 2016

As of the 17 May 2016, no subject randomized to 60 IU/kg CSL830 was up-titrated to 80 IU/kg. Seven subjects randomized to 40 IU/kg CSL830 were up-titrated to 60 IU/kg. All 7 subjects met the protocol-specified criteria for up-titration.

No subject had more than 1 dose increase. One subject randomized to 40 IU/kg had a dose increase to 60 IU/kg during TP1. This subject had fewer HAE attacks after up-titration to 60 IU/kg (4 attacks in 34 weeks) than during treatment with 40 IU/kg (13 attacks in 8 weeks) (Subject (b) (6)). Six subjects randomized to 40 IU/kg had a dose increase to 60 IU/kg during TP2. Five of these 6 subjects did not have an HAE attack after up-titration (range of exposure: 1 to 15 weeks on 60 IU/kg). The remaining

subject (Subject (b) (6)) had 9 attacks in 36 weeks on 40 IU/kg and 5 attacks in 15 weeks after up-titration to 60 IU/kg. In accordance with the ITT analysis, any attacks that occurred after up-titration were attributed to the randomized treatment, and not the actual dose administered at the time of the attack.

Reviewer Comment
Attacks occurring within the first 2 weeks after up-titration were not counted because this was a pre-specified wash-in period.

6.2.11.1 Analyses of Primary Endpoint(s)

Primary Safety Analyses

AEs leading to study discontinuation
Three AEs (1 SAE and 2 non-serious AEs) led to study discontinuation of 3 subjects during the study.

- **Subject** (b) (6) , a 47 year old female, experienced a product-unrelated myocardial infarction SAE during treatment with 60 IU/kg
- **Subject** (b) (6) a 56 year old female, experienced a product-unrelated arthralgia AE during treatment with 40 IU/kg
- **Subject** (b) (6) , a 33 years old female, experienced an product-unrelated arthralgia AE during treatment with 60 IU/kg

Thromboembolic events
One product-unrelated **myocardial infarction** SAE was experienced by a 47 year old female 60 IU/kg subject (b) (6)) (PTIR: 0.02 [95% CI: < 0.005, 0.12]), and led to study discontinuation. See narratives of SAEs, below.

Anaphylaxis events
There were no cases of anaphylaxis in either treatment arm

HAE attacks resulting in hospitalization
No HAE attacks resulted in in-patient hospitalization

Local injection site AE graded as severe
No injection site ARs were graded as severe

Related SAEs
No SAEs were reported as product-related

Anti-C1-INH antibodies
No subjects who tested negative for antibodies to C1-INH at Baseline also tested positive at a post-baseline visit during the study. No subjects had positive results for inhibitory antibodies to C1-INH at baseline or at any post-baseline visit.

6.2.11.2 Analyses of Secondary Endpoints

Systemic SAEs
A total of 11 nonfatal SAEs in 8 subjects were reported: 8 SAEs in six 60 IU/kg subjects and 3 SAEs in two 40 IU/kg subjects, all product-unrelated.

Table 17: Summary of SAEs by Subject

	40 IU/kg CSL830 N=63 N (%)	60 IU/kg CSL830 N=63 N (%)	≥40 IU/kg CSL830 N=126 N (%)
SAEs	2 (3.2)	6 (8.6)	8 (6.3)
Local injection site SAEs	0	0	0
Systemic SAEs	2 (3.2)	6 (8.6)	8 (6.3)
SAEs within 24 h after administration	2 (3.2)	1 (1.4)	3 (2.4)
SAEs leading to study discontinuation	0	1 (1.4)	1 (0.8)
Causality			
Related	0	1 (1.4)	1 (0.8)
Not related	2 (3.2	5 (7.1)	7 (5.6)
Severity			
Mild	0	1 (1.4)	1 (0.8)
Moderate	0	3 (4.3)	3 (2.4)
Severe	2 (3.2)	2 (2.9)	4 (3.2)
Outcome			
Recovered / resolved	1 (1.6)	5 (7.1)	6 (4.8)
Not recovered / not resolved	1 (1.6)	1 (1.4)	2 (1.6)

Adapted from Tables 14.3.1.3.3.1-2, Tables 14.3.1.4.1.1-2, and Tables 14.3.1.5.1.1-2, interim CSR 3002, page 396 or 1155, June 1, 2016

NARRATIVES OF SAEs

1. **Subject** (b) (6), a 47 year-old female, experienced a severe intensity **myocardial infarction** during treatment with 60 IU/kg that resulted in study discontinuation:. The cardiologist concluded that the cause was likely due to spontaneous plaque rupture of an atherosclerotic plaque with associated mild clot formation. The subject was overweight, a heavy smoker (> 20 cigarettes / day for years) and had multiple risk factors including hypercholesterolemia and hypertriglyceridemia. Other than the AMI SAE, no other TEEs were reported. There were no cases of sepsis or bacteremia, or of anaphylaxis.

   Reviewer Comment
   I agree with the investigator's attribution that the AMI was product unrelated.

2. **Subject** (b) (6), a 54-year-old female, experienced a severe intensity, product-unrelated SAE of **lymphoma** during treatment with 40 IU/kg. The event did not lead to study discontinuation. The outcome of the event was not recovered / not resolved.
3. **Subject** (b) (6), a 67-year-old female, experienced two product-unrelated, severe intensity SAEs of **dehydration** and **hypokalemia** during treatment with 40 IU/kg. The events did not lead to study discontinuation. The events were graded as severe. The outcome of the events was recovered / resolved.
4. **Subject** (b) (6), a 25-year-old female, experienced two, moderate intensity, product-unrelated **cholelithiasis** SAEs during treatment with 60 IU/kg. After the data cut-off, the second event was updated to be a continuation of the first event (i.e., the subject experienced 1 cholelithiasis SAE). The events did not

lead to study discontinuation. The outcome of the events was recovered / resolved.

5. **Subject** (b) (6), a 41-year-old female, experienced a mild intensity, product-unrelated **diplopia** SAE during treatment with 60 IU/kg. The event did not lead to study discontinuation. The outcome of the event was not recovered / not resolved.
6. **Subject** (b) (6), a 30-year-old female, experienced a moderate severity, product-unrelated **depression** SAE during treatment with 60 IU/kg. The event did not lead to study discontinuation. The outcome of the event was recovered / resolved.
7. **Subject** (b) (6), a 49-year-old female, experienced moderate intensity, product-unrelated SAEs of **dizziness** and **chest pain** during treatment with 60 IU/kg. The events led to CSL830 interruption but did not lead to study discontinuation. The outcome of the events was recovered / resolved.
8. **Subject** (b) (6), a 68-year-old male, experienced a severe intensity, product-unrelated **pneumonia** SAE during treatment with 60 IU/kg. The event did not lead to study discontinuation. The outcome was recovered / resolved.

Reviewer's Comment

I agree with the investigators' assessments that these SAEs were product-unrelated.

Product-Related Adverse Reactions

In total, 6 subjects experienced an AE attributed to the product as depicted in Table 18.

Table 18: Systemic Product-Related Adverse Reactions

Subject ID	Age Sex	Preferred Term	Treatment (IU/kg)	Action Taken	Outcome	Intensity
(b) (6)	52 Male	Hemorrhage	40	Dose not changed	Recovered, resolved	Mild
	39 Female	Nausea	40	Dose not changed	Recovered, resolved	Mild
	55 Female	Rash	40	Dose not changes	Recovered, resolved	Mild
	36 Female	Abdominal pain, distention	60	Dose interrupted	Recovered, resolved	Moderate
	56 Female	Myalgia	40	Discontinued from study	Recovered, resolved	Moderate
	42 Female	Blurred vision	60	Dose not changed	Recovered, resolved	Mild

Adapted from Table 12-12, page 111 of 1155 and Listing 16.2.7.2, CSR, page 4 of 431, April 15, 2016

Reviewer Comment

All but one of affected subjects were middle-aged females who experienced mild-moderate intensity AEs. One of these subjects discontinued from the study.

Systemic Adverse Reactions

The total incidence of AEs reported (product-related and product-unrelated) was identical across dosing cohorts: 36 (57.1%) subjects (162 events, 3.76 events / treatment year)

during treatment with 40 IU/kg and 40 (57.1%) subjects (155 events, 3.31 events / treatment year) during treatment with 60 IU/kg of product.

Local Injection Site Serious Adverse Events

- None

Local Injection Site Adverse Reactions

Of the 1077 AEs reported, 960 were mild and 107 were moderate, and 1033 had an outcome of recovered / resolved. The majority (762/1077) were assessed as product-related.

- Injection site reactions were reported more frequently with 40 IU/kg (49.2%, 0.11 events / injection) than with 60 IU/kg (32.9%, 0.06 events / injection),
- A large number of local injection site AEs were reported in a relatively small number of subjects. A single subject randomized to treatment with 40 IU/kg (Subject (b) (6)) contributed 140 events over 81 CSL830 injections. Across the study, 8 (6.3%) subjects contributed 488 of 760 (64.2%) local injection site AEs, inclusive of Subject (b) (6) . This included 6 subjects randomized to treatment with 40 IU/kg and 2 subjects randomized to treatment with 60 IU/kg. All of these subjects continued their participation in the study at the time of data cut-off. The majority of AEs reported during the study was mild in severity and had an outcome of recovered / resolved at the time of data cut-off.
- No AEs of severe intensity were reported at either dose.

Table 19 presents the AEs experienced by ≥5% of subjects.

Table 19: Adverse Reactions Experienced by ≥5% of Subjects (Safety Population)

Preferred Term	40 IU/kg CSL830 N=63 N (%)	60 IU/kg CSL830 N=63 N (%)	≥40 IU/kg CSL830 N=126 N (%)
Nasopharyngitis	9 (14.3)	13 (18.6)	21 (16.7)
Injection site pain	13 (20.6)	5 (7.1)	18 (14.3)
Injection site erythema	8 (12.7)	8 (11.4)	15 (11.9)
Injection site reaction	6 (9.5)	9 (12.9)	14 (11.1)
Headache	8 (12.7)	5 (7.1)	13 (10.3)
Injection site bruising	5 (7.9)	3 (4.3)	8 (6.3)
Injection site hematoma	6 (9.5)	3 (4.3)	8 (6.3)
Upper respiratory tract infection	3 (4.8)	4 (5.7)	7 (5.6)

Adapted from Table 12.5, interim CSR 3002, page 98 of 1155, June 1, 2016

Table 20 is a detailed breakdown of local injection site AEs by dose cohort. Almost all cases were of mild intensity and none was of severe intensity.

Table 20: Severity and Duration of Local Injection Site Adverse Reactions: Preferred Terms Reported in ≥5% of Subjects

Preferred Term		40 IU/kg CSL830 N=63 N (%)	60 IU/kg CSL830 N=63 N (%)	≥40 IU/kg CSL830 N=126 N (%)
Injection site bruising		5 (7.9)	3 (4.3)	8 (6.3)
Intensity				
	Mild	5 (7.9)	3 (4.3)	8 (6.3)
	Moderate	0	0	0
	Severe	0	0	0
Duration				
	≤1 Day	2 (3.2)	1 (1.4)	3 (2.4)
	>3Days	2 (3.2)	1 (1.4)	3 (2.4)
Injection site erythema		8 (12.7)	8 (1.4)	3 (2.4)
Intensity				
	Mild	8 (12.7)	7 (10.0)	14 (11.1)
	Moderate	0	2 (2.9)	2 (1.6)
	Severe	0	1 (1.4)	1 (0.8)
Duration				
	≤1 Day	7 (11.1)	6 (8.6)	12 (9.5)
	>3Days	2 (3.2)	2 (2.9)	4 (3.2)
Injection site hematoma		6 (9.5)	3 (4.3)	8 (6.3)
Intensity				
	Mild	6 (9.5)	2 (2.9)	7 (5.6)
	Moderate	0	1 (1.4)	1 (0.8)
	Severe	0	0	0
Duration				
	≤1 Day	4 (6.3)	1 (1.4)	4 (3.2)
	>3Days	2 (3.2)	2 (2.9)	4 (3.2)
Injection site induration		4 (6.3)	2 (2.9)	6 (4.8)
Intensity				
	Mild	4 (6.3)	1 (1.4)	5 (4.0)
	Moderate	0	1 (1.4)	1 (0.8)
	Severe	0	0	0
Duration				
	≤1 Day	3 (4.8)	2 (2.9)	5 (4.0)
	>3Days	0	0	0
Injection site pain		13 (20.6)	5 (7.1)	18 (14.3)
Intensity				
	Mild	13 (20.6)	4 (5.7)	17 (13.5)
	Moderate	1 (1.6)	1 (1.4)	2 (1.6)
	Severe	0	0	0
Duration				
	≤1 Day	13 (20.6)	4 (5.7)	17 (13.5)
	>3Days	0	1 (1.4)	1 (0.8)
Injection site reaction		6 (9.5)	9 (12.9)	14 (11.1)
Intensity				
	Mild	6 (9.5)	9 (12.9(	14 (11.1)
	Moderate	0	0	0
	Severe	0	0	0
Duration				
	≤1 Day	6 (9.5)	9 (12.9)	14 (11.1)
	>3Days	1 (1.6)	2 (2.9)	3 (2.4)

Adapted from Table 12-10, interim CSR 3002, page 107/1055, June 1, 2016

6.2.11.3 Subpopulation Analyses

N/A

6.2.11.4 Dropouts and/or Discontinuations

See 6.2.11.1

6.2.11.5 Exploratory and Post Hoc Analyses

Insert text here

6.2.12 Safety Analyses

6.2.12.1 Methods

The following events were captured:

- Overall AEs
- Serious AEs
- Local injection site AEs (i.e., injection site reactions)
- Systemic AEs
- AEs that began within 24 hours after CSL830 administration
- Suspected adverse drug reactions (ADRs), defined as AEs that began within 24 hours after CSL830 administration, AEs at least possibly related to CSL830 administration, and AEs with no causality assessment
- AEs of special interest
    - Thromboembolic events (TEEs)
    - Anaphylaxis events
    - Sepsis and / or bacteremia events
    - Clinical laboratory assessments: Hematology, Biochemistry, Urinalysis, Coagulation profile, Viral serology, Anti-C1-INH antibodies
- Vital signs, including body weight
- Physical examination
- Clinical score of risk assessment for deep vein thrombosis (DVT) and pulmonary embolism

9.5.1.5.1 Adverse Events

According to the protocol and ICH guidelines

6.2.12.2 Overview of Adverse Reactions

Adverse reactions were reported more frequently (higher percentage of subjects and higher number of events) with 40 IU/kg than with 60 IU/kg, with a total of 8825 CSL830 injections analyzed. Adverse reactions were reported in 46 (73.0%) subjects on 40 IU/kg and in 44 (62.9%) subjects on 60 IU/kg. Local injection site ARs (ie, injection site reactions) were the most common events reported during the study, with no clear dose-relationship.

6.2.12.3 Deaths

No deaths were reported during the study.

6.2.12.4 Nonfatal Serious Adverse Events

Eleven SAEs were experienced by 8 subjects. Three SAEs occurred in 2 subjects on 40 IU/kg and 8 SAEs occurred in 6 subjects on 60 IU/kg. Most SAEs were graded as moderate or severe and had an outcome of recovered/resolved. None of the SAEs was a local injection site SAE or reported as product-related.

6.2.12.5 Adverse Reactions of Special Interest (AESI)

See 6.2.11.1

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

See 6.2.11.1

6.2.13 Study Summary and Conclusions

Interim results from the long-term, open-label Study 3002 demonstrate that the efficacy of CSL830 is maintained over time periods of up to 1 year.

6.3 Trial #: CSL830-2001

An Open-label, Cross-over, Dose-ranging Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of the Subcutaneous Administration of a Human Plasma-derived C1-esterase Inhibitor in Subjects with Hereditary Angioedema

6.3.1 Objectives

1. Primary: To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of the subcutaneous (SC) administration of 3 different dosing regimens of CSL830.
2. Secondary: To evaluate the safety, tolerability, and immunogenicity of the SC administration of 3 different dosing regimens of CSL830.

6.3.2 Design Overview

Prospective, international, multi-center, open-label, cross-over study.

6.3.3 Population

Subjects (N=18) with a history of HAE.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Single IV dose of Berinert 20 U/kg administered 2 to 7 days before CSL830 dosing. Subjects subsequently were allocated to receive 2 of the following 3 dosing regimens of CSL830 SC:

- 1500 IU administered 2 times weekly for 4 weeks
- 3000 IU administered 2 times weekly for 4 weeks
- 6000 IU administered 2 times weekly for 4 weeks

(CSL830 batch numbers: (b) (4))

6.3.5 Directions for Use

Berinert is a C1-esterase inhibitor, provided as a lyophilizate containing 500 U C1-INH to be reconstituted with 10 mL of water for injection. Each vial of Berinert contains (b) (4) protein, 85 to 115 mg glycine, 25 to 30 mg (b) (4) , and 70 to 100 mg sodium chloride. Subjects received a single IV dose of Berinert 20 U/kg body weight administered as a slow IV infusion of approximately 4 mL/minute.
(Berinert batch numbers: (b) (4)

CSL830 is a lyophilizate containing 1500 IU C1-INH to be reconstituted with 3 mL of water for injection. Each vial of CSL830 contains (b) (4) protein, 25.5 to 34.5 mg glycine, 4.5 to 10.5 mg (b) (4) , and 21 to 30 mg sodium chloride.

6.3.6 Sites and Centers

Site Number	Principal Investigator	Address	Sub-investigators and additional personnel
Germany			
2760059	Staubach-Renz, Petra, Prof MD	Johannes Gutenberg-Universitätsklinikum Langenbeckstr. 1 Dermatologie Mainz 55101	Weirich, Oliver MD, SI Groffik, Ariadne MD SI Rudolph, Bernice MD, SI Stranger, Christian MD, SI Rady-Pizarro, Ulrike SC
2760060	Martinez-Saguer, Inmaculada, Prof MD	Klinikum der Johann Wolfgang Goethe-Universität Zentrum für Theodor-Stern-Kai 7 Frankfurt/Main 60596	Aygoren-Pursun, Emel, MD, SI Graff, Jochem, MD, SI Heller, Christine, MD, SI Kuczka, Karina, MD, SI
2760061	Maurer, Marcus, Prof MD	Charité, Universitätsmedizin Berlin, Campus Mitte Medizinis Charitéplatz 1 Berlin 1011	Magerl, Markus, MD, SI Abajian, Marina, MD, SI Krause, Karolina, MD, SI Metz, Martin, MD, SI Steinicke, Maren, SC
United States			
8400008	Levy, Robin, MD	5555 Peachtree Dunwoody Rd, Suite 340 Atlanta, GA 30342	Goodman, Steven, SC
8400143	Li, Henry, MD	5454 Wisconsin Avenue Suite 700 Chevy Chase, MD 20815	White, Martha, MD, SI Kaliner, Michael, MD, SI Economides, Athena, MD, SI Scarpua, Mark, MD, SI Jeong, David, MD, SI Johnson, Tamara, SC
8400185	Bernstein, Jonathan, MD	Bernstein Clinical Research Center, LLC, Cincinnati, OH 45267	Bernstein, David, MD, SI Epstein, Tolly, MD , SI Smith, Andrew, MD, SI Davis, Benjamin, MD SI McKnight, Christopher, MD SI Amin, Priyal, DO, SI Cheng, Gang, MD, SI Tan, Jessica, MD, SI Huesing-Everman, Laura, MD SI Picard, Jillian, RN SC Holmes, Sarah, RN, SC

Site Number	Principal Investigator	Address	Sub-investigators and additional personnel
8400186	Craig, Timothy, MD	Penn State Milton S. Hershey Medical Center 500 University Drive Room:C5860, MC:H041 Hershey, PA 17033	Ghaffari, Gisoo, MD SI Ishmael, Faoud, MD SI Rael, Efren, MD SI Mende, Cathy, CRNP, SC Rhoads, Crystal, MA, SC Bajaj, Puneet, MD SI Bhardwaj, Neeti, MD SI Gutierrez, Maria, MD SI Kalia, Neelu, MD SI Vernon, Natalia MD SI Yanchuk, Patti RN BSN SC Barth, Linda LPN, SC
8400187	Rehman, Syed, MD	Toledo Institute Asthma and Allergy Center 7247 West Central Ave, Suite A Toledo, OH 43617	Tiell, Stephanie,MSN, FNP-C SI Gilpin, Kari, SC Krontz, Jessica, SC

Source: 16.1.4, CSR 2001, June 27, 2013

6.3.7 Surveillance/Monitoring

The duration of the study treatment was up to 18 weeks which included a Screening period, Berinert administration, two CSL830 dosing periods of 4 weeks each run consecutively or with an interval of up to 4 weeks (if approved by the sponsor) and a 1-week follow-up period.

Following a Screening period of up to 30 days, subjects were allocated sequentially to 1 of 6 possible CSL830 treatment sequences (Sequence A to Sequence F), which was preceded by a single IV dose of Berinert 20 U/kg administered 2 to 7 days before the first CSL830 dosing period (Figure 1). The 2 CSL830 dosing periods were run consecutively, unless an interval of up to 4 weeks was approved by the sponsor.

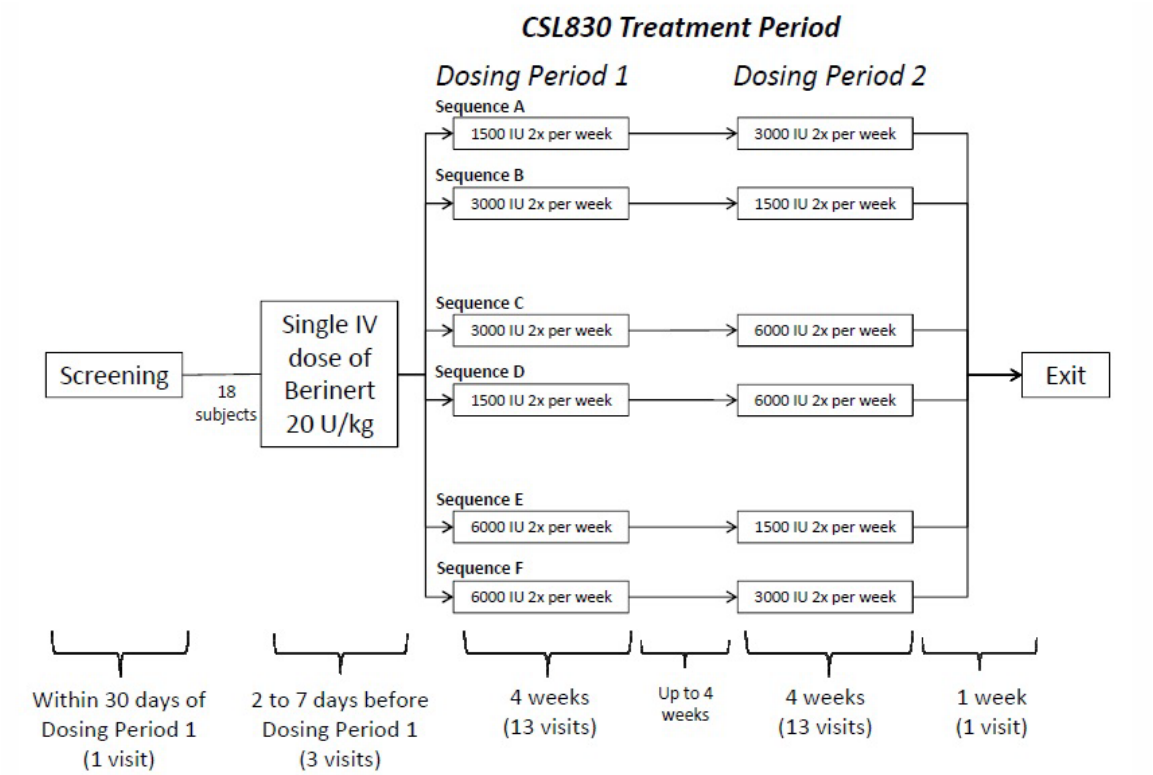


Figure 6: Study schema indicating dosing sequences for Dosing Period 1 and Dosing Period 2.
Source: Figure 9.1, CSR 2001, page 20 of 98, June 27, 2013

One week after completion of study visits associated with the second dosing period, subjects had a follow-up assessment at exit visit. During the study, blood and urine samples were collected at specified times for safety, PK, or PD analyses. Safety and tolerability were evaluated by continuous observation of AEs and by other safety assessments that were conducted at specified times throughout the study (including infusion site tolerability, laboratory parameters, vital signs, body weight, physical examination, risk assessment for deep vein thrombosis, and concomitant medication usage). One week after the completion of the study visits, subjects had a follow-up assessment at the exit visit.

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoint

- Mean trough C1-INH functional activity at the fourth week of each dosing regimen of CSL830, based on modeling and simulation

Secondary Endpoints

- Mean trough C1-INH functional activity at the fourth week of each dosing regimen of CSL830, based on observed data
- Mean trough C1-INH antigen level at the fourth week of each dosing regimen of CSL830, based on observed data
- Mean trough C4 antigen level at the fourth week of each dosing regimen of CSL830, based on observed data

- Mean change from baseline of C1-INH functional activity, C1-INH antigen level and C4 antigen levels to the mean trough level at the fourth week of each dosing regimen of CSL830, based on observed data

Exploratory Endpoints

- Modeling-derived PK/PD parameters (e.g., volume of distribution [V], clearance [CL], SC bioavailability) of C1-INH functional activity for IV Berinert and each CSL830 dosing regimen

Additional safety and tolerability endpoints

- The frequency and intensity of adverse events (AEs)
- The intensity of local injection site AEs at the injection site (pain, swelling, bruising, and itching)
- Clinical laboratory tests and assessments including: hematology, blood chemistry, thrombotic screen, coagulation profile, D-dimer level, anti-C1-INH antibodies, viral safety and urinalysis
- Risk assessment for deep vein thrombosis

6.3.9 Statistical Considerations & Statistical Analysis Plan

The data analysis for the study comprised descriptive statistics. C1-INH functional activity data were subjected to a population-based approach using nonlinear mixed-effects modeling using NONMEM version 7.2 or higher. The exploratory PK/PD parameters were derived from nonlinear mixed-effects modeling and simulation for each dosing regimen. All outputs were produced using SAS® version 9.2.

6.3.10 Study Population and Disposition

Male or female subjects with type I or II HAE aged ≥18 years weighing 50 to 110 kg, who had 5 or fewer HAE attacks within the 3 months prior to the Screening visit, and who were able to provide written informed consent, were included in the study.

6.3.10.1 Populations Enrolled/Analyzed

PK and safety population.

6.3.10.1.1 Demographics

Baseline characteristics were similar across the 3 dosing regimens. The majority of subjects (14/18; 77.8%) reported that they were of white race. Overall, the median age of subjects was 33.9 years and more females (11/18; 61.1%) than males (7/18; 38.9%) participated in the study.

The majority of subjects (16/18; 88.9%) had type I HAE and the median number of HAE attacks in the 3 months prior to screening was 2.0 in all 3 CSL830 dosing regimens. Overall, the median baseline as-observed C1-INH functional activity was 15.2%, the median baseline as-observed C1-INH antigen level was 0.050 mg/mL, and the median baseline as-observed C4 antigen level was 7.0 mg/mL.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The investigator or delegate confirmed receipt of all shipments of product in writing using the receipt form(s) provided by the sponsor. Investigational product was administered by study staff or, if previously approved by the sponsor, by home-care service. The dose, date, and time of IMP administration was recorded in the eCRF.

6.3.10.1.3 Subject Disposition
A total of 22 subjects provided informed consent and were screened for inclusion in this study. Of these, 18 eligible subjects were enrolled and allocated sequentially to receive 1 of 6 CSL830 treatment sequences. All 18 subjects received a single IV dose of Berinert prior to treatment with CSL830 to characterize their individual PK to IV C1-INH. All 18 randomized subjects received at least 1 dose of study product in each period and all 18 subjects completed the study.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint

C1-INH functional activity based on modeling and simulation

- The mean modeling-derived steady-state trough C1-INH functional activity at the fourth week was 30.3%, 45.9%, and 80.6% in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. Mean trough C1-INH functional activity at the fourth week was 31.7%, 44.3%, and 80.5% in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. Mean C1-INH functional activity increased with dose per body weight; mean C1-INH functional activity at the fourth week was 26.8%, 39.3%, 63.4%, and 100.4% in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

> **Reviewer Comment**
> Overall, 5 subjects experienced an HAE event: 2/12 (16.7%) 1500 IU subjects, 2/12 (16.7%) 3000 IU subjects and 1/12 (8.3%) 6000 IU subjects. The sample size is too small to determine trough levels predict clinical response.

6.3.11.2 Analyses of Secondary Endpoints

C1-INH functional activity based on observed data

- The mean steady-state trough C1-INH antigen level at the fourth week was 0.06 mg/mL, 0.15 mg/mL, and 0.23 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.
- The mean as-observed increase in C1-INH antigen level from baseline at the fourth week trough was 0.02 mg/mL, 0.05 mg/mL, and 0.14 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU.

C1-INH antigen level based on observed data

- The mean steady-state trough C1-INH antigen level at the fourth week was 0.06 mg/mL, 0.15 mg/mL, and 0.23 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.

- The mean increase in C1-INH antigen level from baseline at the fourth week trough was 0.02 mg/mL, 0.05 mg/mL, and 0.14 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.
- The mean as-observed C1-INH antigen level increased with the dose per body weight; the mean C1-INH antigen level at the fourth week was 0.05 mg/mL, 0.10 mg/mL, 0.20 mg/mL, and 0.28 mg/mL in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

C4 antigen level

- The mean as-observed steady-state trough C4 antigen level at the fourth week was 11.1 mg/dL, 14.1 mg/dL, and 18.4 mg/dL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.
- The mean as-observed increase in C4 antigen level from baseline at the fourth week was 4.3 mg/dL, 5.6 mg/dL, and 9.1 mg/dL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.
- The mean as-observed C4 antigen level increased with the dose per body weight; the mean as-observed C4 antigen level at the fourth week was 11.3 mg/mL, 11.7 mg/mL, 18.0 mg/mL, and 18.2 mg/mL in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

6.3.11.3 Subpopulation Analyses

N/A

6.3.11.4 Dropouts and/or Discontinuations

See 6.3.10.1.3

6.3.11.5 Exploratory and Post Hoc Analyses

Modeling-derived PK/PD parameters (e.g., volume of distribution [V], clearance [CL], SC bioavailability) of C1-INH functional activity for IV Berinert and each CSL830 dosing regimen.

6.3.12 Safety Analyses

6.3.12.1 Methods

The frequency and intensity of AEs and the intensity of local injection site AEs at the injection site (pain, swelling, bruising, and itching) were captured.

6.3.12.2 Overview of Adverse Reactions

Safety events were not related to either absolute CSL830 dose or dose per body weight. Table 21 presents a detailed breakdown of AEs. There was no evidence of a dose-response relationship between the administered dose of CSL830 and intensity of AEs.

Table 21: Subjects Experiencing Treatment-Emergent Adverse Reactions (Safety Population)

		Dosing Regimen				
		Berinert 20 U/kg N=18 (%)	CSL830 1500 IU N=12 (%)	CSL830 3000 IU N=12 (%)	CSL830 6000 IU N=12 (%)	Overall N=18 (%)
TEAE		4 (22.2)	10 (83.3)	8 (66.7)	9 (75.0)	17 (94.4)
Within in 24 hour of study drug		1 (25.0)	8 (80.0)	6 (75.0)	6 (66.7)	14 (82.4)
SAE		1 (25.0)	0	0	1 (11.1)	2 (11.8)
Death		0	0	0	0	0
Leading to discontinuation		0	0	0	0	0
TEAE intensity						
	Severe	0	3 (25.0)	1 (8.3)	1 (8.3)	5 (27.8)
	Moderate	2 (11.1)	5 (41.7)	4 (33.3)	5 (41.7)	8 (44.4)
	Mild	2 (11.1)	2 (16.7)	3 (25.0)	3 (25.0)	4 (22.2)
TEAE causality						
	Related	0	5 (41.7)	1 (8.3)	2 (16.7)	6 (33.3)
	Not related	4 (22.2)	5 (41.7)	7 (58.3)	7 (58.3)	11 (61.1)
HAE events						
Yes		1 (5.6)	2 (16.7)	2 (16.7)	1 (8.3)	5 (27.8)
	Period 1	NA	1 (8.3)	0	0	NA
	Period 2	NA	1 (8.3)	2 (16.7)	1 (8.3)	NA
No		17 (83.3)	10 (83.3)	10 (83.3)	11 (91.7)	13 (72.2)
	Period 1	NA	5 (41.7)	6 (50.0)	6 (50.0)	NA
	Period 2	NA	5 (41.7)	4 (33.3)	5 (41.7)	NA

Adapted from Table 2, CSR 2001, page 126 of 816, July 14, 2013

6.3.12.3 Deaths

No subject died.

6.3.12.4 Nonfatal Serious Adverse Events

NARRATIVES

- **Subject** (b) (6) was a 23 year old female who experienced **syncope** of moderate intensity that was product-unrelated after receiving 1300 U of Berinert. Her medical history included celiac disease, cholecystectomy, asthma, anxiety, nerve pain, edema, allergy to penicillins, cefaclor and amoxicillin, upper respiratory infection (URI), bronchitis, gastroesophageal reflux disease, and smoking.

  On 21 May 2012, from 10:05 to 10:15 she received Berinert P (plasma derived C1 esterase inhibitor) IV at a dose of 1300 IU according to protocol (for characterization of individual PK). On 23 May 2012 she experienced nasal congestion, cough, chest tightness and chest pain, and at 12:45, syncope. She was transported via ambulance to the emergency room. Associated symptoms/findings were back pain, nausea, shortness of breath, tingling all over the body, body aches, mild respiratory distress, breath sounds decreased on left bases, and sinus pain. Computerized tomography with contrast was performed and showed no acute pulmonary embolism or aortic dissection/aneurysm and no acute pathology otherwise. A radiograph chest showed no acute cardiopulmonary disease. Relevant

laboratory values on 23 May 2012 were within the normal range. The subject was discharged on an unreported date and a cardiology evaluation for arrhythmia was recommended. Outcome for syncope, chest tightness, chest pain, back pain, nausea, shortness of breath, tingling all over the body, body aches, mild respiratory distress, mild respiratory distress, breath sounds decreased on left bases, and sinus pain was reported as recovered on the same day (23 May 2012). The nasal congestion (due to cold) was ongoing.

The investigator assessed this event as product-unrelated.

Reviewer Comment
I agree with the investigator's assessment.

- **Subject** (b) (6) was a 27 year old female with a medical history of HAE, allergy to birch, alder and hazel, and anxiety state who experienced **hypovolemic shock** of severe intensity.

  On 12 November 2012, after receiving CSL830 6000 IU treatment in Period 2 at around 13:00, she experienced an increase of abdominal pain and nausea. At 13:25, she received a 500 IU intravenous dose of Berinert P (plasma derived C1 esterase inhibitor; batch no. not reported) with a slight improvement noted. At 13:50 she experienced increasing nausea, dizziness, and had a brief episode of hypotension lasting approximately 8 to10 seconds. A normal saline bolus was administered and she recovered, with a blood pressure of 90/60 mmHg and pulse of 60 bpm. At 14:05, the subject felt better and had no abdominal pain and no nausea. She was hospitalized on the same day and discharged the next day.

  The differential diagnosis for anaphylactic reaction versus syncope favored the latter based on the following set of signs and symptoms typical for syncope: (a) very small decrease in blood pressure during the event (from 100/70 mmHg to 90/60 mmHg); (b) normal pulse of 60-70 bpm during the event; (c) increasing nausea (probably associated with an abdominal HAE attack) and dizziness without feelings of impending doom and agitation prior to event; (d) normal breathing without signs of sneezing, coughing, wheezing, or labored breathing; (e) rapid recovery on treatment with normal saline IV and resolution of abdominal pain and nausea within 10 minutes after the event.

  The investigator assessed this event as product-unrelated.

  Reviewer Comment
  I agree with the investigator's assessment. There is no evidence for an allergic reaction or an infusion reaction. The patient tolerated subsequent infusions without any problems.

6.3.12.5 Adverse Events of Special Interest (AESI)

No AESI was reported. No risk for deep vein thrombosis was identified based on the clinical model scoring system, which resulted in risk assessment scores < 1 at all time points assessed.

6.3.12.6 Clinical Test Results

No safety issues were observed with laboratory parameters in the hematology, biochemistry, and coagulation laboratory groups.

The presence of anti-C1-INH antibodies (including inhibitory anti-C1-INH antibodies) was assessed by the central laboratory from samples taken at the screening visit, at Week 1 of Dosing Period 2, and at the exit visit. C1-INH antibodies were detected for 7/18 subjects during the study; however, the presence of C1-INH antibodies was not associated with inhibition of C1-INH activity. There was no apparent relationship between the dose of CSL830 administered and the presence of C1-INH antibodies.

No changes in serology results for human immunodeficiency virus (HIV), Hepatitis A virus (HAV), Hepatitis B surface (HBs) and Hepatitis B core (HBc), or Hepatitis C virus (HCV) from screening to exit were observed. Although a few positive results were detected at the exit visit and not baseline, based on all serology and polymerase chain reaction (PCR) results, there was no evidence of new viral infections.

No clinically significant abnormalities in vital signs and body temperature, and no differences related to dose were observed.
Insert text here

6.3.13 Study Summary and Conclusions

The doses of CSL830 (40 IU/kg and 60 IU/kg) used in Study 3001 were selected based on the results of Study 2001. SC administration of CSL830 in Study 2001 increased plasma C1-INH functional activity to clinically relevant levels in a dose-dependent manner: 40 IU/kg (equivalent to 3000 IU for a 75 kg person) twice per week achieved a mean steady-state trough C1-INH functional activity of approximately ≥ 40%, a physiologic target that may be associated with prevention of HAE attacks; 60 IU/kg (equivalent to 4500 IU for a 75 kg person) achieved a mean steady-state trough C1-INH functional activity of approximately 60%. Similar changes to C1-INH functional activity were observed for C1-INH antigen levels. For C4 antigen levels, all 3 CSL830 dosing regimens (1500, 3000 and 4500 IU) resulted in levels that were within the normal range. The influence of body weight was investigated and the C1-INH functional activity, C1-INH antigen level and C4 antigen level increased with the CSL830 dose per body weight.

Subcutaneous administration of CSL830 up to 6000 IU was tolerated with local injection site events. Adverse reactions were not related to either absolute dose or dose per body weight. There were no deaths, no withdrawals due to AEs, no thromboembolic event (TEEs), and no SAEs related to CSL830.

Inhibitory auto-antibodies to C1-INH did not develop in any of the subjects in the study.

Subcutaneous administration of the 3 CSL830 dosing regimens was safe and well tolerated. Functional levels of C1-INH activity and levels of C1-INH antigen and C4 antigen were achieved with each dosing regimen.

6.4 Trial #: CSL830_1001
An Open-label, Cross-over, Dose-ranging Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of the Subcutaneous Administration of a Human Plasma-derived C1-esterase Inhibitor in Subjects with Hereditary Angioedema

6.4.1 Objectives
Primary: To assess the safety of IV CSL830 ((b) (4) presentation of Berinert (CE1145)

Secondary: To determine the relative bioavailability (area under the plasma concentration-time curve extrapolated to infinity [AUC0-inf], observed maximum plasma concentration [Cmax]) of IV CSL830 compared to IV Berinert (CE1145).

6.4.2 Design Overview
Phase 1, randomized, double-blind, single-center, cross-over study to evaluate the safety, relative bioavailability, and PK of two presentations of C1-esterase inhibitor (C1-INH) administered intravenously.

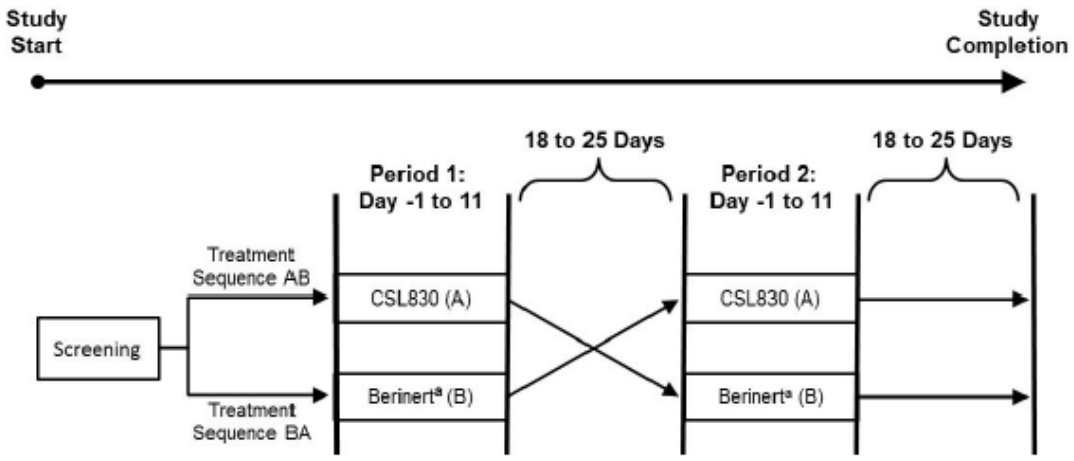
6.4.3 Population
Healthy eligible male and female subjects (N=-16)

6.4.4 Study Treatments or Agents Mandated by the Protocol
Subjects were randomized to receive the following two presentations of Berinert (CE1145):

- A single IV bolus dose of CSL830 (a (b) (4) presentation of Berinert [CE1145]) – 1,500 international units (IU)
- A single IV infused dose of CE1145 (the currently marketed presentation of Berinert) – 1,500 IU

These products were administered in two different treatment sequences (Period 1, Period 2) using a cross-over design:

- Sequence AB: Single 1,500 IU dose of CSL830 x Single 1,500 IU dose of Berinert
- Sequence BA: Single 1,500 IU dose of Berinert x Single 1,500 IU dose of CSL830



[a]Berinert is the currently marketed presentation of CI-INH concentrate, CE1145
AB = CSL830 - Berinert; BA = Berinert - CSL830

Figure 7: Study schematic showing how subjects were randomly allocated to two treatment sequences (CSL830 / Berinert and Berinert / CSL830) for study period 1 and crossed-over for study period 2.
Source: Figure 9-1, CSR 1001, page 20 of 109, November 25, 2013

6.4.6 Sites and Centers

Protocol CSL830_1001 **Investigator List**	
Site Address PAREXEL International GmbH Early Phase Clinical Unit Berlin Klinikum Westend – Haus 17 Spandauer Damm 130 14050 Berlin, Germany	
Role	**Name**
Principal Investigator	Dr. Georg Golor
Sub-Investigators	Dr. Sara Armani Dr. José Banké-Bochita Dr. Astrid Breitschaft Dr. Steffen Haffner Dr. Anke Gauillard Dr. Rüdiger Kornberger Dr. Simone Kerner Dr. Francois Mummert Dr. Alla Radicke Dr. Kathrin Reseski
Unblinded Site Staff *	(b) (6)

* To maintain the blinding, all investigational medicinal products were prepared and administered by unblinded site staff who did not participate in subject assessment or any other study activities.

Source: Description of Investigators and Sites, Section 5.3.3.1, page 1 of 50, November 25, 2013

6.4.7 Surveillance/Monitoring

On Day -1 of Study Period 1 and Study Period 2, eligible subjects underwent baseline safety assessments. On Day 1 of Study Period 1 and Study Period 2 subjects were administered blinded IV CSL830 in one Study Period and IV Berinert (CE1145) in the other Study Period (i.e., administration sequence AB or BA), according to the randomization schedule. To maintain the study blind, CSL830 and Berinert (CE1145) were administered using a double-dummy strategy.

After product administration, subjects attended follow-up visits on Days 2, 3, 5, 7, 9, and 11. A wash out period of 18 to 25 days separated Study Period 1 and Study Period 2. An End of Study visit was conducted 18 to 25 days after completion of Period 2 for final safety and PK assessments. During the study, assessments were conducted to evaluate safety and PK parameters. Safety was evaluated by continuous observation of AEs. Other safety assessments included vital signs, physical examination, electrocardiogram [ECG],

laboratory assessments (hematology, biochemistry, coagulation / thrombotic screening, quantitative D-dimer, urinalysis, viral safety, and anti-INH antibodies), risk assessment for deep vein thrombosis (DVT) and pulmonary embolism (PE), and concomitant medication usage. In each period, 1 pre-dose and 14 post-dose samples were collected from each subject. All PK assessments were based on plasma C1-INH concentrations and functional activity measurements

6.4.8 Endpoints and Criteria for Study Success
Primary

- Incidence of AEs within 24 hours of the CSL830 injection

Secondary

- Incidence of AEs within 10 days (240 hours) of the CSL830 injection
- Relative bioavailability in terms of Cmax and AUC_{0-inf} of CSL830 *vs.* Berinert (CE1145).

Exploratory

- Incidence of AEs within 24 hours and within 10 days (240 hours) of the Berinert (CE1145) injection.
- PK parameters, (area under the plasma concentration-time curve to the last quantifiable concentration [AUC_{0-last}], time to observed maximum plasma concentration C_{max} [T_{max}], volume of distribution based on the terminal phase [Vd], clearance [CL], apparent terminal elimination half-life
- [$T_{1/2}$]) for CSL830 and Berinert (CE1145).

6.4.9 Statistical Considerations & Statistical Analysis Plan
The sample size was calculated so that AEs with a population incidence of 15% had a high likelihood of being observed in at least 1 subject. With 16 subjects, the probability to observe at least 1 AE (with a population incidence rate of 15%) is 93%. Allowing for a 10% drop-out rate, with a sample size of 14 subjects, this probability decreases to 90%.

All AEs were summarized by counts and percentages and by severity, relationship to investigative product and seriousness.

Relative bioavailability in terms of C_{max}, AUC_{0-inf} and AUC_{0-last} of CSL830 versus Berinert (CE1145) was calculated (where possible) using non-zero log-transformed data for these parameters for an analysis of variance (ANOVA) with the treatment sequence, treatment period, and treatment as fixed factors and subject nested within sequence as random term.

The PK endpoints (based on C1-INH antigen concentrations and functional activity levels) were summarized by total number (n), arithmetic mean, standard deviation (SD), 95% confidence intervals (CIs), median, the 25% and 75% quartiles, minimum (min), maximum (max), geometric mean and the related 90% CIs. The geometric means ratios between CSL830 and Berinert (CE1145) were calculated for all PK variables.

6.4.10.1 Populations Enrolled/Analyzed
A total of 16 subjects were planned for enrollment, and 16 subjects were enrolled. All subjects were analyzed for safety, but only 15 subjects were included the PK analyses.

6.4.10.1.1 Demographics
The majority of subjects were male (11/16; 68.8%) and all were White (16/16; 100.0%); median age was 35.0 years and median body mass index was 23.90 kg/m^2.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All products were administered by study staff. The date and time of administration were recorded in the eCRF. Drug accountability was also performed to ensure treatment compliance

6.4.10.1.3 Subject Disposition
All 16 subjects were administered a single dose of 1,500 IU Berinert (CE1145) and 15 subjects were administered a single dose of 1,500 IU CSL830 resulting in a total of 31 subject exposures to IMP. One female subject (0115; randomized to treatment sequence BA) was discontinued from the study following treatment with Berinert (CE1145) in Period 1.

6.4.11 Efficacy Analyses
N/A

6.4.11.1 Analyses of Primary Endpoint
Adverse Events within 24 hours
There were no AEs reported.

6.4.11.2 Analyses of Secondary Endpoints
Adverse Events within 10 days
There were 6 AEs reported within 10 days of CSL830 administration in 5/15 (33.3%) subjects. Of the 6 AEs, nasopharyngitis was the most frequently reported event (4 events). All events were either mild or moderate in severity, none was causally related to product and all events were reported as recovered / resolved at the completion of the study.

The exploratory safety endpoint for the study was the incidence of AEs within 24 hours and within 10 days (240 hours) of Berinert (CE1145) administration.

- There was one AE in one subject (1/16; 6.3%) reported within 24 hours after the administration of Berinert (CE1145). This event, nasopharyngitis, occurred during Period 2 of product administration. The event was assessed as being of moderate severity and not causally related to Berinert (CE1145); the event was reported as recovered / resolved at the completion of the study.
- There were 4 AEs reported within 10 days of Berinert (CE1145) administration in 3/16 (18.8%) subjects. Of the 4 TEAEs reported during the 10-day period after Berinert (CE1145) administration, nasopharyngitis was the most frequently reported TEAE (2 events). All events were either mild or moderate in severity,

none was causally related and all events were reported as recovered / resolved at the completion of the study.

Pharmacokinetic Results

C1-INH antigen concentration

Table 22 shows that after single IV administrations of either 1,500 IU CSL830 or Berinert (CE1145) to healthy volunteers, mean uncorrected plasma C1-INH antigen concentrations over time were very similar between subjects. There was a rapid increase in C1-INH antigen concentration followed by a slow decline over time.

C1-INH functional activity

C1-INH functional activity plasma values were more variable between subjects than for C1-INH antigen. However, the time course profile for C1-INH functional activity was similar to that of C1-INH antigen, with a rapid increase in plasma C1-INH functional activity after CSL830 or Berinert (CE1145) administration, followed by a slow decline over time.

Table 22: PK Parameters for C1-INH Antigen and Functional Activity (PK Population)

Parameter	C1-INH Antigen			C1-INH Functional Activity		
	Units	CSL830 N=15	Berinert N=15	Units	CLS830 N=15	Berinert N=15
			Uncorrected for Baseline			
C_{max}	mg/mL			%		
N		15	15		15	
Mean (SD)		0.3 (0.02)	0.3 (0.02)		171.5 (38.4)	167.9 (26.0)
$AUC_{0\text{-}last}$	h*mg/mL			h*mg/mL		
N		15	15		15	15
Mean (SD		57.8 (4.9)	56.5 (4.3)		29,116 (6181.2)	27,423 (3762.2)
			Corrected for Baseline			
C_{max}	mg/mL			%		
N		15	15		15	15
Mean (SD)		0.1 (0.03)	0.1 (0.02)		73.9 (46.7)	59.9 (16.6)
$AUC_{0\text{-}last}$	h*mg/mL			h*%		
N		15	15		15	15
Mean (SD		7.9 (3.2)	7.3 (3.1)		6702 (7233.1)	3839 (3778.8)

Adapted from Table 14.4.3, page 73 of 306, CSR 1001, September 9, 2013

6.4.11.3 Subpopulation Analyses

N/A

6.4.11.4 Dropouts and/or Discontinuations

See 6.4.10.1.3

6.4.11.5 Exploratory and Post Hoc Analyses

See 6.4.11.1.

6.4.12 Safety Analyses

6.4.12.1 Methods

On Day -1 of Study Period 1 and Study Period 2, eligible subjects underwent baseline safety assessments. On Day 1 of Study Period 1 and Study Period 2, subjects were administered blinded IV CSL830 in one Study Period and IV Berinert (CE1145) in the other Study Period (i.e., administration sequence AB or BA), according to the randomization schedule. To maintain the study blind, CSL830 and Berinert (CE1145) were administered using a double-dummy strategy.

After investigational product administration in each Study Period, subjects attended follow-up visits on Days 2, 3, 5, 7, 9, and 11. A wash out period of 18 to 25 days separated Study Period 1 and Study Period 2. An End of Study visit was conducted 18 to 25 days after completion of Period 2 for final safety assessments.

During the study, assessments were conducted to evaluate safety, which was evaluated by continuous observation of AEs. Other safety assessments included vital signs, physical examination, electrocardiogram [ECG], laboratory assessments (hematology, biochemistry, coagulation / thrombotic screening, quantitative D-dimer, urinalysis, viral safety, and anti-INH antibodies), risk assessment for deep vein thrombosis (DVT) and pulmonary embolism (PE), and concomitant medication usage. In each period, 1 pre-dose and 14 post-dose samples were collected from each subject. All PK assessments were based on plasma C1-INH concentrations and functional activity measurements.

6.4.12.2 Overview of Adverse Events
See 6.4.11.2.

6.4.12.3 Deaths
No subject died.

6.4.12.4 Nonfatal Serious Adverse Events
No nonfatal SAEs were reported.

6.4.12.5 Adverse Events of Special Interest (AESI)
No AESI were reported.

6.4.12.6 Clinical Test Results
Subjects administered CSL830 or Berinert (CE1145) did not experience any clinically significant abnormalities in laboratory parameters, viral safety, vital signs, physical examination, or ECG findings. There were no increases in risk factors for PE or DVT for any subject administered CSL830 or Berinert (CE1145) and no anti-C1-INH antibodies (including inhibitory antibodies) were detected in any subject.

6.4.13 Study Summary and Conclusions
CSL830 demonstrated a good safety profile, with similar safety and PK characteristics to Berinert when administered to healthy volunteers under the conditions of the study.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Prophylaxis of HAE

7.1.1 Methods of Integration

Justification for pooling data from Study 3001 and Study 3002 is based on the fact that approximately half of the subjects randomized in Study 3002 participated in Study 3001 (64/126, 50.8%) as well as the following additional factors.

- Demographic and baseline characteristics of subjects were similar. Both study populations consisted of male or female subjects with a biochemically confirmed diagnosis of HAE type I or II. The minimum age criterion was 12 years in Study 3001 and 6 years in Study 3002.
- The majority of subjects in both studies had HAE type I
- Subjects in both studies must have experienced ≥ 4 HAE attacks over a consecutive 2-month period within the 3 months before the Screening Visit. In Study 3001, subjects also must have experienced ≥ 1 HAE attack during the first 2 weeks of the Run-in Period or ≥ 2 HAE attacks during any consecutive 4-week period of the Run-in Period to be eligible for randomization.
- In Study 3001, the most commonly reported medical history events were in the system organ classes of Respiratory, Thoracic and Mediastinal Disorders (31.1% of all subjects), Nervous System Disorders (30.0%), and Musculoskeletal and Connective Tissue Disorders (26.7%). In Study 3002, the most commonly reported medical history events were in the system organ classes of Respiratory, Thoracic and Mediastinal Disorders (28.6% of all subjects), Musculoskeletal and Connective Tissue Disorders (25.4%), and General Disorders and Administration Site Conditions (24.6%).

7.1.2 Demographics and Baseline Characteristics

Table 23 presents demographic data from the pooled phase 3 studies.

As noted in 6.1 (Study 3001), 66.7% of subjects were female and 93.3% of subjects were White, whereas in Study 3002, 60.3% of subjects were female and 96.0% of subjects were White. Median age was 40 years in Study 3001 and 41 years in Study 3002. The youngest subject enrolled was 12 years old in Study 3001 and 8 years old in Study 3002. A total of 12 pediatric subjects (3 subjects < 12 years old and 9 subjects 12 to 17 years old) and 10 subjects ≥ 65 years old were randomized and treated in the 2 studies.

Table 23: Demographics: Pooled Data from Studies 3001 and 3002 (Safety Population)

	40 IU/kg (N=91)	60 IU/kg (N=98)	≥40 IU/kg (N=148)*	Combined Placebo (N=86)
Age in years, mean (SD)	40.7	39.3 (15.6)	39.9 (15.5)	40.0 (14.9)
<12 years old	2	1	3	0
12 to <17 years	5	7	8	6
17 to <65 years	80	81	127	73
Sex (%)				
Female	54 (59.3)	60 (61.2)	93 (62.8)	56 (65.1)
Male	37 (40.7)	38 (38.8)	55 (37.2)	30 (34.9)
Race				
White	84 (92.3)	94 (95.9)	141 (95.3)	80 (93.0)
Black / African American	4 (4.4)	2 (2.0)	4 (2.7)	4 (4.7)
Asian	1 (1.1)	1 (1.0)	1 (0.7)	1 (1.2)
Other	2 (2.2)	1 (1.0)	2 (1.4)	1 (1.2)

*The number of subjects who received at least 1 dose of CSL830 ≥ 40 IU/kg is not the sum of the subjects in the 40 IU/kg and 60 IU/kg CLS830 columns as it was possible for subjects to receive both doses across the 2 studies or within Study 3002.

Adapted from Table 14.1.2.1, CSR 3001, page 200 of 3005, May 2, 2016 and Table 14.1.2.2, CSR 3002, page 147 of 1155, April 15, 2016

Reviewer Comment

It is notable that less than 5% of subjects were non-White. In retrospect, the protocol could have prespecified a minimum threshold for number of African American and Asian subjects to be enrolled.

7.1.3 Subject Disposition

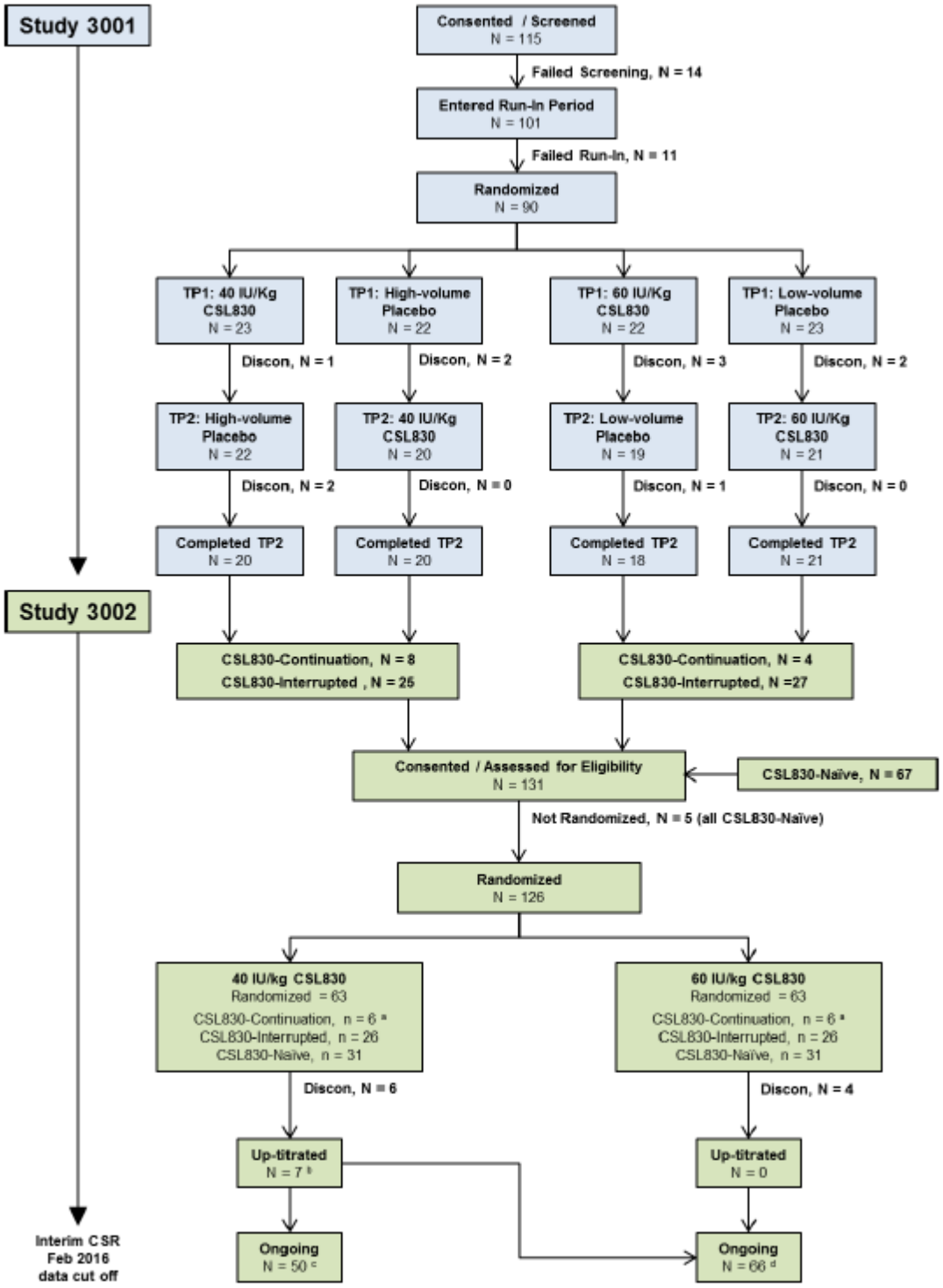


Figure 8: Subject disposition for pooled phase 3 studies.
Source: Figure 3, Summary of clinical efficacy, page 29 of 46, May17, 2016

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of Study 3001 was the time-normalized number of HAE attacks, whereas this endpoint was defined as an exploratory efficacy endpoint in Study 3002. Table 24 shows that in addition to demonstration of a treatment effect, median number of HAE attacks was lower in Study 3002 (0.1, 0.0) than in Study 3001 (0.3, 0.3) for both the 40 and 60 IU/kg dose cohorts.

Table 24: Time-normalized Number of HAE Attacks (Number/Month) by Treatment Cohort

	Study 3001				Study 3002	
	40 IU/kg CSL830	**Placebo**	**60 IU/kg CSL830**	**Placebo**	**40 IU/kg CSL830**	**60 IU/kg CSL830**
No. of subjects	43	44	43	42	63	63
Mean (SD)	1.2 (2.3)	3.6 (2.1)	0.5 (0.7)	4.0 (2.3)	0.4 (0.6)	0.4 (0.7)
Min, Max	0.0, 12.5	0.0, 8.9	0.0, 3.1	0.6, 11.3	0.0, 3.0	0.00, 3.6
Median	0.3	3.8	0.3	3.8	0.1	0.0

Adapted from Table 5 and Table 6, Summary of Clinical Efficacy, pages 32 and 34 of 46, May 17, 2016

Reviewer Comment

Given that approximately 50% of Study 3001 subjects subsequently enrolled in Study 3002, it is uncertain why there was such a large reduction in time-normalized number of HAE attacks among Study 3002 subjects (median: 0.1 *vs.* 0.3, Study 3002 *vs.* Study 3001, respectively). One possibility is that the duration of exposure to CSL830 in Study 3002 was much longer than in Study 3001, resulting in gradual accumulation of CSL830 in tissues. Given an upper limit for elimination half-life of 250 h (Table 2, Clinical Overview, page 20 of 48, October 12, 2016), it is plausible this phenomenon accounted for the difference, despite a mean elimination half-life of 68.7 h.

7.1.5 Analysis of Secondary Endpoints

Percent of Responders

Study 3001 subjects with a ≥ 50% reduction in attack rate were classified as responders. "Success" was defined *a priori* as a lower limit of >33% (lower limit, 95% confidence interval) for the observed responder rate on the combined active treatments. As shown in Table 25, the percent of responders (95% CI) with a ≥ 50% reduction in the time-normalized number of HAE attacks on CSL830 relative to placebo was 82.9% (73.4%, 89.5%), i.e., success was declared.

Table 25: Percent Reduction of ≥50% in Time-normalized Number of HAE Attacks by Treatment

	40 IU/kg	**60 IU/kg**	**≥40 IU/kg**
No. of subjects	42	40	82
Responder, % (N)	76.2 (32)	90 (36)	83 (68)
95% Wilson CI	(61.5, 86.5)	(76.9, 96.0)	(73.4, 89.5)
Difference in % of Responders			
60 IU/kg — 40 IU/kg (%)		13.8	-
95% Wilson CI		(-2.8, 29.7)	-

Adapted from Table 7, Summary of Clinical Efficacy, page 35 of 46, May 17, 2016

Study 3002 is not designed to capture responders..

Time-normalized Number of Uses of Rescue Medication
As depicted in Table 26, twice per week SC doses of 40 IU/kg or 60 IU/kg CSL830 in Study 3001 reduced the use of rescue medication relative to placebo.

Table 26: Time-normalized Number of Uses of Rescue Medication (Number/Month) by Treatment

	40 IU/kg Treatment Sequences (N=45)		**60 IU/kg Treatment Sequences (N=45)**	
	CSL830	**Placebo**	**CSL830**	**Placebo**
No. of subjects	43	44	43	42
Mean (SD)	1.2 (2.5)	5.5 (10.8)	0.2 (0.5)	3.6 (3.0)
Min, Max	0.0, 13.3	0.0, 73.1	0.0, 2.8	0.0, 13.4
Treatment difference (within-subjects)	**40 IU/kg — High-volume Placebo**		**60 IU/kg — Low-volume Placebo**	
LS Mean (95% CI)	-4.4 (-8.0, -0.8)		-3.6 (-4.5, -2.6)	
Nominal p-value	0.018		<0.001	
Treatment difference (between subjects)	**60 IU/kg — 40 IU/kg**			
LS Mean (95% CI)	-0.8 (-2.3, 0.7)			
Nominal p-value	0.310			

Adapted from Table 9, Summary of Clinical Efficacy, page 38 of 46, May 17, 2016

Study 3002 is not designed to capture uses of rescue medication.

7.1.6 Other Endpoints (Exploratory)

Severity of HAE Attacks
In Study 3001, the investigator graded the severity of each HAE attack as Mild = 1, Moderate = 2, or Severe = 3 in a blinded manner based on the intensity of the most severe symptom. The average severity of HAE attacks was lower on CSL830 relative to placebo.

Of the 45 subjects randomized to a 40 IU/kg CSL830 treatment sequence, 9 (20.0%) subjects on 40 IU/kg CSL830 had at least 1 severe HAE attack compared with 33 (73.3%) subjects on high-volume placebo. Of the 45 subjects randomized to a 60 IU/kg CSL830 treatment sequence, 4 (8.9%) subjects on 60 IU/kg CSL830 had at least 1 severe HAE attack compared with 31 (68.9%) subjects on low-volume placebo. Overall, 13 subjects had a total of 52 severe HAE attacks on CSL830, and 64 subjects had a total of 252 severe HAE attacks on placebo.

Of 34 subjects in the 40 IU/kg CSL830 treatment sequences who had a response of “none,” “poor,” or “fair” on high-volume placebo, 25 (73.5%) had a response of “good” or “excellent” on 40 IU/kg CSL830.

Of 34 subjects in the 60 IU/kg CSL830 treatment sequences who had a response of "none," "poor," or "fair" on low-volume placebo, 33 (97.1%) had a response of "good" or "excellent" on 60 IU/kg CSL830.

Global Assessments of Therapeutic Response
Of the 45 subjects randomized to a 40 IU/kg CSL830 treatment sequence, a response of "excellent" was reported for 60.0% of subjects on 40 IU/kg CSL830 and 2.2% of subjects on high-volume placebo. A response of "good or excellent" was reported for 71.1% of subjects on 40 IU/kg CSL830 and 13.3% of subjects on high-volume placebo.

Of the 45 subjects randomized to a 60 IU/kg CSL830 treatment sequence, a response of "excellent" was reported for 68.9% of subjects on 60 IU/kg CSL830 and 4.4% of subjects on low-volume placebo. A response of "good or excellent" was reported for 88.9% of subjects on 60 IU/kg CSL830 and 11.1% of subjects on low-volume placebo.

Reduction to Less Than 1 HAE Attack per 4-Week Period
In Study 3001, a higher percentage of subjects on 60 IU/kg (71.1%) than on 40 IU/kg (53.3%) had a reduction from ≥ 1 HAE attack per 4-week period on placebo to < 1 HAE attack per 4-week period on CSL830.

Of the 45 subjects randomized to a 40 IU/kg CSL830 treatment sequence, 28 (62.2%) subjects on 40 IU/kg CSL830 had < 1 HAE attack per 4-week period compared with 5 (11.1%) subjects on high-volume placebo. Of the 45 subjects randomized to a 60 IU/kg CSL830 treatment sequence, 37 (82.2%) subjects on 60 IU/kg CSL830 had < 1 HAE attack per 4-week period compared with 3 (6.7%) subjects on low-volume placebo.

Time-normalized Number of Days of HAE Symptoms
In Study 3001, twice per week SC doses of 40 IU/kg or 60 IU/kg CSL830 reduced the time-normalized total number of days of HAE symptoms relative to placebo.

For subjects randomized to a 40 IU/kg CSL830 treatment sequence, the mean (SD) time-normalized total number of days of HAE symptoms was 1.57 (2.644) days per month on 40 IU/kg CSL830 and 7.00 (5.752) days per month on high-volume placebo. For subjects randomized to a 60 IU/kg CSL830 treatment sequence, the mean (SD) time-normalized total number of days of HAE symptoms was 1.61 (4.388) days per month on 60 IU/kg CSL830 and 7.51 (5.588) days per month on low-volume placebo.

Subject Reported Outcome Measures
The pre-specified analysis of subject reported outcomes in Study 3001 compared the effect of 40 IU/kg CSL830 vs high-volume placebo and 60 IU/kg CSL830 vs low-volume placebo on the EQ-5D, HADS, TSQM, and WPAI measures. For each measure, the comparison was based on the Week 14 Visit within-subject median change scores with 99.787% CIs.

The Screening Visit (baseline) scores for the 4 TSQM dimensions and WPAI Presentism, Work Productivity Loss, and Activity Impairment indicated some deficits in treatment satisfaction and work / activity impairment, and room for improvement with effective

treatment. The pre-specified treatment comparisons (median difference [99.787% CI]) showed that the 40 IU/kg dose had a large effect on TSQM Effectiveness compared with high-volume placebo (38.89 [11.11, 94.44]). Similar large effects were observed for 60 IU/kg on Effectiveness (27.78 [0.00, 77.78]) and for 40 IU/kg (36.11 [0.00, 94.44]) and 60 IU/kg (22.22 [0.00, 55.56]) on TSQM Overall Satisfaction. Results of post-hoc analyses confirm and extend the results of the pre-specified analyses by showing evidence of treatment effects in favor of CSL830 for TSQM Effectiveness, TSQM Overall Satisfaction, WPAI Work Productivity Loss, and WPAI Activity Impairment in comparison with placebo treatment.

The above findings suggest that routine prophylaxis with SC CSL830 was effective, enabled subjects with HAE to be more active and productive, and increased overall satisfaction with treatment.

7.1.7 Subpopulations

In Study 3001, subgroup analyses of the primary endpoint and the secondary percentage of responders endpoint were performed by region (US, non-US), sex, race, age class (12 to < 17 years, 17 to < 65 years, ≥ 65 years), use of oral prophylaxis during study, and use of IV C1-INH prophylaxis or oral prophylaxis for ≥ 1 month in the 3 months before Screening. Subgroup analyses included all subjects in the ITT Population. The subgroups of oral prophylaxis use during the study and use of oral antifibrinolytics for ≥ 1 month in the 3 months before Screening contained no subjects.

Subgroup results for the time-normalized number of HAE attacks were similar to the overall analysis results (i.e., the rate of attacks was lower on CSL830 than placebo, and 60 IU/kg had a better treatment effect than 40 IU/kg CSL830.

Subgroup results for the percentage of responders were similar to the overall analysis results (i.e., the percentages of responders were higher on 60 IU/kg than on 40 IU/kg CSL830.

The majority of subjects were White (84/90, 93.3%), which precluded meaningful assessments by race.

Subgroup analyses of the exploratory efficacy endpoint in Study 3002 were not performed.

7.1.8 Persistence of Efficacy

Study 3001 demonstrated the clinical efficacy of routine prophylaxis with SC doses of 40 IU/kg or 60 IU/kg CSL830 twice per week for 16 weeks in 90 subjects with HAE.

As of the 17 May 2016 4-month safety update in ongoing Study 3002, 126 subjects with HAE were treated for a mean duration of 37 weeks (maximum duration of exposure: 58 weeks). Cumulatively, subjects who participated in both studies were exposed to CSL830 for up to 74 weeks. The interim, exploratory efficacy results of open-label Study 3002

support the efficacy of SC CSL830 for routine prophylaxis to prevent HAE attacks, and demonstrate that the effect is maintained over time periods of up to 1 year.

No association was identified between treatment with CSL830 and detection of non-inhibitory anti-CI-INH antibodies, and no inhibitory anti-CI-INH antibodies were detected.

7.1.11 Efficacy Conclusions

- Efficacy results from the double-blind, placebo-controlled Study 3001 support the efficacy of SC CSL830 for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.
- In pivotal Study 3001, a dose-response was observed across efficacy endpoints, with 60 IU/kg consistently showing better efficacy than 40 IU/kg. Since laryngeal HAE attacks are serious and life-threating, the 60 IU/kg twice weekly dosing regimen as proposed in the draft Prescribing Information is the dose that should be approved.
- Interim results from Study 3002 demonstrate that the effect of CSL830 is maintained over time periods of up to 1 year.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

See 6.1.12.1.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The two controlled studies, Study 3001 and 3002, and the dose-finding study, 2001, were used to evaluate safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 27 depicts the duration of exposure within the study population, which were balanced in both studies.

Table 27: Exposure to CSL830: Pooled Data from Studies 3001 and 3002 (Safety Population)

	Exposure (Weeks)			
	40 IU/kg (N=91)	60 IU/kg (N=98)	≥40 IU (N=148)	Combined Placebo (N=86)
		Aggregate Population		
Cumulative Exposure				
Mean (SD)	32.4 (16.2)	32.0 (16.1)	41.1 (16.7)	15.3 (3.3)
Minimum, Maximum	2, 72	1, 72	2, 74	3, 19
Median	30.7	34.7	41.1	16.3
Continuous Exposure				
Mean (SD)	26.2 (12.5)	26.2 (13.0)	33.4 (16.0)	15.3 (3.3)
Minimum, Maximum	2, 57	1, 56	2, 74	3, 19
Median	18.0	17.3	361.	16.3
		12 to <17 years		
	(N=5)	(N=7)	(N=8)	(N=6)
Cumulative Exposure				
Mean (SD)	34.4 (20.5)	27.0 (13.0)	45.1 (18.4)	13.2 (5.0)
Minimum, Maximum	16, 63	16, 51	16, 67	5, 17
Median	28.4	24.3	43.0	15.9
Continuous Exposure				
Mean (SD)	25.3 (13.8)	27.0 (13.0)	39.4 (19.2)	13.2 (5.0)
Minimum, Maximum	16, 48	16, 51	16,67	5, 17
Median	17.0	24.3	39.1	15.9
		17 to <65 years		
	(N=80)	(N=81)	(N=127)	(N=73)
Cumulative Exposure				
Mean (SD)	32.0 (16.0)	32.2 (16.0)	40.7 (16.8)	15.4 (3.1)
Minimum, Maximum	2, 72	1, 72	2, 74	3, 19
Median	30.4	36.1	41.1	16.3
Continuous Exposure				
Mean (SD)	26.5 (12.7)	26.4 (13.3)	33.5 (16.2)	15.4 (3.1)
Minimum, Maximum	2, 57	1, 56	2, 74	3, 19
Median	21.9	17.3	36.1	16.3
		≥65 years		
	(N=4)	(N=9)	(N=10)	(N=7)
Cumulative Exposure				
Mean (SD)	35.1 (23.2)	34.2 (20.4)	44.8 (17.6)	15.9 (3.3)
Minimum, Maximum	15, 63	8, 69	14, 69	9, 19
Median	31.1	33.1	43.6	16.4
Continuous Exposure				
Mean (SD)	16.3 (1.0)	23.7 (12.3)	27.8 (11.9)	15.9 (3.3)
Minimum, Maximum	15, 17	8, 40	14, 47	9, 19
Median	16.5	16.7	27.9	16.4

Adapted from Table 14.1.5.1, CSR 3001, page 368 of 300, May 2, 2016 and Table 14.1.5.2, CSR 3002, page 292 of 1155, April 15, 2016

8.2.3 Categorization of Adverse Reactions

The percentage of subjects experiencing AEs In the pooled population was similar during treatment with 40 IU/kg (73.6%) and 60 IU/kg (70.4%). The annualized rate of AEs was similar for combined active treatments (13.58 events / treatment year) and the combined placebo (13.68 events / treatment year).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Pooled data are subject to revision since Study 3002 is ongoing at this time.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in any study.

8.4.2 Nonfatal Serious Adverse Events

As depicted in Table 28, three subjects in the 40 IU/kg cohort and six subjects in the 60 IU/kg cohort compared with one low-volume placebo and one high-volume placebo subjects, experienced one or more nonfatal SAEs.

Reviewer Comment
All SAEs were product-unrelated. The MI in subject (b) (6), originally adjudicated as product-related (placebo) before the blind was broken, was re-assessed subsequently by the cardiologist as unrelated. I agree with this assessment.

As depicted in Table 29, in Study 2001, 2 SAEs were reported: 1 subject who had received 1300 IU of Berinert treatment (Subject (b) (6); moderate Syncope) and 1 subject on the first day of CSL830 6000 IU (80 IU/kg) treatment in TP2 (Subject (b) (6); severe hypovolemic shock). The 2 SAEs were reported as not related to investigational product and resolved on the same day.

Reviewer Comment
I agree with this assessment.

Table 28: Serious Safety Events in Phase 3 Studies 3001 and 3002 (Safety Population)

Study/TP	Subject ID	Age/Sex	Preferred Term	Start Day/Stop Day	Duration (Days)	Intensity	Causality	Action Taken/Outcome
Low-volume Placebo								
3001/1	(b) (6)	19/F	Syncope	10/10	1	Moderate	Not related	Dose not changed/Recovered
High-volume Placebo								
3001/1	(b) (6)	50/F	Pulmonary embolism	53 / NR	119	Severe	Related	Dose withdrawn/Recovered
CSL830 40 IU/kg								
3001/2	(b) (6)	66/F	Urosepsis	4/6	3	Severe	Not related	Dose not changed/Recovered
3002/2	(b) (6)	66/F	Dehydration Hypokalemia	5/6	2	Severe	Not related	Dose not change/Recovered
3002/2	(b) (6)	54/F	Lymphoma	58/NA	Ongoing	Severe	Not related	Dose not changed/Not resolved
CSL830 60 IU/kg								
3002/2	(b) (6)	47/F	MI	35/39	5	Severe	Not related	Dose withdrawn/Recovered
3002/2	(b) (6)	48/F	Dizziness	89/89	1	Moderate	Not related	Dose interrupted/Recovered
3002/2	(b) (6)	67/M	Pneumonia	158/168	11	Severe	Not related	Dose not changed/Recovered
3002/1	(b) (6)	25/F	Cholelithiasis	18/106	89	Moderate	Not related	Dose not changed/Recovered
				106/107	2	Moderate	Not related	Dose not changed/Recovered
3002/1	(b) (6)	41/F	Diplopia	113/NA	Ongoing	Mild	Not related	Dose not changed/Not resolved
3002/1	(b) (6)	30/F	Depression	74/109	36	Moderate	Not related	Dose not changed/Recovered

NA = not applicable; TP = Treatment Period
Adapted from Listing 16.2.7.4, CSR 3001, page 425 of 449, May 2, 2016 and Listing 16.2.7.4, CSR 3002, page 409 of 431, April 15, 2016

Table 29: SAEs from Study 2001 (Safety Population)

Period/Dose	Subject ID	Age/Sex	Preferred Term	Duration (Days)	Intensity	Causality	Action Taken/ Outcome
Berinert	(b) (6)	23/F	Syncope	1	Moderate	Not related	Dose not changed / Recovered
Period 2 / CSL830 6000 IU	(b) (6)	27/F	Hypovolemic shock	1	Severe	Not related	Dose not changed / Recovered

Adapted from Appendix 16.2, Listing 8.2.5, CSR 2001, page 350 of 352, May 20, 2013

8.4.3 Study Dropouts/Discontinuations

Study 3001: Three subjects had safety events leading to study discontinuation. One 60 IU/kg subject (2.3%) had a related **urticaria** (AR) and 2 subjects (2.3%) on placebo had 2 SAEs, a related **pulmonary embolism** (SAR) and a non-serious, unrelated **hepatic enzyme elevation** AE.

Study 3002: Four subjects had 4 AEs leading to study discontinuation during treatment with CSL830. Three subjects (4.3%) had 3 AEs on 60 IU/kg (an SAE of **acute myocardial infarction**, assessed as not related; a non-serious AE of **arthralgia**, assessed as not related; a non-serious AR of **headache**, assessed as related), and 1 subject (1.6%) had 1 AE on 40 IU/kg (a non-serious AR of **myalgia**, assessed as related).

Pooled phase 3 population: In the pooled phase 3 population, annualized rates of AEs leading to study discontinuation were low and did not show a dose dependency (0.01 events / treatment year on 40 IU/kg; 0.05 events / treatment year on 60 IU/kg; 0.08 events / treatment year on placebo).

Study 2001: No subjects had AEs leading to study discontinuation.

8.4.4 Common Adverse Reactions

In terms of **subjects**: More subjects in the CSL830 cohort than in the placebo cohort experienced local injection site AEs: N=71/148 [48.0%) *vs.*21/86 (24.4%), respectively. A similar imbalance was reported for local injection site ARs: (N=98/148 (66.2%) *vs.* 48/86 (55.8%).

In terms of **events**: The number and rate of ARs/injection for local injection site ARs was higher in the CSL830 cohort than in the placebo cohort: n=1137 and 0.10 *vs.* 212 and 0.09, respectively. A similar imbalance was reported in the number and rate of ARs/injection for local injection site ARs: n=445 and 3.82 *vs.* 13.3 and 5.27.

Table 30 shows that the majority of ARs were of mild intensity in all treatments and the percentage of subjects with severe ARs was similar in both the 40 IU/kg (5.5%) and 60 IU/kg (6.1%) dose cohorts.

Table 30: Summary of Adverse Reactions by Subject by Treatment (Pooled Date from Studies 3001 and 3002 (Safety Population)

	40 IU/kg (N=91)		60 IU/kg (N=98)		≥40 IU/kg (N=148)		Combined Placebo (N=86)	
	N	%	N	%	N	%	N	%
Any TEAE	67	73.6	69	70.4	115	77.7	57	66.3
TEAE Intensity								
Mild	62	68.1	58	59.2	103	69.6	46	53.5
Moderate	30	33.0	35	35.7	60	40.5	24	27.9
Severe	5	5.5	6	6.1	11	7.4	6	7.0
SAE	5	5.5	6	6.1	8	5.4	2	2.3
Related SAE*	0	0	0	0	0	0	1	1.2
TEAEs within 24 h of injection	58	63.7	60	61.2	103	69.6	43	50.0
TEAEs leading to discontinuation	1	1.1	2	2.0	2.0	3	2.0	1
Death	0		0		0		0	
Not recovered/Not resolved	12	13.2	20	20.4	30	20.3	10	11.6
Recovered / resolved	66	72.5	67	68.4	113	76.4	54	62.8
Recovering / resolving	4	4.4	3	3.1	7	4.7	1	1.2

***** There were no SAEs reported as related to CSL830. At the time of the initial interim data cut-off for Study 3002 (February 11, 2016), the single local injection site SAE of acute myocardial infarction reported was assessed by the investigator as related to CSL830. After the interim data cut-off, the investigator's revised assessment was received, indicating that the infarction was not related to CSL830 (cited in the 4-month Safety Update dated October 12, 2016. This event led to study discontinuation.
Adapted from Table 14.3.1.3.1.1, CSR 3001, page 1425 of 3005, May 2, 2016 and Table 14.3.1.3.1.2, CSR 3002, page 347 of 1155, April 15, 2016

8.4.5 Clinical Test Results

Hematology
There were no clinically relevant differences observed over time or between treatments for Study 3001, 3002 or 2001.

Biochemistry
There were no apparent differences of clinical relevance observed over time or across the treatments for Study 3001, 3002 or 2001.

Coagulation
A number of abnormal results were observed during Study 3001 and 3002 but the majority were assessed as not clinically significant in terms of increased thrombotic risk, as HAE patients typically experience abnormal coagulation values for D-dimer, plasmin-α2-antiplasmin (PAP) complex, and prothrombin fragment 1 and 2.

- In Study 3001 there were no differences of clinical relevance observed over time across treatments for fibrinogen and the 2 global coagulations tests, activated partial thromboplastin time and prothrombin international normalized ratio.
- In Study 3002, increases (i.e., moved towards normal) from Baseline were seen for activated partial thromboplastin time in 40 IU/kg and the 60 IU/kg treatment arms. Median increases were similar on 60 IU/kg and 40 IU/kg.
- Prothrombin fragment 1 and 2 concentrations above the normal range were reported at Baseline, with values as high as (b) (4) (the upper limit of quantification of the assay). However, during treatment with CSL830, the

prothrombin fragment 1 and 2 concentrations decreased (i.e., moved towards normal), and the decreases were greater on 60 IU/kg than on 40 IU/kg. This decrease was not observed during treatment with placebo.

- D-dimer concentrations above the normal range were reported at Baseline in subjects during Study 3001 and 3002. During treatment with CSL830, D-dimer concentrations decreased. In contrast, D-dimer concentrations similar to values reported at Baseline were seen during treatment with placebo. In Study 2001, concentrations of D-dimer above the normal range were reported at baseline. Mean (SD) changes in D-dimer from Screening to the Exit Visit ranged from -0.464 (1.742) mg FEU/L (fibrinogen equivalent units; normal: <0.5 ug/mL FEU) to 0.929 (7.466) mg FEU/L across the 3 CSL830 dosing regimens, respectively. A few outliers skewed mean levels, so some summary results are above the reference range. A higher proportion of subjects treated with the CSL 1500 IU (20 IU/kg) dosing regimen (16.7% [2 / 12]) experienced shifts from normal to high D-dimer values from Screening to the Exit Visit compared to the 3000 IU (40 IU/kg) and 6000 IU (80 IU/kg) dosing regimens (8.3% [1 / 12] each).
- Plasmin-α2-antiplasmin (PAP) levels were only measured in Study 3001, and were elevated at Baseline. The PAP levels remained elevated throughout the study during treatment with placebo whereas normalization of PAP complexes was seen on CSL830, with a greater effect on 60 IU/kg than 40 IU/kg.
- Two shifts in coagulation parameters (Blood Fibrinogen Decreased and Fibrin D-dimer Increased) were reported during Study 3001.
    - Blood Fibrinogen Decreased was reported for Subject (b) (6) while on 40 IU/kg CSL830. The event was moderate in intensity and was reported as not related to 40 IU/kg CSL830. The outcome of the event was recovering / resolving at the time of this report.
    - Fibrin D-dimer Increased was reported for Subject (b) (6) while on high-volume placebo. The event was moderate in intensity and was reported as related to high-volume placebo. The outcome of the event was recovered / resolved. No other AEs associated with coagulation parameters were reported. No clinically relevant changes over time were observed for coagulation parameters during Study 2001.

  No clinically relevant changes over time were observed for coagulation parameters during Study 2001.

Antibodies to C1-esterase Inhibitor

No inhibitory antibodies to CI-INH were detected in any subject during Study 3001. There was no identified relationship between treatment with CSL830 and the formation of non-inhibitory antibodies during the study. Similarly, no inhibitory antibodies to C1-INH were detected in any subject during Study 3002 at the time of the data cut-off. There was no identified relationship between treatment with CSL830 and the formation of non-inhibitory antibodies. No inhibitory antibodies to C1-INH were detected in any subject during Study 2001. There was no identified relationship between the dose of CSL830 administered and the presence of non-inhibitory antibodies to C1-INH.

8.4.6 Local injection site Adverse Reactions

Table 31 shows that the proportion of pooled CSL830 subjects (85%) who experienced local injection site AEs (66.2%) compared with the number of subjects who experienced any AE (77.7%) was identical (85%) to the proportion of placebo subjects (84%) who experienced these events (55.8%) compared with the total number of AEs (66.3%). The majority of local injection site AEs was reported as unrelated, mild in severity, and with an outcome of recovered / resolved.

Table 31: Local injection site Adverse Reactions Reported in ≥5% of Subjects (Pooled Data from Studies 3001 and 3002, Safety Populations)

	40 IU/kg (N=91)		60 IU/kg (N=98)		≥40 IU/kg (N=148)		Combined Placebo (N=86)	
	N	%	N	%	N	%	N	%
Any AE	67	73.6	69	70.4	115	77.7	57	66.3
Local injection site AEs	53	58.2	60	61.2	98	66.2	48	55.8
Nasopharyngitis	10	11.0	21	21.4	30	20.3	6	7.0
Headache	8	8.8	7	7.1	15	10.1	3	3.5
Upper respiratory tract infection	5	5.5	6	6.1	11	7.4	6	7.0
Fatigue	3	3.3	2	2.0	4	2.7	6	7.0
Back pain	4	4.4	3	3.1	7	4.7	5	5.8

Adapted from Table 14.3.1.2.2.1, CSR 3001, page 1343 of 3005, May 2, 2016 and Table 14.3.1.3.2.2, CSR 3002, page 385 of 1155, April 15, 2016

Reviewer Comment

Local injection site ARs occurred in more CSL830 subjects (66.2%) than placebo subjects (55.8%). There was no relationship between CSL830 dose and local injection site events.

8.4.7 Local Reactogenicity[5]

Table 32 shows that the proportion of pooled CSL830 subjects (62%) who experienced local injection site ARs (48.0%) compared with the number of subjects who experienced any AR (77%) was larger than the proportion of placebo subjects (37%) who experienced these events (24.4%) compared with the total number of ARs (66.3).

5 Local reactions subsequent to SC injection are product-related and termed ARs in this memo. The etiology of systemic reactions could be from the product and/or from the disease and thus are termed AEs.

Table 32: Local injection site Adverse Reactions (Preferred Term) Reported in ≥5% of Subjects (Pooled Data from Studies 3001 and 3002, Safety Populations)

	40 IU/kg (N=91)		60 IU/kg (N=98)		≥40 IU/kg (N=148)		Combined Placebo (N=86)	
	N	%	N	%	N	%	N	%
Any AR	67	73.6	69	70.4	115	77.7	57	66.3
Local injection site AEs	40	44.0	38	38.8	71	48.0	21	24.4
Injection site pain	19	20.9	12	12.2	30	20.3	9	10.5
Injection site erythema	15	16.5	17	17.3	29	19.6	13	15.1
Injection site reaction	6	6.6	9	9.2	14	9.5	0	0
Injection site bruising	6	6.6	7	7.1	13	8.8	5	5.8
Injection site induration	7	7.7	6	6.1	12	8.1	2	2.3
Injection site hematoma	8	8.8	3	3.1	10	6.8	1	1.2
Injection site hemorrhage	6	6.6	3	3.1	9	6.1	4	4.7
Injection site edema	6	6.6	0	0	6	4.1	3	3.5

Adapted from Table 14.3.1.2.2.1, CSR 3001, page 1343 of 3005, May 2, 2016 and Table 14.3.1.3.2.2, CSR 3002, page 385 of 1155, April 15, 2016

Reviewer Comment

Local injection site ARs occurred in more CSL830 subjects (48.0%) than placebo (24.4%) subjects, especially injection site pain where the rate was almost twice that of placebo subjects (20.3% *vs.* 10.5%). Most likely due to random variation, the rate of local injection site ARs was slightly higher in the 40 IU/kg cohort than either the 60 IU/kg (38.8%) or placebo (24.4%) cohorts.

8.4.8 Adverse Events of Special Interest

Two TEEs were observed in the pooled phase 3 studies: a pulmonary embolism in Study 3001and an acute myocardial infarction in Study 3002. At the time of reporting, the investigator was blinded and assessed the pulmonary embolism as related to investigational product (i.e., placebo). No other SAEs, including the event of myocardial infarction, were ultimately reported as related to CSL830.

NARRATIVES

- **Subject** (b) (6), a 50-year-old female, experienced an SAE of **pulmonary embolism** during treatment with high-volume placebo in TP1 of Study 3001. The subject was not exposed to CSL830 during the study, and was using Berinert and Firazyr to treat emerging HAE attacks. The event was severe, led to study discontinuation, and had an outcome of recovered / resolved. The subject had a family history of TEEs (father, brother, and sister experiencing TEEs at a similar age). The subject had a history of heavy smoking and was symptomatic before the first administration of the investigational product in Study 3001.
- **Subject** (b) (6), a 47-year-old female, experienced an SAE of **myocardial infarction** during treatment with 60 IU/kg CSL830. At the time of the interim data cut-off for Study 3002, the SAE was reported by the investigator as related to CSL830. However, after the interim data cut-off, the investigator's revised assessment was received that it was not related to CSL830. The cardiologist's evaluation concluded that the cause was likely due to a "spontaneous plaque rupture of an atherosclerotic plaque with associated mild clot formation, rather

than a spontaneous coronary thrombosis". The subject was overweight, was a heavy smoker (> 20 cigarettes / day for years), and had hypercholesterolemia and hypertriglyceridemia. The event led to study discontinuation. The event was graded as severe. The outcome of the event was recovered / resolved.

Reviewer Comment
I concur with the investigator's assessment.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

There was no dose-response noted for AEs.

8.5.2 Time Dependency for Adverse Reactions

The majority of local injection site AEs occurred within 24 hours after injection and then resolved within 24 hours after onset.

8.5.3 Product-Demographic Interactions

In general, there was no pattern in any of the age subgroups that indicated a relevant effect of age on the frequency or rate of AEs. An analysis of AEs by sex was not performed because there is no clinical rationale to expect that there should be a difference in the safety profile of CSL830. An analysis of AEs by race was not performed because most subjects (> 90% in any treatment) in the CSL830 clinical program were White.

8.5.4 Product-Disease Interactions

In the pooled population, 60 / 152 subjects overall had a cumulative study duration of > 1 year, whereas most subjects had a cumulative study duration of ≤ 1 year (92 / 152 subjects). The type, frequency, and rate of AEs reported in the SOCs were generally similar in both subgroups; in the SOCs with differences between the subgroups, no meaningful clinical differences were observed

8.5.5 Product-Product Interactions
Very few subjects used oral prophylaxis for the treatment of HAE attacks, and thus comparison in these subgroups is difficult.

8.5.6 Human Carcinogenicity

Not studied.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

An overdose of CSL830 was not been reported in the clinical studies. As a part of Study 2001, doses of CSL830 up to 6000 IU (i.e., up to 80 IU/kg) were administered to 18 subjects twice weekly for 4 weeks and were well tolerated. Five subjects in this study were exposed to > 80 IU/kg, and 2 of these subjects were exposed to > 100 IU/kg (ie, 104.0 IU/kg and 117.6 IU/kg). No data related to withdrawal or rebound effects are available.

8.5.8 Immunogenicity (Safety)

See 8.4.5.

8.5.9 Person-to-Person Transmission, Shedding
Not studied.

8.6 Safety Conclusions

For the pooled phase 3 population,

- The proportion of subjects experiencing any AE was similar during treatment with 40 IU/kg (73.6%) and 60 IU/kg (70.4%), but higher than during administration of placebo (66.3%)
- Systemic AEs
  - Reported in 66.2% of CSL830 subjects *vs.* 58.8% of placebo subjects
  - Most cases were non-serious, of mild severity, and unrelated to CSL830
- Local injection site ARs
  - Reported in 48.0% of CSL830 subjects *vs.*24.4% of placebo subjects
  - The majority occurred within 24 hours after injection and then resolved within 24 hours after onset
  - Most cases were of mild severity and none was graded as severe, serious or resulting in discontinuation of treatment
  - The most common ARs were Injection Site Pain and Injection Site Erythema
- No product-related TEEs were reported.
- No cases of anaphylaxis were reported.
- No cases of transmission of viral infections (ie, HIV, HBV, or HCV) were reported.
- No inhibitory antibodies to C1-INH were observed.

9. Additional Clinical Issues

9.1 Special Populations

Not studied.

9.1.1 Human Reproduction and Pregnancy Data

Limited data are available related to the use of CSL830 in pregnant women. The only pregnancy reported during the phase 3 studies was for a 19 year old, female (Subject (b) (6)) treated with 60 IU/kg CSL830 in Study 3002. On 27 November 2015 (Day 159), CSL Behring was informed of the subject's pregnancy (confirmed by urine and serum testing). The subject had received CSL830 between 22 June 2015 and 23 November 2015 (Day 1 to 155). A total of 15 doses of CSL830 were administered between 01 October 2015 and 23 November 2015 (Day 102 to 155). The subject was discontinued from the study on 27 November 2015 (Day 159). Her estimated date of delivery was 03 July 2016. The subject will be followed up to assess the outcome of the pregnancy. No other pregnancies were reported in subjects during their participation in the CSL830 clinical program.

9.1.2 Use During Lactation

No data related to the use of CSL830 in lactating women are available

9.1.3 Pediatric Use and PREA Considerations

N/A

9.1.4 Immunocompromised Patients

The number of immunocompromised subjects was too small to make a meaningful conclusion.

9.1.5 Geriatric Use

The number of geriatric subjects was too small to make a meaningful conclusion.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

- The benefit of CSL830 clearly outweighs the risks. ARs were of mild intensity and short duration. No product-related TEEs or cases of anaphylaxis, transmission of viral infections (i.e., HIV, HBV, or HCV) or inhibitory antibodies to C1-INH were reported.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

HAE is a serious and at times, life-threatening condition that can occur without warning. Failure to rapidly and effectively treat laryngeal involvement, in particular, can result in asphyxiation. Effective prophylaxis is preferable to on-demand treatment but long-term therapy is limited to Cinryze, a plasma-derived C1-inhibitor administered intravenously. Even though HAEGARDA also is plasma-derived, subcutaneous administration offers an attractive alternative to patients who dislike the inconvenience of intravenous Cinryze. Patients should be made aware that HAEGARDA can be associated with the class effects as other C1-INH products.

Table 33: Risk-Benefit Analysis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HAE is a serious and potentially life-threatening condition that can occur without warning.	• HAE prophylaxis reduces the incidence of attacks.
Unmet Medical Need	• Therapy (intravenous) is available for prophylaxis (CINRYZE) of HAE in adolescent and adult patients.	• There is not an unmet medical need.
Clinical Benefit	• HAEGARDA prophylaxis therapy reduces the risk of attacks in adolescent and adult patients.	• Twice-weekly prophylaxis therapy is effective in patients who prefer the subcutaneous route of administration.
Risk	• Class effects include hypersensitivity reactions, thromboembolic events and transmission of infectious agents (HAEGARDA is plasma-derived). Injection site reactions (pain and erythema), hypersensitivity, nasopharyngitis and dizziness were the most frequent safety events reported with use of HAEGARDA.	• HAEGARDA prophylaxis is associated with local injection site reactions in approximately 30% of subjects. Other reactions occur less frequently. Adverse reactions are dose-related.
Risk Management	• Patients should be made aware of potential signs/symptoms of serious adverse reactions such as hypersensitivity, thrombosis and transmission of infectious agents, as well as local injection site reactions.	• Monitor for signs of hypersensitivity, thrombosis, infections local injection site reactions.

11.2 Risk-Benefit Summary and Assessment

Clinical benefit associated with subcutaneous C1-INH treatment outweighs risks associated with HAEGARDA and other products in this class.

11.3 Discussion of Regulatory Options

Approval is the most appropriate regulatory action because it provides an option for patients who prefer the convenience of SC administration and can tolerate potential local injection site reactions.

11.4 Recommendations on Regulatory Actions

I recommend approval of the BLA.

11.5 Labeling Review and Recommendations

See annotated PI.

11.6 Recommendations on Postmarketing Actions

None (other than routine surveillance).

Do Not Change Anything Below This Line