BLA Clinical Review Memorandum

Application Type	Efficacy
STN	125606.185
CBER Received Date	November 29. 2019
PDUFA Goal Date	September 28, 2020
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Rosa Sherafat-Kazemzadeh, MD
Review Completion Date / Stamped Date	September 22, 2020 Rosa Sherafat-kazemzadeh -S Digitally signed by Rosa Sherafat kazemzadeh -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=00135 36897 cn=Rosa Sherafat kazemzadeh -S Date: 2020 09 22 18:33:02 04'00'
Supervisory Concurrence	Lei Xu, MD, PhD Lei Xu -S3 Digitally signed by Lei Xu -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lei Xu -S3, 0.9.2342.19200300.100.1.1=2000424164 Date: 2020.09.22 20:37:14 -04'00' Ilan Irony, MD Ilan Irony -S Digitally signed by Ilan Irony -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ilan Irony -S, 0.9.2342.19200300.100.1.1=1300157710 Date: 2020.09.23 08:27:51 -04'00'
Applicant	CSL Behring
Established Name	C1 Esterase Inhibitor Subcutaneous [Human]
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 International Units per kg body weight by subcutaneous injection
Dosing Regimen	Twice weekly (every 3 or 4 days)
Indication(s) and Intended Population(s)	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older
Orphan Designated (Yes/No)	Yes

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GLOSSARY

Adverse Reaction	An adverse event at least possibly related to study medication
BLA	Biologics License Application
C1-INH	C1-esterase inhibitor
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.
IGART	Investigator's Global Assessment of Response to Therapy
MedDRA	Medical Dictionary for Regulatory Activities
PopPK	Population Pharmacokinetic
Pre-procedure preventions	Administration of a hereditary angioedema (HAE) medication before a medical, dental, or surgical procedure to prevent an HAE attack. Pre-procedure prevention is also called short-term prophylaxis.
PTIR	Person-time incidence rate
Routine Prophylaxis	Regular administration of an HAE medication (eg. twice per week) to prevent an HAE attack: Routine prophylaxis is also called long-term prophylaxis.
SMQ	Standardized MedDRA Query

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 Page 2 prophylactic treatment of hereditary angioedema.
TP1	Treatment Period 1
TP2	Treatment Period 2
Suspected adverse drug reaction	In this study, suspected adverse reactions included adverse events (AEs) than happen within 24 hours after CSL830 administration. AEs reported as at least possibly related to CSL830 administration, and AEs with no causality assessment.

1. EXECUTIVE SUMMARY

HAEAGARDA is a plasma-derived concentrate of C1-esterase inhibitor (human) (C1-INH) to be reconstituted for subcutaneous (SC) administration. HAEAGARDA is also referred to as CSL830. HAEAGARDA was licensed in the United States in 2017. HAEAGARDA is approved in the United States for routine prophylaxis of hereditary angioedema (HAE) attacks in adolescent and adult patients. The approved dose is 60 International Units per kg body weight (IU/kg) twice weekly via SC administration. HAEGARDA has an orphan designation for the approved indication of routine prophylaxis of HAE attacks.

In this BLA efficacy supplement, the applicant, CSL Behring, submitted the final study report of Study CSL830_3002 (also known as Study 3002) seeking approval to expand the indication for routine prophylaxis to prevent HAE attacks to include pediatric patients, and to update the "Clinical Studies" and "Use in Specific Populations" sections of Package Insert (PI) of HAEGARDA. At the time of the original BLA submission, Study 3002 was ongoing and interim data (data cut-off date of 17 May 2016) were submitted in the 120-day safety update.

Study 3002 was a Phase 3, multicenter, randomized, open-label, parallel-arm study to evaluate long-term (≥ 1 year) safety and efficacy of SC CSL830 for the prophylactic treatment of HAE. This study was an open-label safety and pharmacokinetic extension of Study 3001, which provided primary evidence of effectiveness and safety to form the basis for FDA-approval of HAEGARDA for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

Study 3002 included two CSL830 dose groups (low dose 40 IU/lg and high dose 60 IU/kg) and consisted of two treatment periods (TP). TP1 was a fixed-dose period of 24 weeks. TP2 was a dose-adjustment period of 28 weeks to allow for individual optimization of routine prophylaxis. The study assessed 120 adult and pediatric subjects with symptomatic HAE type I or II . The median (range) age of subjects was 41.0 (8-72) years. Patients who experienced at least 4 HAE attacks over a consecutive 2-month period before the Study 3002 Screening Visit were enrolled and treated for a mean of 1.4 years. Among the 120 subjects, 59 subjects participated in Study 3001 and 61 subjects did not participate in Study 3001. There were nine pediatric subjects. Three of the nine pediatric subjects were less than 12 years old. There were no subjects younger than age 8 years. The primary endpoints defined in the final SAP were related to the assessment of safety, and efficacy was evaluated as secondary and exploratory endpoints. The efficacy endpoints included: 1) the percentage of subjects who were responders (defined as a ≥ 50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks used to qualify the subject for participation in this study), 2) percentage of subjects with time-normalized HAE attack frequency of less than 1 HAE attack per 4-week period. The percentages of subjects with ≥50% reductions in the time-normalized number of HAE attacks on HAEGARDA relative to the time-normalized number of HAE attacks at baseline were 93.1% in the 40 IU/kg and 60 IU/kg treatment groups, respectively. The percentages of subjects with time normalized HAE attack frequency of less than 1 HAE attack per 4-week period were 79.7% on 40 IU/kg and 86.8% on 60 IU/kg.

The primary (safety) endpoint was incidence of adverse events (AEs) leading to premature study discontinuation, thromboembolic events (TEEs), anaphylaxis, HAE attacks resulting in hospitalization, local injection site AEs, related serious AEs (SAR), and anti-C1-INH antibodies. The percentage of subjects experiencing AEs was similar between the two treatment groups: 81.3% in the 40 IU/kg group and 74.5% in the 60 IU/kg group. Injection site reactions were the most common adverse events and were reported in a similar percentage of subjects during treatment with 40 IU/kg (55.6%) and with 60 IU/kg (45.7%). No subjects had positive results for inhibitory antibodies to C1-INH at Baseline or at any post-Baseline Visit. Ten subjects who tested negative for non-inhibitory antibodies to C1-INH at Baseline tested positive at a subsequent visit. Four subjects discontinued the study prematurely due to AE. No subjects in either treatment group had anaphylaxis, TEEs likely related to product, HAE attacks resulting in hospitalization, or related SARs. No deaths were reported. Safety data from Study 3002 was consistent with the safety data from Study 3001.

Subgroup analysis of the 9 pediatric subjects between 8 and 17 years of age suggested that the safety and efficacy of HAEGARDA were comparable between pediatric population and the overall study population in Study 3002.

Pharmacokinetics (PK) data and analysis indicated that the observed mean steady state C1-INH functional activity for children (8 to <12 years) was within the range of the adolescent (12 to < 18 years) and adult values (18-65 years). The bodyweight adjusted clearance (CL) is about 16% and 13% higher in children (8 to <12 years) and adolescent (12 to < 18 years) as compared to adult subjects (18-65 years), respectively. Therefore, from clinical pharmacology perspective, efficacy extrapolation down to patients 6 years of age was justifiable considering minimal physiological difference between 6- and 8-year old children, and the minimal trend for change in clearance in patients 6 years of age and older. However, the efficacy extrapolation cannot be extended to children younger than 6 years due to physiological difference and expected higher clearance.

From review of the submitted data, this reviewer considers that the efficacy and safety data of Study 3002 and available PK data support a favorable benefit / risk profile to expand the indication for routine prophylaxis to prevent HAE attacks to include pediatric patients 6 years of age and older at the FDA-approved dose of 60 IU/kg twice weekly via SC administration.

This reviewer recommends approval of HAEGARDA at the 60 IU/kg dose, administered subcutaneously twice weekly for routine prophylaxis to prevent HAE attacks in patients age 6 years of age and older.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographic and baseline characteristic information for the 120 subjects in Study 3002 is shown in Table 1. Mean age of the subjects was 40.5 years ranging from 8 years to 72 years. There were more females than males. Most subjects were and White (95.8%). The number of subjects in each age group is shown in Table 2. There were 4 pregnant women in the study.

Table 1. Demographic and Baseline Characteristics for Study 3002

Treatment Arm	40 IU/kg n=59	60 IU/kg n=61	>=40 IU/kg n=120
Age (years)			
Mean (SD)	40.9 (14.62)	40.1 (15.98)	40.5 (15.27)
Min, Max	8, 66	10, 72	8, 72
Median	43	41	41
Sex (n (%))			
Male	22 (37.3)	26 (42.6)	48 (40)
Female	37 (62.5)	35 (57.4)	72 (60)
Race (n (%))			
American Indian/Alaska Native	0	0	0
Asian	0	1 (1.6)	1 (0.8)
Black or African American	1 (1.7)	1 (1.6)	2 (1.7)
Native Hawaiian/Pacific Islanders	0	0	0
White	56 (94.9)	59 (96.7)	115 (95.8)
Other	2 (3.4)	0	2 (1.7)

Source: Modified from Table 14.1.2.1. of Response to 08 and 10 JAN 2020 Information Request, submitted 22 JAN 2020, 125606/185/2 (Seq 0250)

Table 2. Overview of Number of Subjects per Age Group for Study 3002

Age Group (years)	No. of subjects per age group
8-11	3
12-17	6
18-65*	104
>65	7
Total	120

* There were 4 pregnant women in this age group.
Source: Adapted from Response to 08 and 10 JAN 2020 Information Request, submitted 22 JAN 2020, 125606/185/2 (Seq 0250)

1.2 Patient Experience Data

No patient experience data were submitted (Table 3).

Table 3. Patient Experience Data Submitted in this Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other:	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hereditary Angioedema (HAE) is characterized clinically by unpredictable and recurrent attacks of edema affecting the subcutaneous 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 estimated to affect approximately 1 in 50,000 individuals, with no ethnic predominance, suggesting that more than 6,000 individuals are affected in the United States (U.S.).

There are two main types of HAE: HAE type I and HAE type II. Both types of HAE are caused by mutations *SERPING1* gene on Chromosome 11 that provides functional C1-INH. HAE type I (approximately 85% of patients) is due to deficiency of C1-INH. HAE type II (approximately 15% of patients) is due to dysfunction of C1-INH. Inheritance of both type I and type II HAE is autosomal dominant.

C1-INH is a serine protease inhibitor (serpin) that regulates activation of the complement, contact (kallikrein/kinin) and coagulation systems by binding to and inactivating target serine proteases. Dysregulation of these systems because of C1-INH deficiency or dysfunction results in 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 absent or greatly reduced C1-INH or C1-INH functional activity. C4 is a component of the classical complement pathway. C4 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.

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

Anadelumab-flyo (TAKHZYRO) is a kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older. It is administered subcutaneously twice a week.

Danazol is a synthetic steroid derived from ethisterone indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females.

Stanozolol (Winstrol) is indicated prophylactically to decrease the frequency and severity of attacks of hereditary angioedema. Given the serious potential adverse reactions, patients should be placed on the lowest possible effective dose (Winstrol Prescribing Information. Facts and Comparisons, online version 2005)

2.3 Safety and Efficacy of Pharmacologically Related Products

CINRYZE is a human plasma-derived C1-inhibitor indicated for routine prophylaxis of adult, adolescent and pediatric patients (6 years of age and older) with HAE. The product is administered intravenously. 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 randomized, placebo-controlled, double-blind study, supported by two randomized, double-blind, placebo-controlled studies. Adverse reactions (≥ 2% of subjects) reported in clinical trials were headache, nausea, and diarrhea.

BERINERT is a plasma-derived C1-inhibitor is indicated for intravenous treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients. 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.

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

Study 3001 provided primary evidence of effectiveness and safety of HAEGARDA that led to FDA-approval for routine prophylaxis to prevent HAE attacks in adolescent and adult patients. The study enrolled 90 adult and adolescent subjects with symptomatic HAE type I or II. Subjects were randomized to receive either 60 IU/kg or 40 IU/kg HAEGARDA in one 16-week treatment period and placebo in the other 16-week treatment period. Patients self-administered HAEGARDA or placebo subcutaneously twice per week. Efficacy was evaluated for the last 14 weeks of each treatment period. The most common adverse reactions included injection site reaction, hypersensitivity, nasopharyngitis and dizziness. Of the injection site reactions occurring after treatment with HAEGARDA, 95% were of mild intensity and 83% resolved within 1 day after onset. At the recommended subcutaneous dose of 60 IU/kg, a causal relationship between thromboembolic events (TEEs) and the use of HAEGARDA has not been established.

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

Not applicable.

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 states that Study 3002 was carried out in accordance with the ICH (International Conference on Harmonization) Good Clinical Practice (GCP) guidelines.

A disqualified clinical investigator, Dr. James Baker at Site 8400147, participated in study 3002, and data collected from this study site were submitted in this BLA supplement. The disqualification was based on previous BIMO inspections.

Reviewer Comment:
Applicant was asked to re-analyze and re-submit all key safety and efficacy data of 3002 by excluding data of the six subjects from site 8400147. The clinical review excluded data of the six subjects from site 8400147.

3.3 Financial Disclosures

No significant issues with financial disclosures were identified that could lead to undue bias in the data submitted in support of this BLA (Table 4).

Table 4. Financial Disclosure

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: 33		
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)

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

4.1 Chemistry, Manufacturing, and Controls

No CMC updates were submitted for this BLA efficacy supplement.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

No updates were submitted for this efficacy supplement.

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. Since patients with HAE 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 SC administration of 60 IU/kg HAEGARDA were in the normal range (16 to 38 mg/dL).

4.4.3 Human Pharmacokinetics (PK)
The Applicant submitted an updated population pharmacokinetic (PopPK) model with the inclusion of pharmacokinetic (PK) data from ≥ 8 years, and exploratory PK/pharmacodynamic (PD) correlation analysis. There were 22 PK concentrations from three children (8 to <12 years). The observed mean steady state C1-INH functional activity for these children was within the range of the adolescent and adult values. The previously developed PopPK model reasonably described the C1-INH functional activity for subjects in the # Study 3200. Bodyweight is the only significant covariates included in the final PopPK model. The bodyweight adjusted clearance (CL) is about 16% and 13% higher in children (8 to <12 years) and adolescent (12 to < 18 years) as compared to adult subjects (18-65 years), respectively. For PK and efficacy extrapolation up to 6 years we considered: 1) similarity of the underlying disease, 2) minimal physiological difference between 6- and 8-year old children, and 3) the minimal trend for change in clearance in patients 6 years of age and older. However, these considerations cannot be extended to younger children (< 6 years) due to physiological difference and expected higher clearance. Overall the clinical pharmacology data and analysis support the proposed 60 IU/kg twice weekly dosing for HAE patients 6 years of age and older.

Please see clinical pharmacology review for details.

4.5 Statistical

The Statistics review team confirmed the results of safety and efficacy endpoints. Please see the statistical review for details.

4.6 Pharmacovigilance

Original post-marketing pharmacovigilance plan was submitted with the original BLA. An updated post-marketing pharmacovigilance plan, Version 3.0, was submitted with this supplement. Review of post-market safety data did not reveal any unexpected safety concerns. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post marketing requirement or commitment (PMR/PMC) study. The Pharmacovigilance review team from Division of

Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE) agreed with the applicant's plan for routine pharmacovigilance (PV) to:

1. Systematically collect all suspected adverse drug reaction reports from all post marketing sources and clinical trials.
2. Conduct real time and periodic medical assessment of single and aggregate data.
3. Perform signal detection activities to enable early detection of potential signals.

The applicant aims to employ questionnaires in its routine PV activities to capture data specific to its Important Identified Risk (Hypersensitivity/Anaphylactic reactions) and Potential Risks (TEEs) and Transmission of infectious agents), as well as to Missing Information (e.g., Limited experience in pregnancy/lactation).

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

5.1 Review Strategy

This reviewer focused on efficacy, safety and PK data from Study 3002 to assess whether there is favorable benefit / risk profile to expand the indication for routine prophylaxis to prevent HAE attacks to include children younger than 12 years of age.

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

The sources for this review include: (1) the BLA supplement, which includes safety, efficacy and PK data from the completed Study 3002; (2) BLA 125606/0 Clinical Review Memorandum (2017); (3) Safety data from Study 3001.

5.3 Table of Studies/Clinical Trials

At the time of the original BLA submission, Study 3001 was completed. Study 3002 was ongoing and interim data (data cut-off date of 17 May 2016) were submitted in the 120-day safety update. The focus of this clinical review is the final standalone data from the completed Study 3002 (last subject last visit: 21 September 2017) (Table 5).

Table 5. Phase 3 Studies (3001, 3002)

Study Number; Status	Phase; Study Design	Location of Study Center (N)	Primary Objective(s)	Subject Population; Median Age (Range)	Treatment; Route; Dose	Primary and Secondary Efficacy Variables
Study 3001; completed	Phase 3; Multicenter; Randomized, double-blind, Placebo-controlled, Incomplete crossover study	Australia (1) Canada (6) Czech Republic (2) Hungary (1) Israel (2) Italy (2) Romania (2) Spain (4) UK (2) US (19)	Demonstrate clinical efficacy of SC CSL830 in prophylaxis of HAE attacks; compare clinical efficacy of 40 IU/kg with 60 IU/kg	90 subjects with HAE type I or II randomized (60 females / 30 males); Mean: 40 years (12-72 years); Subgroups: <12 years: 0 subjects; <17 years: 6 subjects; >= 65 years:7 subjects	Single SC injection of CSL830 or placebo twice per week for 16 weeks in 2 consecutive treatment periods; CSL830 40 IU/kg or 60 IU/kg crossover with high-volume or low-volume placebo	Primary endpoint: Time-normalized number of HAE attacks Secondary endpoints: -Percentage of responders: subjects with a>=50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830 compared with placebo -Time-normalized number of uses of rescue medication
Study 3002; completed	Phase 3; Multicenter; Randomized, open-label, parallel-arm study	Australia (1) Canada (4) Czech Republic (1) Germany (4) Hungary (1) Israel (2) Italy (2) Romania (1) Spain (3) UK (1) US (12)	Assess safety of SC CSL830 in long-term prophylaxis of HAE attacks	120 subjects with HAE type I or II randomized (72 females/48 males); 41 years (8-72 years); Subgroups: <12 years: 3 subjects; <17 years: 9 subjects; >= 65 years:7 subjects	Single SC injection of CSL830 40 IU/kg or 60 IU/kg 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	Primary endpoint: Person-time incidence rate of: -AEs leading to premature study discontinuation; thromboembolic events; anaphylaxis; HAE attacks resulting in hospitalization; severe solicited AEs; related SAEs; antibodies to C1-INH. Secondary endpoints: -Percentage of responders: subjects with >=50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830 compared with the number of attacks used to qualify the subjects for study participation -Percentage of subjects with a time-normalized HAE attack frequency of <1 HAE attack per 4-week period

Source: Module 2.7.3 Summary of Clinical Efficacy

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)
No Advisory Committee meeting was held because initial review of information submitted in the BLA supplement did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations
Not applicable.

5.5 Literature Reviewed (if applicable)

During review of the BLA supplement, this reviewer reviewed FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature reviewed is listed below:

De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. jean.de.serres@aventis.com. Transfus Apher Sci. 2003;29(3):247-254.

Gandhi PK, Gentry WM, Bottorff MB. Thrombotic events associated with C1 esterase inhibitor products in patients with hereditary angioedema: investigation from the United States Food and Drug Administration adverse event reporting system database. Pharmacotherapy. 2012 Oct;32(10):902-9.

Jose J, Zacharias J, Craig T. Review of Select Practice Parameters, Evidence-Based Treatment Algorithms, and International Guidelines for Hereditary Angioedema. Clin Rev Allergy Immunol. 2016;51(2):193-206.

Aygören-Pürsün E, Soteres DF, Nieto-Martinez SA, Christensen J, Jacobson KW, Moldovan D, Van Leerberghe A, Tang Y, Lu P, Vardi M, Schranz J, Martinez-Saguer I. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. Pediatr Allergy Immunol. 2019 Aug;30(5):553-561.

Gupta R, Balduzzi J, Davis-Lorton M. C1-esterase inhibitor (Cinryze®) use in the treatment of pediatric hereditary angioedema. Immunotherapy. 2018 Jun;10(8):635-642. doi: 10.2217/imt-2017-0049. Epub 2018 Mar 23.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Completed Phase 3 Extension Trial, Study CSL830_3002 (Study 3002)

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

Study Period:
First Subject Visit: 31 December 2014
Last Subject Visit: 21 September 2017

6.1.1 Objectives
Primary Objective:

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

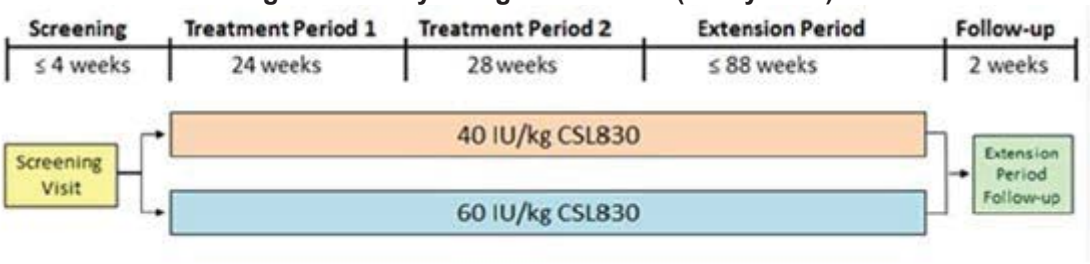
Secondary Objectives:

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

6.1.2 Design Overview
Study 3002 was a Phase 3, multicenter, randomized, open-label, parallel-arm study to evaluate long-term (≥ 1 year) safety and efficacy of SC CSL830 for the prophylactic treatment of HAE. This study was an extension of Study 3001. Study 3001 provided primary evidence of effectiveness and safety to form the basis for FDA-approval of HAEGARDA for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

Study 3002 consisted of 2 treatment periods (TP). TP1 was a fixed-dose period of 24 weeks. TP2 was a dose-adjustment period of 28 weeks to allow for individual optimization of routine prophylaxis. The study duration for an individual subject (including assessment of eligibility and follow-up) was up to 58 weeks. In addition, subjects in the US who completed TP2 were eligible to continue treatment with CSL830 in an optional Extension Period of 88 weeks to collect additional long-term safety, efficacy, PK / PD, and quality of life data. The study duration for participating US subjects (including assessment of eligibility and follow-up) was up to 146 weeks (Figure 1).

Figure 1. Study Design Schematic (Study 3002)



6.1.3 Population
The study population consisted of male or female subjects aged 8 years or older with:

- Clinical diagnosis of HAE type I or II, as determined by a clinical history consistent with HAE and C1-esterase inhibitor (C1-INH) functional activity < 50%, concurrent with C4 antigen concentrations below normal limits,

- Experienced at least 4 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period before the Study 3002 Screening Visit and before start of treatment with intravenous (IV) C1-INH prophylaxis (for “CSL830-Naïve” Subjects using IV C1-INH prophylaxis),

- 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 types of subjects were enrolled depending on their prior exposure to CSL830:

- “CSL830-Naïve” Subjects: subjects who did not participate in Study 3001 or subjects who participated in Study 3001 but did not receive CSL830 in Study 3001,

- “CSL830-Interrupted” Subjects: subjects who completed participation in Study 3001, but delayed entry into Study 3002 [i.e., > 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 (i.e., Screening Visit)],

- "CSL830-Continuation" Subjects: subjects who completed participation in Study 3001 and continued directly on to participate in Study 3002 [i.e., ≤ 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 TP1].

The diagnosis of HAE type I or II and the number of HAE attacks in the 3 months before Screening were confirmed in Study 3002 for "CSL830-Naïve" Subjects, and in Study 3001 for "CSL830-Continuation" Subjects and "CSL830-Interrupted" Subjects.

"CSL830-Interrupted" Subjects and "CSL830-Naïve" Subjects participated in a Screening Visit to confirm their eligibility. "CSL830-Continuation" Subjects were not required to participate in a Screening Visit. Instead, data from Study 3001 were used to confirm their eligibility.

6.1.4 Study Treatments or Agents Mandated by the Protocol
Eligible subjects were randomized in a 1:1 allocation ratio to either 40 IU/kg CSL830 or 60 IU/kg CSL830 group. Subjects were stratified by enrollment classification to ensure that "CSL830-Continuation" Subjects, "CSL830-Interrupted" Subjects, and "CSL830-Naïve" Subjects were evenly distributed between the 2 treatment groups.

After formal training, subjects or their caregivers administered CSL830 as a single SC injection twice per week for the duration of the study. The 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.

- During the fixed-dose TP1, subjects who experienced ≥ 12 attacks within a 4-week evaluation period were eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg).
- Beginning with the Week 25 Visit and throughout TP2, subjects who experienced ≥ 3 HAE attacks within an 8-week evaluation period were eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg).
- During the Extension Period, subjects were eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg) according to the rules outlined for TP2.

All CSL830 dose increases were optional and were made in eligible subjects. An evaluation period for any dose increase was defined as beginning after a dose-stable period (i.e., 2 weeks after the initiation or dose increase of CSL830).

6.1.5 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. Subjects or their caregivers administered CSL830 subcutaneously twice per week for up to 140 weeks. Abdomen was the preferred injection site.

If a subject was required the use of rescue C1-INH medication within 24 hours before a scheduled injection of CSL830, it was acceptable to delay the scheduled injection by up to 24 hours.

6.1.6 Sites and Centers
There were 72 subjects (60% of the study population) in Study 3002 from study sites outside of the United States (Table 6). Both Foreign and US sites conducted the study under the same protocol, originally submitted to IND 14992 on 09 September 2014. A country-specific protocol for the United States (amendment No. 1, dated 10 July 2015), was submitted to the IND.

Table 6. Enrollment in Study 3002 by Country

Country	Frequency	Percent	Cumulative frequency	Cumulative percent
Australia	3	2.50	3	2.50
Canada	12	10	15	12.50
Czech Republic	4	3.33	19	15.83
Germany	22	18.33	41	34.17
Spain	4	3.33	45	37.50
Great Britain	2	1.67	47	39.17
Hungary	6	5	53	44.17
Israel	14	11.67	67	55.83
Italy	1	0.83	72	60.00
Romania	1	0.83	72	60.00
USA	48	40	120	100.00

Source: Modified from Table 1 of Response to 08 and 10 JAN 2020 Information Request, submitted 22 JAN 2020, 125606/185/2 (Seq 0250)

Reviewer's Comment:
Per FDA's request, the clinical data from the 6 subjects at the disqualified site [Site 8400147 (James W. Baker, MD, Baker Allergy, Asthma and Dermatology Research Center, LLC)] were excluded from the safety and efficacy analysis.

Five of these 6 subjects were rolled over from Study 3001, and 1 subject was naïve. Of these 6 subjects, 1 was an adolescent (15 years of age), 2 were above 65 years (67 and 68 years of age), and 3 were between 18 and 65 years (23, 30, and 44 years of age).

6.1.7 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.

6.1.8 Endpoints and Criteria for Study Success
Primary Endpoint:

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

- Adverse events (AEs) leading to premature study discontinuation
- Thromboembolic event (TEEs)
- Anaphylaxis
- HAE attacks resulting in in-patient hospitalization (where hospitalization was the
- consequence of the need for emergent medical care)

- Solicited AEs (injection site reactions at the CSL830 injection site) graded as severe by the investigator
- Related serious adverse events (SAEs), other than events specified above.
- Anti-C1-INH antibodies (inhibitory or non-inhibitory)

Secondary Endpoints (safety):

- AEs, SAEs, solicited AEs (i.e., injection site reactions), unsolicited AEs, AEs that began within 24 hours after CSL830 administration, and 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 (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.

Secondary Endpoints (efficacy):

- The percentage of subjects who were responders, defined as a ≥ 50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks that was used to qualify the subject for participation in this study.
- The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.

Exploratory Endpoints:

The time-normalized number of HAE attacks reported as:

- the rate of HAE attacks per month
- The time-normalized number of uses of rescue medication per month
- The time-normalized number of days of HAE symptoms per month
- Investigator's Global Assessment of Response to Therapy (IGART)
- SGART
- Subject reported outcome measures (EQ-5D, WPAI, TSQM, and HADS)
- Percentage of subjects who:
    - Did not have a CSL830 dose increase
    - Had 1 CSL830 dose increase
    - Had 2 CSL830 dose increases
    - Discontinued study participation because of lack of efficacy.
- The time from randomization to the first CSL830 dose increase
- The time from randomization to the second CSL830 dose increase

For subjects who did not participate in the Extension Period, the End of Study Visit was at Week 53.

For subjects who participated in the Extension Period, the End of Study Visit was at Week 140.

6.1.9 Statistical Considerations & Statistical Analysis Plan
Planned Analysis:

- Subject disposition was summarized for all subjects who provide informed consent/ assent (as appropriate).
- HAE attacks during the Screening Period for "CSL830- Naïve" Subjects and "CSL830-Interrupted" Subjects were summarized using the intend-to-treat (ITT) and Safety Population.
- Demographic and subject characteristics were summarized using the ITT and Safety Populations. All safety data were summarized using the Safety Population.
- The exploratory efficacy endpoints were summarized using the ITT Population. Continuous variables were described using mean with the respective 95% confidence intervals (CI; were applicable); standard deviation; range; 25th, 50th (median), and 75th percentiles; and counts of missing and non-missing values. Categorical values were described by counts and percentages.

Please see the statistical review for details.

6.1.10 Study Population and Disposition
Study 3002 was initiated during the ongoing conduct of Study 3001. Subjects were randomized into Study 3002 to maintain the blind of Study 3001 treatment assignments for "CSL830-Continuation" Subjects and "CSL830-Interrupted" Subjects. Eligible subjects were randomized in a 1:1 allocation ratio to either 40 IU/kg CSL830 or 60 IU/kg CSL830. Subjects were stratified by enrollment classification to ensure that "CSL830-Continuation" Subjects, "CSL830-Interrupted" Subjects, and "CSL830-Naïve" Subjects were evenly distributed between the 2 treatment arms.

A total of 125 subjects provided informed consent / assent and were assessed for eligibility to participate in the study. Five subjects were not randomized because they did not meet all eligibility criteria. A total of 120 subjects were randomized into the study (ITT Population), 59 subjects to the 40 IU/kg CSL830 treatment arm and 61 subjects to the 60 IU/kg CSL830 treatment arm. All 120 subjects in the ITT Population received at least 1 dose of CSL830 (Safety Population). A diagram of subject disposition in Study 3002 is presented in Table 7.

Table 7. Subject Disposition - Study 3002

Treatment Arm	Before administration n (%)	40 IU/kg n (%)	60 IU/kg n (%)	>=40 IU/kg n (%)
Provided Informed consent/assent	125 (-)			
CSL830-Naiive	66 (52.8)			
CSL830-Interrupted	47 (37.6)			
CSL830-Continuation	12 (9.6)			
Not Randomized	5 (4)			
Randomized		59 (100)	61 (100)	120 (100)
Participated in Extension Period		19 (32.2)	23 (37.7)	42 (35)
ITT Population (as Randomized)		59 (100)	61(100)	120 (100)
Safety Population (as Treated)		59 (100)	68 (111.5)	120 (100)
PK Population		57 (96.6)	68 (111.5)	118 (98.3)
Completed		52 (88.1)	54 (88.5)	106 (88.3)
Discontinued		7 (11.9)	7 (11.5)	14 (11.7)
Reason for Discontinuation		7 (100)	7 (100)	14 (100)
Adverse Event		1 (14.3)	3 (42.9)	4 (28.6)
Withdrawal by Subject		5 (71.4)	1 (14.3)	6 (42.9)
Other (Pregnancy)		1 (14.3)	3 (42.9)	4 (28.6)

Source: Modified from Table 14.1.1.1. of Response to 08 and 10 JAN 2020 Information Request, submitted 22 JAN 2020, 125606/185/2 (Seq 0250)

6.1.10.1 Populations Enrolled/Analyzed
Analysis populations included Intent to Treat (ITT) and Safety Populations:

- 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).

6.1.10.1.1 Demographics
Key demographic information for both the low-dose cohort and the high-dose cohort is summarized in Table 1. There were more female subjects than male subjects. Most subjects were white and not of Hispanic or Latino ethnicity. The mean age of subjects enrolled in the low-dose and high-dose cohorts were similar.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.1.10.1.3 Subject Disposition

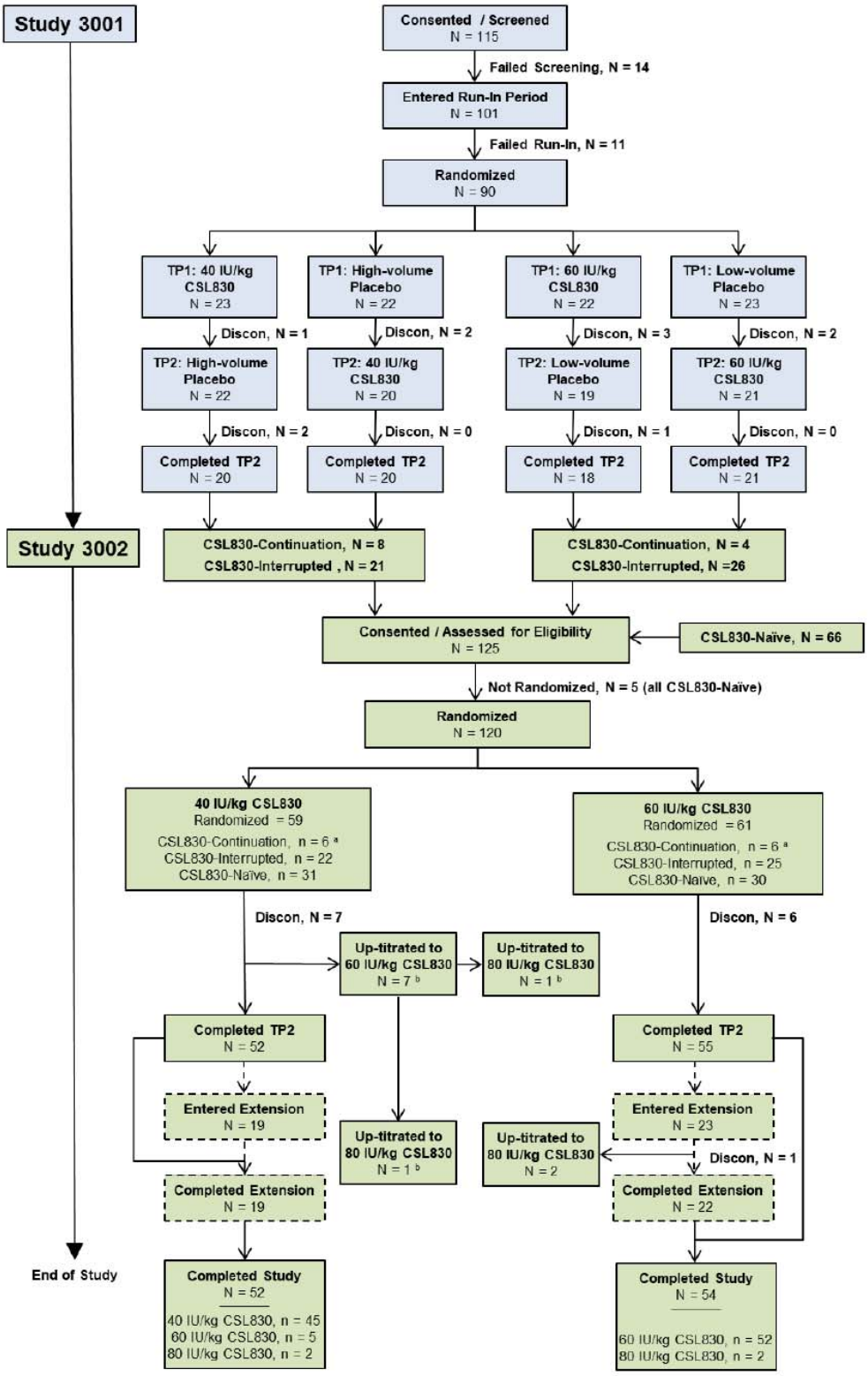
A total of 125 subjects provided informed consent / assent and were assessed for eligibility to participate in the study. Five subjects were not randomized because they did not meet all eligibility criteria. A total of 120 subjects were randomized into the study (ITT population), 59 subjects to the 40 IU/kg CSL830 treatment group and 61 subjects to the 60 IU/kg CSL830 treatment group.

The number of "CSL830-Continuation" Subjects, "CSL830-Interrupted" Subjects, and "CSL830-Naïve" Subjects are similar between the two treatment groups. All 120 subjects in the ITT Population received at least 1 dose of CSL830 (Safety Population) ().
Two subjects randomized to the 60 IU/kg CSL830 treatment group had their dose up-titrated to 80 IU/kg. Seven subjects randomized to the 40 IU/kg CSL830 treatment group had their dose up-titrated. Five of these 7 subjects were up-titrated once from 40 to 60 IU/kg and 2 subjects were up-titrated twice from 40 to 60 and then to 80 IU/kg.

Of the 9 pediatric subjects who participated in Study 3002, 3 subjects were < 12 years old. All 3 subjects were "CSL830-Naïve" Subjects. The duration of exposure of these 3 subjects was as follows:

- Subject (b) (6) (8 years old) received 40 IU/kg CSL830 for 52.1 weeks (i.e., 1.0 year).
- Subject (b) (6) (10 years old) received 40 IU/kg CSL830 for 121.9 weeks (i.e., 2.3 years).
- Subject (b) (6) (10 years old) received 60 IU/kg CSL830 for 53.4 weeks (i.e., 1.0 year).

Figure 2. Subject Disposition (Study 3001 and Study 3002



Source: Addendum to the Summary of Clinical Efficacy (Module 2.7.3), BLA 125606/185/13.

6.1.11 Efficacy Analyses
6.1.11.1 Analyses of Efficacy Endpoint(s)

1. Efficacy endpoint #1: The percentage of subjects who were responders "Response" was defined as a ≥ 50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830, compared with the time-normalized number of attacks that was used to qualify the subject for participation in this study.

   In the 40 IU/kg treatment group, among the 58 subjects whose response can be calculated, 54 (93.1%) subjects were responders. In the 60 IU/kg treatment group, among the 58 subjects whose response can be calculated, 53 (91.4%) subjects were responders (Table 8).

Table 8. Efficacy Summary: Percentage of Responders (Study 3002)

	40 IU/kg n (%)	60 IU/kg n (%)
Subjects Included in Analysis	58	58
Responder	54 (93.1)	54 (93.1)
Non- Responder	4 (6.9)	4 (6.9)
95% Wilson CI for Percentage of Responders	(83.6, 97.3)	(83.6, 97.3)

Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315).

Reviewer Comment:
The following formula was used to calculate response:

100%[1 – (the time-normalized number of HAE attacks when treated with CSL830) / (the time-normalized number of HAE attacks used to qualify for participation in Study 3002)]*

The response cannot be calculated in 4 subjects:

- Three subjects who participated in study 3001: Their HAE medical history data from Study 3001 were integrated into the dataset for study 3002. No additional time-normalized number of HAE attack data were collected to qualify for participation in study 3002 for these subjects. Their time-normalized number of HAE attacks prior to the screening visit for Study 3001 was 0 attacks due to the utilization of prophylactic medications for HAE attack prevention. These 3 subjects were randomized into the 60 IU/kg treatment group.
- 1 subject: The subject discontinued study 3002 after administration of 3 doses of 40 IU/kg CSL830, with the reason: "withdrawal by subject: Did not want to give the time to do the assessments." This subject discontinued the study prior to the start of the efficacy evaluation period (defined as starting on Day 1 of Week 3 for any subject). Thus, this subject's data was excluded from analyses of efficacy endpoints, including the responder analysis.

So, there were 58 subjects included in analysis for 40 IU/kg and for 60 IU/kg groups, respectively.

To evaluate the efficacy in subpopulations, post hoc subgroup analyses were performed for three age groups (≤ 17 years, > 17 years to < 65 years, and ≥ 65 years). The percentage of responders of different age groups in the two treatment groups is shown in Table 9. All 9 pediatric subjects, including the 3 subjects age <12 years old, were responders.

Table 9. Percentage of Responders by Age Group (Study 3002)

9.1 Age 8-11 years

	40 IU/kg n (%)	60 IU/kg n (%)
Subjects Included in Analysis	4	4
Responder	4 (100)	4 (100)
95% Wilson CI for Percentage of Responders	(34.2, 100)	(34.2, 100)

9.2 Age 12-64 years

	40 IU/kg n (%)	60 IU/kg n (%)
Subjects Included in Analysis	53	47
Responder	49 (95.7)	45 (95.7)
95% Wilson CI for Percentage of Responders	(82.1, 97)	(85.8, 98.8)

9.3 Age 65-72 years

	40 IU/kg n (%)	60 IU/kg n (%)
Subjects Included in Analysis	1	6
Responder	1 (100)	4 (66.7)
95% Wilson CI for Percentage of Responders	(20.7, 100)	(30, 90.3)

Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315)

2. Efficacy endpoint #2: The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period

The percentages of subjects with time normalized HAE attack frequency of < 1 HAE attack per 4-week period were 79.7% on 40 IU/kg and 86.9% on 60 IU/kg (Table 10).

Table 10. Time-Normalized Merged HAE Attack Frequency of Less Than 1 HAE Attack per 4-Week Period (ITT)

	40 IU/kg n (%)	60 IU/kg n (%)
Subjects Included in Analysis	59	61
Time-Normalized Number of Attacks < 1 per 4-Week Period (n (%))	47 (79.7)	53 (86.9)
Time-Normalized Number of Attacks >= 1 per 4-Week Period (n (%))	11 (18.6)	8 (13.1)
Missing*	1 (1.7)	0

*Number missing = number of subjects with missing data after 2 weeks within corresponding treatment group
Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315)

3. Exploratory Efficacy Endpoints:

#1: The rate of HAE attacks per month: In all age groups, the mean number of HAE attacks per month in both treatment groups reduced to less than 1 attack/month (Table 11).

Table 11. Time-Normalized Number of Merged HAE Attacks by Treatment (number/month) and (number/year) (ITT)

Treatment arm	Age group (n)	Mean	Standard Deviation	Min	Median	Max
40 IU/kg	8-11 yrs (2)	0.062	0.036	0.036	0.062	0.087
40 IU/kg	12-17 yrs (2)	0.583	0.483	0.241	0.583	0.925
40 IU/kg	18-64 yrs (53)	0.459	0.781	0	0.087	3.382
40 IU/kg	65-72 yrs (1)	0.518		0.518	0.518	0.518
60 IU/kg	8-11 yrs (1)	0		0	0	0
60 IU/kg	12-17 yrs (4)	0.281	0.357	0.033	0.149	0.792
60 IU/kg	18-64 yrs (49)	0.421	0.873	0	0.085	3.998
60 IU/kg	65-72 yrs (7)	0.678	0.909	0	0.439	2.412

Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315)

- #2: The time-normalized number of uses of rescue medication per month:
  For 40 IU/kg and 60 IU/kg, median rescue medication use was 0.0 and 0.0 times per year, respectively (Table 12).

Table 12. Time-normalized Number of Uses of Rescue Medication (Number / Month)

	40 IU/kg	60 IU/kg
Age 8-17 yrs: n	4	5
Age 8-17 yrs Mean (SD)	0.11 (0.081)	0.08 (0.154)
Age 8-17 yrs Median	0.13	0
Age 18-72 yrs: n	54	56
Age 18-72 yrs Mean (SD)	0.28 (0.609)	0.32 (0.835)
Age 18-72 yrs Median	0	0

Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315)

#3: The proportion of HAE attack-free subjects throughout the study duration with a maximum exposure of >2.5 years was 35.6% and 44.3% in the 40 IU/kg and 60 IU/kg treatment arms, respectively (Table 13).

Table 13 . Proportion of attack free patients by treatment (ITT)

n (%)	40 IU/kg	60 IU/kg
Missing	1 (1.60)	0
Not attack free	37 (62.71)	34 (55.74)
Attack free	21 (35.59)	27 (44.26)
Total	59	61

Source: Table 14.2.1.1a. of Response to 14 SEP 2020 Information Request, submitted 16 SEP 2020, 125606/185/17 (Seq 0315)

6.1.11.3 Subpopulation Analyses
The percentage reduction in time-normalized HAE attacks on HAEGARDA relative to the pre-study period for the 3 pediatric subjects < 12 years old was as follows:

- 8-year-old; 40 IU/kg: 97.1% reduction,
- 10-year-old; 40 IU/kg: 96.4% reduction,
- 10-years-old; 60 IU/kg: 100% reduction.

There were nine subjects between 65 and 72 years of age. Seven subjects received the 60 IU/kg dose and two subjects received the 40 IU/kg dose. The maximum number of HAE attacks per month was highest in subjects age >65 years (range 0-2.44).

Reviewer Comment:
Results of the subgroup analyses of 9 pediatric subjects (8 to <17 years of age) seem to be consistent with the overall study population.

Studies of HAEGARDA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

6.1.11.4 Dropouts and/or Discontinuations
A total of 14 subjects discontinued from the study and 106 subjects completed the study.

Thirteen subjects discontinued in the TP1 and TP2 (7 subjects in the 40 IU/kg treatment arm and 6 subjects in the 60 IU/kg treatment group), and 1 subject discontinued in the

Extension Period (in the 60 IU/kg treatment group). Reasons for study discontinuation included AEs (4 subjects), withdrawal by subject (8 subjects), and pregnancy (4 subjects).

6.1.12 Safety Analyses
6.1.12.1 Methods
The primary endpoint of Study 3002 was safety assessed by the person-time incidence rates of: AEs leading to premature study discontinuation; thromboembolic events; anaphylaxis; HAE attacks resulting in in-patient hospitalization; severe solicited AEs; related serious AEs; antibodies to C1-INH.

Safety databased for Study 3002 consisted of 59 subjects who participated in Study 3001 and 61 subjects who did not participate in Study 3001 (total n=120).

The mean duration of exposure was similar between the two dose groups. Mean duration of exposure was 65.2 and 72.5 weeks and in 40 IU/kg and 60 IU/kg group, respectively (Table 14). Mean duration of exposure of pediatric subjects (age 8-17 years old) was 89 and 81.3 weeks and in 40 IU/kg and 60 IU/kg group, respectively (Table 15).

Table 14 . Duration of Exposure (Study 3002) Safety Population

Duration of Exposure in Weeks	40 IU/kg (n=59)	60 IU/kg (n=68)
Mean (SD)	65.2 (39.1)	72.5 (37.8)
Min, Max	2, 137	8, 139
Median	52.4	52.6

Source: Modified from Table 14.2.6.1. of Study 3002 CSR (Module 5.3.5.2.)

Reviewer Comment:
In study 3002, seven subjects who were originally randomized into 40 IU/kg group, were up-titrated to 60 IU/kg group as per protocol.

Table 15. Duration of Exposure of Pediatric Subjects age <=17 years (Study 3002)

Duration of Exposure in Weeks	40 IU/kg (n=4)	60 IU/kg (n=5)
Mean (SD)	89.0 (41.6)	81.3 (40.0)
Min, Max	52, 128	51, 133
Median	87.8	53.4

6.1.12.2 Overview of Adverse Events
In study 3002, the percentage of subjects experiencing adverse reaction in >4% of subjects was similar during treatment with 40 IU/kg (81.3%) and 60 IU/kg (74.5%) (Table 16).

Table 16. Adverse Reactions in >4% of Subjects Treated with HAEGARDA Study 3002 (Safety Population)

MedDRA System Organ Class	Adverse Reaction	40 IU/kg N=59 n (%)	60 IU/kg N=68 n (%)
General Disorders and Administration Site Conditions	Injection Site Reactions*	31 (52.5)	30 (44.1)
Nervous System Disorders	Headache	9 (15.3)	10 (14.7)
Gastrointestinal Disorders	Nausea	4 (6.8)	4 (5.9)
Musculoskeletal and Connective Tissue Disorders	Myalgia	4 (6.8)	1 (1.5)
General Disorders and Administration Site Conditions	Fatigue	3 (5.1)	2 (2.9)

* Injection Site Reaction' includes the following more specific adverse reactions: Injection site bruising, Injection site discomfort, Injection site erythema, Injection site extravasation, Injection site hematoma, Injection site hemorrhage, Injection site hypoesthesia, Injection site induration, Injection site edema, Injection site pain, Injection site papule, Injection site pruritus, Injection site rash, Injection site reaction, Injection site swelling, Injection site urticaria.

Source: Modified from Table 2 of Information Request submitted 2 SEP 2020, 125606/185/15 (Seq 0310)

Solicited AEs (i.e., injection site reactions at the CSL830 injection site) were the most common adverse events and were reported in a similar percentage of subjects during treatment with 40 IU/kg (52.5%, 0.07 events / injection) than with 60 IU/kg (44.1%, 0.06 events / injection). Of the injection site reactions occurring after treatment with HAEGARDA, 98% were of mild intensity and 91% resolved within 1 day after onset.

Reviewer's comment:
Injection site reactions in study 3002 included additional injection site complaints (discomfort, extravasation, hypoesthesia, and injection site papule) that were not included in study 3001.

Four subjects discontinued the study due to adverse events. The 4 AEs included:

- One SAE of acute myocardial infarction in a subject in the 60 IU/kg group, assessed as likely not related to the study product considering subject's other cardiovascular risk factors. The subject recovered within 8 days.

- Three non-serious AEs of myalgia (in the 40 IU/kg group), headache and arthralgia (in the 60 IU/kg group).

Reviewer's Comment:
There are reports of increased risk of thromboembolic events with the use of C1-INH in the literature. TEEs are noted in Section 5 (Warnings and Precautions) of the package insert. The sponsor's PV plan includes administration of a questionnaire specific to TEEs.

One 47-year-old, female subject receiving 60 IU/kg CSL830 experienced an SAE captured within MedDRA SMQ of 'embolic and thrombotic events. Four days after study drug administration, the subject experienced an acute myocardial infarction. This SAE was considered not related to CSL830 due to subject's concomitant cardiovascular risk factors. The subject recovered after 8 days. The subject was discontinued from study due to SAE. This reviewer agrees with the assessment of MI not being related to study drug and this event should not be categorized as a TEE in study 3002. No embolic and thrombotic events were reported in any other age group.

No anaphylaxis, HAE attacks resulting in in-patient hospitalization, solicited AEs (injection site reaction) graded as severe by the investigator, or other related serious AEs occurred in either dose group.

Reviewer's Comment:
The Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) terms were used to screen for hypersensitivity reactions, and anaphylaxis/anaphylactic reactions in Study 3002. The events that were identified using these SMQs were medically reviewed to further assess if these were suggestive of Hypersensitivity Reactions. Four events in 2 subjects were assessed as related (1 event of Rash and 3 events of Injection Site Urticaria). None of these events led to change in dose and all 4 events had an outcome of recovered / resolved.

The events that were identified using these SMQs were medically reviewed and none were considered to be systemic allergic / anaphylactic reactions as defined in the protocol. There were no confirmed cases of anaphylaxis/anaphylactic reactions during the study.

Table 17 summarized the person-time incidence rates (PTIRs) of AEs leading to premature study discontinuation, thromboembolic events, anaphylaxis, HAE attacks resulting in in-patient hospitalization, solicited AEs (injection site reaction) graded as severe by the investigator, other related serious AEs and antibodies to C1-INH.

Table 17. Percent-Time Incidence Rates (PTIR) Study 3002

Treatment Arm	40 IU/kg n=59 PTIR (95% CI)	60 IU/kg n=61 PTIR (95% CI)	>=40 IU/kg n=120 PTIR (95% CI)
AE leading to premature study discontinuation	0.01 (<0.005, 0.07)	0.03 (0.01, 0.09)	0.02 (0.01, 0.05)
Thromboembolic event (TEEs)	0	0	0
Anaphylaxis	0	0	0
HAE attacks resulting in in-patient hospitalization	0	0	0.01* (<0.005, 0.03)
Solicited AEs (injection site reactions at the CSL830 injection site) graded as severe by the investigator	0	0	0
Related serious adverse events (SAEs), other than events specified above	0	0	0
Anti-C1-INH antibodies (inhibitory or non-inhibitory)	0.06 (0.02, 0.14)	0.09 (0.04, 0.17)	0.07 (0.04, 0.13)

* One subject on 80 IU/kg had one HAE attack requiring hospitalization
Source: Module 2.7.4 Summary of Clinical Safety.

6.1.12.3 Deaths

No deaths were reported in Study 3002.

6.1.12.4 Nonfatal Serious Adverse Events

Twelve SAEs (excluding thromboembolic events, anaphylaxis, HAE attacks resulting in in-patient hospitalization, injection site reaction graded as severe by the investigator) occurred in 9 subjects: 5 SAEs in 4 subjects on 40 IU/kg (bronchitis; contusion; lymphoma; dehydration and hypokalemia), 6 SAEs in 5 subjects on 60 IU/kg (acute myocardial infarction; cholelithiasis; diplopia; dizziness and chest pain; pneumonia), and 1 SAE in 1 subject on 80 IU/kg during the Extension period (hereditary angioedema) (Table 18). None of these SAEs were considered related.

Table 18. List of other Serious Adverse Events - Study 3002

Subject Age, Sex	Preferred Term	Treatment Group	Relatedness	Severity	Outcome
25, F	Cholelithiasis	60 IU/kg	Not Related	Moderate	Recovered/Resolved
54, F	Diffuse large B-cell lymphoma	40 IU/kg	Not Related	Severe	Recovered/Resolved
55, M	Contusion	40 IU/kg	Not Related	severe	Recovered/Resolved
41, F	Diplopia	60 IU/kg	Not Related	Mild	Not Recovered/Not Resolved
47, F	Acute myocardial infarction	60 IU/kg	Not Related	Severe	Recovered/Resolved
49, F	Dizziness	60 IU/kg	Not Related	Moderate	Recovered/Resolved
49, F	Chest pain	60 IU/kg	Not Related	Moderate	Recovered/Resolved
22, F	Bronchitis	40 IU/kg	Not Related	Moderate	Recovered/Resolved
67, F	Dehydration	40 IU/kg	Not Related	Severe	Recovered/Resolved
68, M	Hypokalemia	40 IU/kg	Not Related	Severe	Recovered/Resolved
68, M	Pneumonia	60 IU/kg	Not Related	Severe	Recovered/Resolved
68, M	Hereditary angioedema	80 IU/kg	Not Related	Severe	Recovered/Resolved

Source: Module 2.7.4 Summary of Clinical Safety.

6.1.12.5 Adverse Events of Special Interest (AESI)
No AESIs were reported in Study 3002. One event of acute myocardial infarction in a 47-year-old female, on 60 IU/kg, was mis-classified as TEE.

Reviewer Comment:
There are reports of increased risk of thromboembolic events with the use of C1-INH in the literature. TEEs are noted in Section 5 (Warnings and Precautions) of the package insert. The sponsor's PV plan includes administration of a questionnaire specific to TEEs.

One 47-year-old, female subject receiving 60 IU/kg CSL830 experienced an SAE captured within MedDRA SMQ of 'embolic and thrombotic events. Four days after study drug administration, the subject experienced an acute myocardial infarction. This SAE was considered not related to CSL830 due to subject having concomitant cardiovascular risk factors and the subject recovered after 8 days. The subject was discontinued from study due to SAE. This reviewer agrees with the assessment of MI not being related to study drug. No embolic and thrombotic events were reported in any other age group.

6.1.12.6 Clinical Test Results
There were no reports of clinically significant abnormal test results during Study 3002. No seroconversion for HIV, HBV, HCV were reported during the Study 3002.

No subjects had positive results for inhibitory antibodies to C1-INH at Baseline or at any post-Baseline Visit. Ten subjects who tested negative for non-inhibitory antibodies to C1-INH at Baseline tested positive at a subsequent visit. The PTIRs for antibodies to C1-INH were 0.06 events / treatment year on 40 IU/kg and 0.09 events / treatment year on 60 IU/kg.

6.1.13 Study Summary and Conclusions
The overall safety outcomes from Study 3002 was consistent with the safety outcomes from Study 3001. No SAEs in any of the clinical studies were solicited AEs or assessed as related to HAEGARDA. No deaths were reported.

Twice per week SC administration of 40 IU/kg or 60 IU/kg CSL830 is safe and effective for routine prophylaxis of HAE attacks in children age 6 years and older. The clinical pharmacology data and analysis in this BLA supplement support the approval of HAEGARDA for routine prophylaxis to prevent HAE attacks in HAE patients 6 years of age and older. Similar to Study 3001, of the 2 doses evaluated in Study 3002, 60 IU/kg seems to provide better efficacy based on some efficacy outcome measures than the 40 IU/kg dose, with no evidence of dose-dependent safety concerns.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

HAEGARDA is indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older.

7.1.1 Methods of Integration

Since the application contains only Study 3002, there is no integration or pooling of results in this review. Please see Section 6 for detailed efficacy analysis.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable as the review only included Study 3002. Please see Section 6 for details.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data
In Study 3002, four women with type I HAE, age 19 to 32 years, who received HAEGARDA became pregnant and discontinued the study. These subjects received 40 or 60 IU/kg for 4 to 8 weeks (9 - 15 doses) during the first trimester. No complications were reported during pregnancy or delivery.

9.1.2 Use During Lactation
There is no data available for the use of HAEGARDA during lactation.

9.1.3 Pediatric Use and PREA Considerations
HAEGARDA has an orphan designation for the indication of routine prophylaxis to prevent HAE attacks. So PREA is not triggered. In Study 3002, 10 pediatric subjects were enrolled and treated.

9.1.4 Immunocompromised Patients
There are no data available in this patient population.

9.1.5 Geriatric Use
In Study 3002, eight subject age 65-72 years received the high 60 IU/kg dose and one subject who received the 40 IU/kg dose, in Study 3001 and Study 3002. Clinical studies of HAEGARDA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10. CONCLUSIONS

The efficacy and safety data of Study 3002 and available PK data from Study 3002 and other studies support the expansion of indication for routine prophylaxis to prevent HAE attacks to include pediatric patients 6 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 19. Risk-Benefit Summary

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	• There is available intravenous therapy (CINRYZE) for prophylaxis of HAE in pediatric age group older than 6 years. • HAEGARDA is approved for subcutaneous administration for prophylaxis of HAE in adolescents and adults.	• There is unmet medical need for self (or caregiver) administered treatments for prophylaxis of HAE attacks in children.
Clinical Benefit	• HAEGARDA prophylaxis therapy reduces the risk of attacks in children age 8 years and older based on data from Study 3002. • Due to the limited number of pediatric subjects age 8 years and older in this study, PK parameters from pediatric subjects are used to further justify the dose and dosing regimen in children age 6-8 years.	• Twice-weekly subcutaneous injections of 60 IU/kg is safe and effective in reducing the number of HAE attacks in patients 6 years of age and older 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 is associated with local injection site reactions in approximately 30% of subjects. Other reactions occur less frequently.
Risk Management	The risk management plan includes: • Applicant's plan for routine pharmacovigilance • Adequate information provided in package insert	• The risks can be mitigated through routine medical management, adequate PI and the postmarketing plan proposed by the applicant without requiring other regulatory measures such as REMS, PMR, or clinical PMC.

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