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Application Type	BLA Supplement
STN	125606/185
CBER Received Date	November 29, 2019
PDUFA Goal Date	September 28, 2020
Division / Office	DB/OBE
Committee Chair	Rosa Sherafat-Kazemzadeh, M.D.
Clinical Reviewer(s)	Rosa Sherafat-Kazemzadeh, M.D.
Project Manager	Juliane Carvalho, M.S.
Priority Review	None
Reviewer Name(s)	Shuya (Joshua) Lu, Ph.D.
Review Completion Date / Stamped Date	Shuya Lu -S Digitally signed by Shuya Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shuya Lu -S, 0.9.2342.19200300.100.1.1=2001391331 Date: 2020.09.17 15:10:23 -04'00'
Supervisory Concurrence	Renée Rees, Ph.D. Team Leader, FDA/CBER/OBE/DB/TEB Boguang A. Zhen -S Dig tal y signed by Boguang A Zhen S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0.9 2342 19200300 100 1 1=1300140624 cn=Boguang A Zhen S Date: 2020 09 17 15:47:43 04'00' -- Signed for Dr. Rees
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB Boguang A. Zhen -S D gitally signed by Boguang A Zhen S DN: c US o U S Government ou HHS ou FDA ou People 0.9 2342 19200300 100 1 1 1300140624 cn Boguang A Zhen S Date: 2020 09 17 15 50:26 04 00
Applicant	CSL Behring
Established Name	C1 Esterase Inhibitor (Human)
(Proposed) Trade Name	HAEGARDA
Pharmacologic Class	ATC Code: B06AC01
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for reconstitution (b) (4) IU C1-INH per single-use vial
Dosing Regimen	(b) (4) 60,(b) (4) IU/kg
Indication(s) and Intended Population(s)	Current: For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients Extend: For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in pediatric patients 6 years and older

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GLOSSARY

AE	Adverse Event
BLA	Biologics License Application
BMI	Body mass index
C1-INH	C1-esterase inhibitor
CSR	Clinical Study Report
CI	Confidence interval
FDA	Food and Drug Administration
HAE	Hereditary angioedema
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IU	International Unit
IV	Intravenous
PTIRs	Person-time incidence rates
PD	Pharmacodynamic
PK	Pharmacokinetic
SAEs	Serious adverse events
SC	Subcutaneous
US	United States

1. Executive Summary

HAEGARDA (human plasma-derived C1 esterase inhibitor [recombinant]) is an FDA licensed product for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients since June 2017. The purpose of this supplemental Biologics License Application (sBLA) is to expand the indication to include pediatric patients (6 years of age and older) and update the “Clinical Studies” and “Use in Specific Populations” section based on data from completed phase 3 study CSL830_3002.

CSL830_3002 is a Phase 3b, multicenter, randomized, open-label, parallel-arm (40 IU/kg or 60 IU/kg) study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of HAEGARDA in the prophylactic treatment of HAE. The primary (safety) endpoint is Person-time incidence rates (PTIRs) of Adverse events (AEs).

There are two efficacy endpoints which are secondary endpoints in this study. The first efficacy endpoint is 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 HAEGARDA, compared with the time-normalized number of attacks that was used to qualify the subject for participation in this study. The second efficacy endpoint is the percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.

Six subjects enrolled at one site were removed from the final analysis due to the investigator being disqualified. After removing these subjects, the percentage of responders for the remaining 120 subjects was 93.1% and the 95% Wilson confidence interval (CI) was (83.6%, 97.3%)) in the 40 IU/kg treatment arm and 91.% (81.4%, 96.3%) in the 60 IU/kg treatment arm. The proportion of subjects with a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period was 79.7% in the 40 IU/kg treatment arm and 86.9% in the 60 IU/kg treatment arm.

Incidence of AEs was 12.0 events per patient-year for 40 IU/kg treatment arm and 8.6 events per patient-year for 60 IU/kg treatment arm. The safety evaluation from the clinical reviewer revealed that no subjects developed any SAEs that might be a safety concern.

There were no statistical issues in this submission. The efficacy results support the proposed extended indication of routine prophylaxis to prevent acute angioedema attacks in pediatric patients at least 6 years of age with HAE.

2. Clinical and Regulatory Background

HAEGARDA is a highly purified, lyophilized C1-esterase inhibitor (C1-INH) concentrate derived from human plasma. It is intended for subcutaneous (SC) administration after reconstitution with sterile water for injection (concentration: 500 IU of C1-INH per mL). It is approved in the United States (US) for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

2.1 Disease or Health-Related Condition(s) Studied

HAE is an autosomal dominant disease caused by a gene mutation on chromosome 11 that affects the production of C1-INH protein [*Gower et al, 2011*]. 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. HAE is estimated to affect approximately 1 in 50,000 individuals, with no ethnic predominance [*Bowen et al, 2010; Constantino et al, 2012*], suggesting that more than 6000 individuals are affected in the US.

The age of onset of HAE is variable. For the majority of patients, the disease first presents in childhood or adolescence with age of onset ranging from 4.4 to 18 years and a mean age at first attack of 10 years [*Cicardi et al, 1982; Farkas et al, 2017*]. Early onset of symptoms is associated with a more severe disease course [*Bork et al, 2006*] and attacks become more severe and symptoms worsen during puberty, particularly in female subjects [*Farkas et al, 2017*].

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

Despite the availability of Intravenous (IV) C1-INH therapy and oral attenuated androgens, HAE remains a serious clinical condition with a need for prophylactic treatment. Limitations of IV C1-INH prophylaxis include the frequency of breakthrough attacks and the burden of venous access [*Zuraw et al, 2010; Dychter et al, 2012*]. Long-term use of attenuated androgens is associated with substantial safety and tolerability issues, and the effectiveness of androgens diminishes over time [*Agostoni et al, 2004; Bowen et al, 2010; Gower et al, 2011; Craig et al, 2012*].

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

The clinical development program of HAEGARDA was designed to determine the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of HAEGARDA in subjects with HAE, and consists of four completed studies: 1001, 2001, 3001, and 3002. Study 1001 was a phase 1, single-center study that evaluated the safety, bioavailability, and PK in healthy subjects. Study 2001 was a phase 1/2, multicenter, open-label, dose-ranging, crossover study that evaluated the PK, PD, and safety of SC administration of three dosing regimens of HAEGARDA in subjects with HAE type I or II. Study 3001 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of SC administration of HAEGARDA for routine prophylaxis to prevent HAE attacks in adolescent and adult subjects with HAE type I or II. Study 3002 is reviewed in this memo.

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

All four studies were conducted under IND 14992. There was no pre-sBLA meeting for this submission. This applicant requested an adolescent, but not a pediatric, indication in the original BLA for HAEGARDA; it was not approved.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

One of the principal investigators for study CSL830_3002, Dr. James Baker, was issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter by the FDA on March 23, 2018. Therefore, the six

subjects (one is less than 18 years old, three are between 18 and 65, and two are older than 65) enrolled at Dr. Baker's site (8400147) were removed from the final analysis.

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

5.1 Review Strategy

Study CSL830_3002 is considered the pivotal study for the routine prophylaxis indication in pediatric patients. It was the only study submitted in this sBLA, therefore only CSL830_3002 is reviewed in this memo.

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

sBLA	**125606/185.0**	
	Module 1.14	Labeling
	Module 2.5	Clinical Overview
	Module 5.3.5.2	Study Reports CSL830_3002: study report body, protocol, statistical analysis plan.
	Module 5.3.5.2	Data Files adsl.xpt, adbe.xpt
	125606/185.2	
	Module 1.11.3	Clinical Information Amendment
	125606/185.13	
	Module 1.11.3	Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Table 1 Summary of Clinical Studies in the sBLA

Study; Status; Report Location	**Type of Study**	**Phase; Study Design**	**Primary Objective(s)**	**Subject Population; Median Age (Range)**	**Treatment; Route; Dose; Duration**	**Location; Number of Study Centers**
Study 3002; Completed;	Safety, efficacy, PK, PD, and QoL	Phase 3b, multicenter, randomized, open-label, parallel-group study	Assess the safety of SC HAEGARDA in the long-term prophylactic treatment of HAE	Subject Population: 126 subjects with HAE type I or II (76 females / 50 males); Median Age (Range); 41 years (8 to 72 years) Subgroups: < 12 years: 3 subjects < 17 years: 10 subjects ≥ 65 years: 10 subjects	Single SC injection of 40 IU/kg or 60 IU/kg HAEGARDA 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	Australia (1) Canada (4) Czech Republic (1) Germany (4) Hungary (1) Israel (2) Italy (2) Romania (1) Spain (3) United Kingdom (1) United States (12)

Source: sBLA 125606/185.0; Module 2.5 Clinical Overview Table 1.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 CSL830_3002

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:
To assess the clinical safety of SC administered HAEGARDA in the long-term (i.e., routine) prophylactic treatment of HAE.

Secondary Objectives:

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

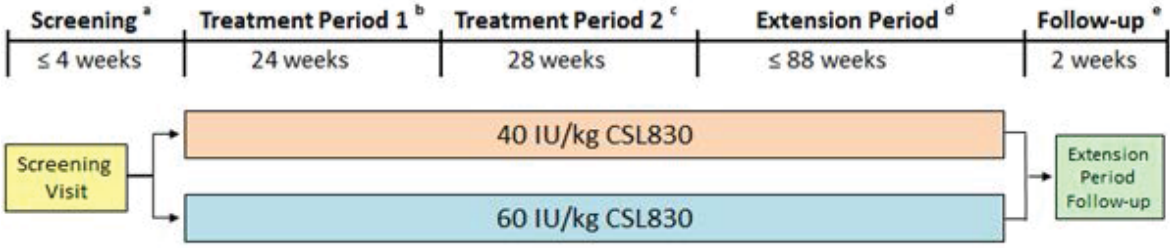
6.1.2 Design Overview

Eligibility for all subjects was assessed at a screening visit, followed by randomization to either 40 IU/kg or 60 IU/kg HAEGARDA in the 24-week fixed-dose treatment period 1 (TP1). Subjects recorded HAE attacks with an electronic recording system (eDiary); any rescue medication taken during treatment of an HAE attack was also recorded in the eDiary. During TP1, subjects who experienced frequent HAE attacks (i.e., ≥ 12 attacks within a 4-week evaluation

period) were eligible for dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). Beginning at Week 25, subjects experienced treatment period 2 (TP2) which was a dose-adjustment period to allow for individual optimization of routine prophylaxis. Subjects who experienced ≥ 3 HAE attacks within an 8-week evaluation period during TP2 were eligible for dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). TP2 ended at Week 53.

Additionally, a Country-specific Protocol Amendment included an optional Extension Period (88 weeks followed by 2-week follow-up) to allow subjects from the US who completed TP2 according to the protocol to then continue receiving treatment with open-label HAEGARDA. The Extension Period followed TP2, with the last visit of TP2 serving as the first visit of the Extension Period (except for subjects who elected to take a rest period of up to 30 days between TP2 and the Extension Period). An overview of the study is depicted in Figure 1.

Figure 1 Study Plan



Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Figure 9-1.

6.1.3 Population

The main inclusion criteria were:

1. Male or female.
2. Aged 6 years or older at the time of providing written informed consent / assent (as appropriate).
3. A diagnosis of HAE (type I or II), as determined by the following: a clinical history consistent with HAE and C1-INH functional activity levels < 50%, concurrent with C4 antigen concentrations below normal limits.
4. Have experienced HAE attacks (requiring acute treatment, medical attention or causing significant functional impairment).
5. Use of oral medication for prophylaxis against HAE attacks (i.e., androgens, tranexamic acid, progestins) within 3 months of their first study visit.

The main exclusion criteria were:

1. Enrollment in Study 3001 and withdrew before completion of that study for any reason.
2. Known incurable malignancies at the time of the first study visit.
3. Any clinical condition that was likely to interfere with evaluation of HAEGARDA or

4. Satisfactory conduct of the study.
5. A clinically significant history of poor response to C1-INH therapy for the management of HAE.
6. A suspected or confirmed diagnosis of acquired HAE or HAE with normal C1-INH (ie, HAE type III).

6.1.4 Study Treatments or Agents Mandated by the Protocol

During all treatment periods, subjects administered their randomized dose of HAEGARDA (40 IU/kg or 60 IU/kg) via a single SC injection, twice per week. Dose increases were allowed as described in section 6.1.2.

6.1.6 Sites and Centers

Thirty-two study centers were initiated, including centers in Australia (1 center), Canada (4), the Czech Republic (1), Germany (4), Hungary (1), Israel (2), Italy (2), Romania (1), Spain (3), the United Kingdom (1), and the United States (12).

6.1.7 Surveillance/Monitoring

A HAEGARDA 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 Safety Endpoints:
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 was the consequence of the need for emergent medical care).
- Solicited AEs (injection site reactions at the HAEGARDA 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 Efficacy Endpoints (no success criteria specified):

- 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 HAEGARDA, compared with the time-normalized number of attacks that was used to qualify the subject for participation in this study. Use of rescue medication did not alter responder assessment.
- The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.

Exploratory Efficacy Endpoints include:

- Time-normalized Number of HAE Attacks

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size:
It was planned that 100 subjects would complete the study. The sample size was determined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E1 guidelines on the extent of population exposure to assess clinical safety. When no AE is observed with this sample size the one-year true incidence rate is no greater than 3% at 95% confidence.

Analysis Populations:
The following analysis sets were considered:

Intent-to-treat (ITT) Population: the ITT population comprised all subjects who were randomized, regardless of whether they received HAEGARDA.

Safety Population (SAF): the Safety population comprised all subjects who were randomized, and received at least one dose or a partial dose of HAEGARDA.

Per-protocol (PP) Population: the PP population comprised all subjects in the ITT population, excluding subjects who had a major protocol deviation.

Quality of Life (QoL) Population: the QoL population comprised all subjects in the ITT population who provided at least one subject-reported outcome measure.

The efficacy endpoints were evaluated using the ITT and PP populations. The ITT and PP populations were analyzed as randomized. However, for the secondary efficacy endpoint percentage of responders, the percentage reduction may not be evaluable, and those subjects were excluded from the ITT population.

Secondary Efficacy Endpoint Analysis
The evaluation period for efficacy analysis was from the start (Day 1) of Week 3 of a treatment in TP1 until the End of Study Visit (Week 53 for subjects who did not participate in the Extension Period, or Week 88 for subjects who participated in the Extension Period) or the last administration of CSL830 + 4 days (whichever was first).

- **The percentage of subjects who were responders**:
  The percentage reduction in the time-normalized number of HAE attacks was calculated per subject as:

$$P = 100 * (1 - \frac{N_1}{N_2}) \quad [1]$$

where
P = percentage reduction in the time-normalized number of HAE attacks
N_1 = the time-normalized number of HAE attacks when treated with HAEGARDA
N_2 = the time-normalized number of HAE attacks used to qualify for participation in the study

The time-normalized number of HAE attacks was calculated according to equation [2] below:

$$\text{Time-normalized number of HAE attacks} = \frac{\text{Number of HAE attacks}}{\text{Length of stay of the subject in the treatment}} \quad [2]$$

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

A subject was classified as a responder if the percentage reduction in time-normalized number of HAE attacks during treatment with HAEGARDA was ≥ 50%. The number and percentage of responders and non-responders and the difference in the percentage of responder between the 60 IU/kg and 40 IU/kg treatments was summarized and 95% Wilson CIs were calculated for all percentages.

A subject whose time-normalized number of attacks could not be calculated in the treatment periods (e.g., due to $N_2 = 0$) was to be excluded from the calculation of the percentage of responder analysis.

- **The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period**:
  For the calculation of the HAE attacks per 4-week period, the time-normalized number of HAE attacks (as described in equation [3]) were multiplied by 28. 95% Wilson CIs were calculated for all percentages.

$$N = n/L \quad [3]$$

Where
N = Time-normalized number of HAE attacks
n = Number of HAE attacks
L = Length of stay of the subject in the treatment

Missing Data:
No imputations for missing data were planned.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 126 subjects were randomized into the study that constitute the ITT population. 63 subjects were assigned to the 40 IU/kg treatment arm and 63 subjects to the 60 IU/kg treatment arm. Each treatment arm comprised 6 (9.5%) "HAEGARDA-Continuation" subjects, 26 (41.3%) "HAEGARDA-Interrupted" subjects, and 31 (49.2%) "HAEGARDA-Naïve" subjects. Since all 126 subjects in the ITT Population received at least one dose of HAEGARDA, they also constitute the Safety population. The PP population included 111 subjects.

6.1.10.1.1 Demographics

Of the 126 subjects in the Safety population, 76 (60.3%) were female and 121 (96.0%) were White. The mean (SD) age was 40.5 (15.56) years. The other baseline characteristics and demographic data for the Safety population are described in Table 2 and Table 3.

Table 2 Baseline Characteristics, Safety Population (N=126)

Parameter	**40 IU/kg (N = 63)**	**60 IU/kg (N = 70[a])**	**≥ 40 IU/kg (N = 126)**
Age (years)			
n	63	70	126
Mean (SD)	40.8 (14.96)	40.8 (16.01)	40.5 (15.56)
Min, Max	8, 67	10, 72	8, 72
Median	43.0	41.5	41.0
Age <18 (years)			
n	5	5	10
Mean (Mix, Max)	12.6 (8, 16)	14.0 (10, 16)	13.3 (8, 16)
Age >= 65 (years)			
n	2	8	10
Mean (Mix, Max)	66.5 (66, 67)	68.3 (65, 72)	67.9 (65, 72)
Weight (kg)			
n	63	70	126
Mean (SD)	86.05 (23.270)	84.91 (24.603)	85.16 (23.679)
Min, Max	45.5, 143.2	29.4, 148.6	29.4, 148.6
Median	87.20	80.00	83.00
BMI (kg/m^2)			
n	63	70	126
Mean (SD)	29.62 (6.919)	29.00 (7.428)	29.21 (7.230)
Min, Max	16.7, 47.1	15.1, 54.2	15.1, 54.2
Median	29.36	27.93	28.29

a Seven subjects who were up-titrated from 40 IU/kg to 60 IU/kg were included in both treatments in the Safety Population.

Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Table 11-1.

Table 3 Demographics, Safety Population (N=126)

Parameter	40 IU/kg (N = 63)	60 IU/kg (N = 70[a])	≥ 40 IU/kg (N = 126)
Sex, n (%)			
Female	40 (63.5)	41 (58.6)	76 (60.3)
Male	23 (36.5)	29 (41.4)	50 (39.7)
Race, n (%)			
White	60 (95.2)	67 (95.7)	121 (96.0)
Black or African American	1 (1.6)	1 (1.4)	2 (1.6)
Asian	0	1 (1.4)	1 (0.8)
Other	2 (3.2)	1 (1.4)	2 (1.6)

a Seven subjects who were up-titrated from 40 IU/kg to 60 IU/kg were included in both treatments in the Safety Population.

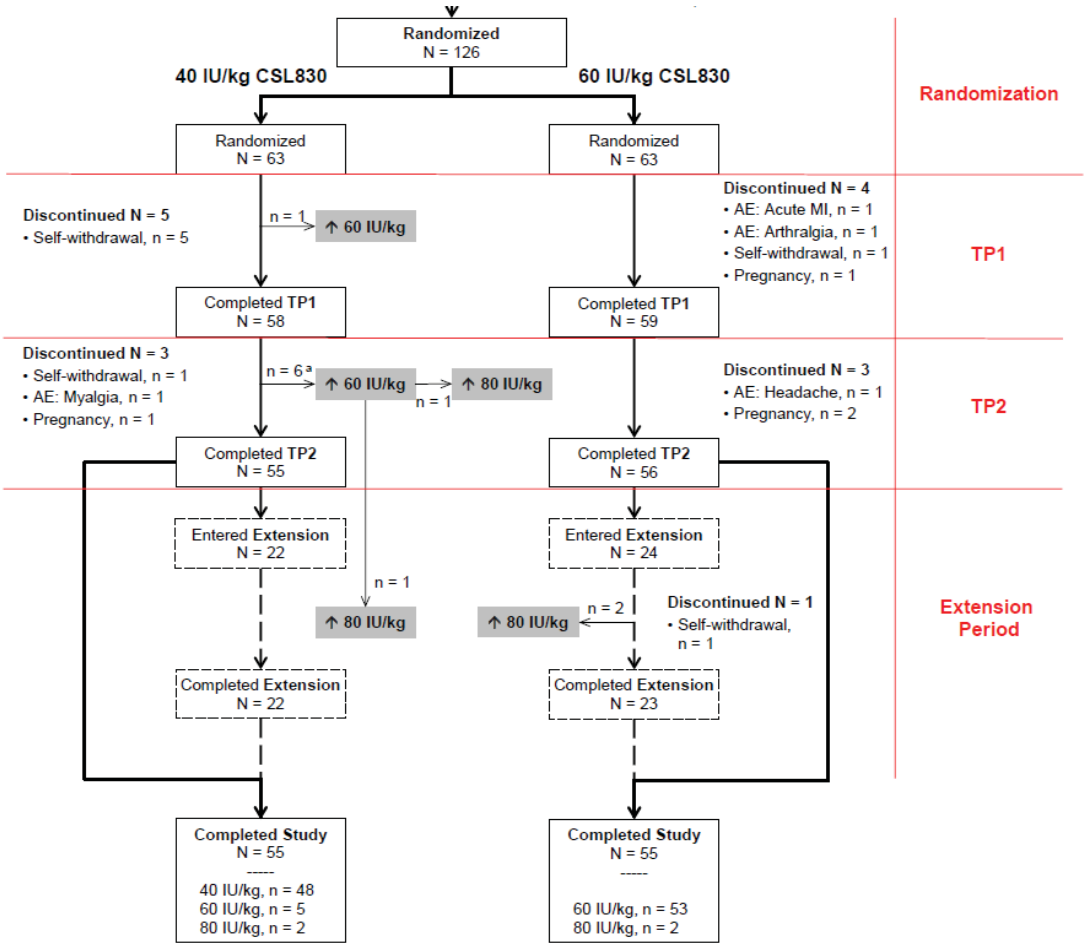
Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Table 11-1.

6.1.10.1.3 Subject Disposition

Two subjects randomized to the 60 IU/kg treatment arm were up-titrated to 80 IU/kg. Seven subjects randomized to the 40 IU/kg treatment arm were 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 then to 80 IU/kg.

A total of 16 subjects discontinued from the study. Nine subjects discontinued in TP1 (5 subjects in the 40 IU/kg treatment arm and 4 subjects in the 60 IU/kg treatment arm), 6 subjects discontinued in TP2 (3 subjects in the 40 IU/kg treatment arm and 3 subjects in the 60 IU/kg treatment arm), and 1 subject discontinued in the Extension Period (in the 60 IU/kg treatment arm). Figure 2 presents the subject disposition of this study.

Figure 2 Subject Disposition



Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Figure 10-1.

The reasons for study discontinuation included pregnancy, AEs, and withdrawal by subject.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoints in this study are for the safety investigation.

6.1.11.2 Analyses of Secondary Endpoints

- **Percentage of Subjects Who were Responders**:

The percentage of responders based on HAE attacks was 93.5% and the 95% Wilson CI was (84.6%, 97.5%) in the 40 IU/kg treatment arm and 91.7% with 95% Wilson CI (81.9%, 96.4%) in the 60 IU/kg treatment arm. Table 4 presents the analysis results.

Table 4 Percentage of Responders Based on HAE Attacks (ITT Population)

	40 IU/kg (N = 63)	**60 IU/kg (N = 63)**	**≥ 40 IU/kg (N = 126)**
n	62	60	122
Responder, % (n)[a]	93.5% (58)	91.7% (55)	92.6% (113)
95% Wilson CI	(84.6, 97.5)	(81.9, 96.4)	(86.6, 96.1)
Difference in % of Responders[b]			
60 IU/kg– 40 IU/kg %	-1.9%		-
95% Wilson CI	(-12.4, 8.3)		-

a Percentages were based on the number of subjects (n) included in the analysis. Subjects whose time-normalized number of attacks was not available were excluded from the analysis.
b The difference between HAEGARDA doses was assessed using Wilson asymptotic confidence limits for the difference in percentages.
Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Table 11-6.

Reviewer Comment:

1. *For the reason mentioned in Section 3.2, Table 5 presents the updated analysis results after removing the subjects from site 8400147. The results are similar as the original results.*
2. *For three subjects (60 IU/kg) the time-normalized number of HAE attacks prior to the study was 0 attacks, thus no assessment of response was possible. One subject (40 IU/kg) discontinued the study prior to the start of the efficacy evaluation period, so the subject's data was excluded from analyses of efficacy endpoints, including the responder analysis. Therefore, these four subjects were excluded from analysis (see footnote 'a'). Please refer to Section 6.1.11.4 for the sensitivity analysis.*

Table 5 Percentage of Responders Based on HAE Attacks (ITT Population) (Excluding Subjects from Site 8400147)

	40 IU/kg (N = 59)	***60 IU/kg (N = 61)***	***≥ 40 IU/kg (N = 120)***
n	*58*	*58*	*116*
Responder, % (n)[a]	*93.1% (54)*	*91.4% (53)*	*92.2% (107)*
95% Wilson CI	*(83.6, 97.3)*	*(81.4, 96.3)*	*(85.9, 95.9)*
Difference in % of Responders[b]			
60 IU/kg– 40 IU/kg %	*-1.7 %*		-
95% Wilson CI	*(-12.6, 9.0)*		-

a Percentages were based on the number of subjects (n) included in the analysis. Subjects whose time-normalized number of attacks was not available were excluded from the analysis.
b The difference between HAEGARDA doses was assessed using Wilson asymptotic confidence limits for the difference in percentages.
Source: sBLA 125606/185.2; Module 1.11.3 Clinical Information Amendment Table 14.2.1.5.

- **The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period:**

The proportion of subjects with a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period was 79.4% in the 40 IU/kg treatment arm and 85.7% in the 60 IU/kg treatment arm. The mean (SD) change in the number of HAE attacks was -6.82 attacks (11.809) in the 40 IU/kg treatment arm and -6.83 attacks (16.346) in the 60 IU/kg treatment arm. Table 6 presents the analysis results.

Table 6 Time-normalized HAE Attack Frequency of Less Than 1 HAE Attack per 4-week Period (ITT Population)

	40 IU/kg (N = 63)	**60 IU/kg (N = 63)**	**≥ 40 IU/kg (N = 126)**
< 1 HAE Attack per 4-week Period, n (%)	50 (79.4)	54 (85.7)	104 (82.5)
≥ 1 HAE Attack per 4-week Period, n (%)	12 (19.0)	9 (14.3)	21 (16.7)
Missing, n (%)	1 (1.6)	0	1 (0.8)
Number of Attacks Experienced Following Treatment with HAEGARDA Minus Number of Attacks Pre-Study			
Mean (SD)	-6.82 (11.809)	-6.83 (16.346)	-6.82 (14.220)
95% CI	(-9.82, -3.82)	(-10.94, -2.71)	(-9.34, -4.31)

Source: sBLA 125606/185.0; Module 5.3.5.2 CSR Study CSL830_3002 Table 11-7.

Reviewer Comment:

3. *For the reason mentioned in Section 3.2, Table 7 presents the updated analysis results after removing the subjects from site 8400147. The results are similar as the original results.*

Table 7 Time-normalized HAE Attack Frequency of Less Than 1 HAE Attack per 4-week Period (ITT Population) (Excluding Subjects from Site 8400147)

	40 IU/kg (N = 59)	***60 IU/kg (N = 61)***	***≥ 40 IU/kg (N = 120)***
< 1 HAE Attack per 4-week Period, n (%)	*47 (79.7%)*	*53 (86.9%)*	*100 (83.3%)*

Source: sBLA 125606/185.13; Module 1.11.3 Clinical Information Amendment Table 1.

6.1.11.3 Subpopulation Analyses

- **Percentage of Subjects Who were Responders:**

The percentage of responders based on HAE attacks (95% Wilson CI) for the subgroup ≤ 17 years was 100% (56.6%, 100.0%) for both the 40 IU/kg (5 subjects) and the 60 IU/kg treatment arm (5 subjects). The percentage of responders for the subgroup > 17 years was 93.0% (83.3%, 97.2%) in the 40 IU/kg treatment arm (57 subjects) and 90.9% (80.4%, 96.1%) in the 60 IU/kg treatment arm (55 subjects). Note that four subjects were excluded from the analysis; see Reviewer Comment #2.

Reviewer Comment:

4. *For the reason mentioned in Section 3.2, Table 8 presents the updated analysis results after removing the subjects from site 8400147*.

Table 8 Subgroup Analysis of Responders Based on HAE Attacks (ITT Population) (Excluding Subjects from Site 8400147)

	40 IU/kg (N = 59)	***60 IU/kg (N = 61)***	***≥ 40 IU/kg (N = 120)***
≤ 17 years			
Subjects included in analysis	*4*	*5*	*9*
Responder n (%)	*4 (100%)*	*5 (100%)*	*9 (100%)*
17 < Age < 65			
Subjects included in analysis	*53*	*47*	*100*
Responder n (%)	*49 (92.5%)*	*45 (95.7%)*	*94 (94%)*
≥ 65 years			
Subjects included in analysis	*1*	*6*	*7*
Responder n (%)	*1 (100%)*	*4 (66.7%)*	*5 (71.4%)*

Source: sBLA 125606/185.13; Module 1.11.3 Clinical Information Amendment Table 3.

- **The percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period:**

The proportion of subjects with a time-normalized number of HAE attacks < 1 per 4-week period (95% Wilson CI) for the subgroup ≤ 17 years was 100% for both the 40 IU/kg (5 subjects) and the 60 IU/kg treatment arm (5 subjects). The proportion of subjects with a time-normalized number of attacks < 1 per 4-week period for the subgroup > 17 years was 77.6% in the 40 IU/kg treatment arm (58 subjects) and 84.5% in the 60 IU/kg treatment arm (58 subjects).

Reviewer Comment:

5. *For the reason mentioned in Section 3.2, Table 9 presents the updated analysis results after removing the subjects from site 8400147*.

Table 9 Subgroup Analysis of Time-normalized HAE Attack Frequency of Less Than 1 HAE Attack per 4-week Period (ITT Population) (Excluding Subjects from Site 8400147)

	40 IU/kg (N = 59)	***60 IU/kg (N = 61)***	***≥ 40 IU/kg (N = 120)***
≤ 17 years			
Subjects included in analysis	*4*	*5*	*9*
Responder n (%)	*4 (100%)*	*5 (100%)*	*9 (100%)*
17 < Age < 65			
Subjects included in analysis	*54*	*49*	*103*
Responder n (%)	*42 (77.8%)*	*43 (87.8%)*	*85 (82.5%)*
≥ 65 years			
Subjects included in analysis	*1*	*7*	*8*
Responder n (%)	*1 (100%)*	*5 (71.4%)*	*6 (75%)*

Source: sBLA 125606/185.13; Module 1.11.3 Clinical Information Amendment Table 2.

6.1.11.4 Dropouts and/or Discontinuations

Sixteen subjects discontinued from the study prematurely. Please see section 6.1.10.1.3 for more details. Reasons for discontinuation can be found in Figure 2 of section 6.1.10.1.3. No sensitivity analysis was performed for these missing data since their data was included in the time-normalized outcomes.

As discussed in Section 6.1.11.2, four subjects have missing data in the final analysis for the percentage of responders. I did a sensitivity analysis by taking these four subjects as non-responders to investigate the influence of the missing data. Table 10 presents the results. The results are similar as the original results.

Table 10 Sensitivity Analysis of Responders Based on HAE Attacks (ITT Population) (Excluding Subjects from Site 8400147)

	40 IU/kg (N = 59)	**60 IU/kg (N = 61)**	**≥ 40 IU/kg (N = 120)**
Responder, % (n)	91.5% (54)	86.9% (53)	89.2% (107)

6.1.12 Safety Analyses

Incidence of AEs was 12.0 events per patient-year for 40 IU/kg treatment arm and 8.6 events per patient-year for 60 IU/kg treatment arm.

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Twelve SAEs were experienced by nine subjects. Five SAEs occurred in four subjects during treatment with 40 IU/kg, six SAEs occurred in five subjects during treatment with 60 IU/kg, and one SAE occurred in one subject during treatment

with 80 IU/kg. One SAE of acute myocardial infarction (assessed as not related) led to study discontinuation. The majority of SAEs were moderate or severe and had an outcome of recovered / resolved.

6.1.12.5 Adverse Events of Special Interest (AESI)

A single thromboembolic event was reported during the study (acute myocardial infarction during treatment with 60 IU/kg; assessed as not related to HAEGARDA). No cases of anaphylaxis, sepsis, or bacteremia were identified. No seroconversions for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus were identified. No inhibitory antibodies were detected.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

There is no major statistical issue in this sBLA submission. This submission includes the final analysis of the pivotal study CSL830_3002, a phase 3b, multicenter, randomized, open-label, parallel-arm (40 IU/kg or 60 IU/kg) study. There are two efficacy endpoints which are secondary endpoints in this study: (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 HAEGARDA, and (2) the percentage of subjects who experienced a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period.

After excluding the six subjects from the disqualified site, the percentage of responders (95% CI) for the remaining 120 subjects was 93.1% (83.6%, 93.7%) for 40 IU/kg treatment and 91.4% (81.4%, 96.3%) on 60 IU/kg treatment. The proportion of subjects with a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period was 79.7% in the 40 IU/kg treatment arm and 86.9% in the 60 IU/kg treatment arm. A subgroup analysis based on age (≤17 years, >17 years) showed similar results for both efficacy endpoints.

The safety evaluation revealed that no deaths, sepsis or bacteremia were reported during the study. No inhibitory antibodies were detected.

10.2 Conclusions and Recommendations

Based on the efficacy results of pivotal study CSL830_3002, I conclude that the statistical evidence supports the proposed indication of the routine prophylaxis to prevent HAE attacks in adult and pediatric patients 6 years and older.