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| Application Type | Original BLA |
| STN | 125606/0 |
| CBER Received Date | June 30, 2016 |
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| Division / Office | OTAT |
| Committee Chair | Ewa Marszal, Ph.D. |
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| Project Manager | Nannette Cagungun, M.S. |
| Priority Review | No |
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| Review Completion Date / Stamped Date | |
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| Applicant | CSL Behring GmbH |
| Established Name | C1 Esterase Inhibitor (Human) |
| (Proposed) Trade Name | HAEGARDA |
| Pharmacologic Class | |
| Formulation(s), including Adjuvants, etc | |
| Dosage Form(s) and Route(s) of Administration | Lyophilized powder/ subcutaneous use after reconstitution only |
| Dosing Regimen | 40 IU/kg, 60 IU/kg |
| Indication(s) and Intended Population(s) | Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients |

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## GLOSSARY

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|---|---|
| AE | Adverse Event |
| BLA | Biologics License Application |
| BMI | Body mass index |
| C1-INH | C1-esterase inhibitor |
| CI | Confidence interval |
| CSLB | CSL Behring GmbH |
| CSR | Clinical Study Report |
| EQ-5D | European quality of life-5 dimensions questionnaire |
| FDA | Food and Drug Administration |
| HADS | Hospital anxiety and depression scale |
| HAE | Hereditary angioedema |
| IND | Investigation new drug |
| ITT | Intent- to-treat |
| IU | International Unit |
| IV | Intravenous |
| LS | Least squares |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PD | Pharmacodynamics |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SC | Subcutaneous |
| TP1 | Treatment Period 1 |
| TP2 | Treatment Period 2 |
| TSQM | Treatment satisfaction questionnaire for medication |
| US | United States |
| WPAI | Work productivity and activity impairment questionnaire |

## 1. EXECUTIVE SUMMARY

This is an original Biologics License Application (BLA) for the applicant's human plasma-derived C1-esterase inhibitor (C1-INH) concentrate product with the trade name of HAEGARDA (also refer to as CSL830 in this review). HAEGARDA is a (b) (4) Berinert, a CSL Behring GmbH's (CSLB) intravenous C1-INH product the Food and Drug Administration (FDA) approved in 2009 for the treatment of Hereditary Angioedema (HAE) attacks.

HAEGARDA is proposed for the indication of routine prophylaxis to prevent HAE attacks in adolescent and adult patients. This BLA contains four clinical studies. Studies 1001 and 2001 examined the safety and pharmacokinetics (PK) of HAEGARDA; their results are not covered in this review and are deferred to the clinical pharmacologist. Study 3002 is an ongoing phase 3b study investigating the long-term clinical safety and efficacy of HAEGARDA. Since the efficacy objectives of this study were considered exploratory, the study is not reviewed in this memo. Study 3001 is considered pivotal and is reviewed herein.

**Study 3001** was a double-blind, randomized, placebo-controlled, crossover study designed to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema. The primary efficacy variable was the time-normalized number of HAE attacks and the primary analysis was conducted in 90 randomized subjects aged 12 to 72 years.

Of the 45 subjects randomized to a 60 IU/kg HAEGARDA treatment sequence, 43 subjects received 60 IU/kg HAEGARDA, 42 subjects received low-volume placebo, and 40 subjects received both 60 IU/kg HAEGARDA and placebo. The least squares (LS) mean (95% confidence interval [CI]) time-normalized number of HAE attacks was 0.52 (0.00, 1.04) attacks per month on 60 IU/kg HAEGARDA (median: 0.29 attacks per month) and 4.03 (3.51, 4.55) attacks per month on low-volume placebo (median: 3.81 attacks per month). Of the 40 subjects who received both 60 IU/kg HAEGARDA and low-volume placebo, the within-subject treatment difference was statistically significant ($p< 0.001$). Therefore, the hypothesis testing of 40 IU/kg HAEGARDA against high-volume placebo was performed according to a pre-specified hierarchical testing approach. Of the 45 subjects randomized to a 40 IU/kg HAEGARDA treatment sequence, 43 subjects received 40 IU/kg HAEGARDA, 44 subjects received high-volume placebo, and 42 subjects received both 40 IU/kg HAEGARDA and placebo. The LS mean (95% CI) time-normalized number of HAE attacks was 1.19 (0.54, 1.85) attacks per month on 40 IU/kg HAEGARDA (median: 0.29 attacks per month) and 3.61 (2.96, 4.26) attacks per month on high-volume placebo (median: 3.75 attacks per month). Of the 42 subjects who received both 40 IU/kg HAEGARDA and high-volume placebo, the within-subject treatment difference was statistically significant ($p< 0.001$). The between-subject comparison of doses showed that 60 IU/kg had a numerically better treatment effect than 40 IU/kg. The difference between doses in the time-normalized number of HAE attacks (LS mean [95% CI]: -0.64 [-1.43, 0.16] attacks per month) was not statistically significant ($p = 0.114$).

The percentage of responders (95% CI) defined as individuals with a ≥50% reduction in the time-normalized number of HAE attacks on HAEGARDA relative to placebo was 82.9% (73.4%, 89.5%). Ninety percent of subjects on 60 IU/kg responded to treatment and 76.2% of subjects on 40 IU/kg responded to treatment. HAEGARDA reduced the time normalized number of uses of rescue medication compared with placebo. The 60 IU/kg dose reduced the mean rate of rescue medication use to 0.32 uses per month from 3.89 uses per month on placebo. The 40 IU/kg dose reduced the mean rate of rescue medication use to 1.13 uses per month from 5.55 uses per month on placebo.

There were a total of 6 subjects with at least one laryngeal attack on 40 IU/kg CSL830, 12 subjects with at least one laryngeal attack on high-volume placebo, and 8 subjects with at least one laryngeal attack on low-volume placebo. No subjects had laryngeal attacks on 60 IU/kg CSL830.0.

Four serious adverse events (SAEs) occurred in three subjects during the study. One SAE occurred during treatment with 40 IU/kg HAEGARDA and three SAEs occurred during treatment with placebo. A single SAE of Pulmonary Embolism was reported as related to the investigational product (high-volume placebo) and led to study discontinuation. None of the SAEs were solicited AEs (i.e., injection site reactions). No subjects died during participation in the study.

I verified the primary and secondary efficacy results for study 3001. No discrepancies were found. The statistical evidence supports the applicant's proposed indications for HAEGARDA in BLA 125606/0.

## 2. CLINICAL AND REGULATORY BACKGROUND

HAEGARDA is a highly purified, lyophilized C1-INH concentrate derived from human plasma. It is intended for SC administration after reconstitution with sterile water for injection. HAEGARDA is proposed for the indication of routine prophylaxis to prevent HAE attacks in adolescent and adults patients. It will be available as a single-use vial in two sizes: 2000 IU with 4mL water for injection and 3000 IU with 6mL water for injection each containing 500 IU/ml C1-esterase inhibitor after reconstitution.

HAEGARDA is intended to be administered as a single SC injection twice per week, and to prevent HAE attacks by directly replacing and sustaining therapeutic concentrations of the functional C1-INH protein that patients with HAE lack. In the United States (US), CSL Behring currently markets Berinert, an IV administered human plasma-derived C1-INH product (concentration: 50 IU of C1-INH per mL) indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE. The manufacturing process of HAEGARDA and Berinert (b) (4)

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## 2.1 Disease or Health-Related Condition(s) Studied

### Prevalence

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. Hereditary angioedema type I (approximately 85% of patients) is characterized by low concentrations of functional C1-INH protein. Hereditary angioedema 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.

### Clinical presentation

C1-INH is a serine protease inhibitor (serpin) that regulates activation of the complement, contact, and coagulation systems by binding to and inactivating target serine proteases (Davis AE 3rd, 2008). Dysregulation of these systems because of C1-INH deficiency results in the uncontrolled production of vasoactive peptides that promote inflammation through increased vascular permeability and excessive fluid accumulation in body tissues (Kaplan and Joseph, 2010). Clinically, HAE is characterized by unpredictable and recurrent attacks of edema affecting the SC tissues of the face, trunk, or limbs, or the submucosal tissues of the respiratory, gastrointestinal, or genitourinary tracts (Zuraw et al, 2013a; Bork et al, 2006). Attacks can be painful, disfiguring, disabling, and sometimes fatal (Davis AE 3rd, 2008). The potential for life-threatening laryngeal attacks is the most serious concern in HAE (Bork et al, 2003).

The diagnosis of HAE is confirmed by low complement component 4 (C4) antigen and absent or greatly reduced C1-INH antigen (protein) or C1-INH functional activity (Gompels et al, 2005). C4 is a component of the classical complement pathway that is digested by active C1 when C1 is not inhibited by C1-INH (Späth and Wüthrich, 1998). 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 (Späth et al, 1984).

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

Therapeutic approaches to HAE include acute or "on-demand" treatment administered after an HAE attack begins, long-term or routine prophylaxis to prevent or minimize attacks, and short-term prophylaxis to prevent attacks caused by known triggers such as medical, dental, or surgical procedures (Craig et al, 2012; Zuraw et al, 2013b). Many "on-demand" treatments are currently available to patients with HAE, but treatment options for patients who require long-term prophylaxis are generally limited to oral administration of attenuated androgens or twice per week IV infusions of plasma-derived C1-INH (Craig et al, 2012).

Antifibrinolytics are not recommended for long-term prophylaxis, but they are sometimes used despite a lack of data supporting their efficacy (Craig et al, 2012). Androgens such as danazol and stanozolol are associated with substantial safety and tolerability issues (Bork et al, 2008). A practical limitation of long-term IV C1-INH therapy is the need for chronic venous access.

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

HAEGARDA has only been used in investigational settings to date.

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

HAEGARDA has been developed under the Investigational New Drug (IND) application 14992 using a developmental name of CSL830. There were multiple pre-submission interactions between the FDA and the applicant. A summary of regulatory history with statistical implications is given below:

- A pre-IND meeting was held on November 10, 2011 to obtain FDA's comments and concurrence on their clinical and non-clinical development plans for prevention of HAE attacks. The applicant acknowledged FDA's comments concerning the design of the Phase 3 study. They indicated that they would discuss those comments with FDA during an End-of-Phase 2 meeting.
- An End-of-Phase 2 meeting was held on May 2, 2013, to obtain FDA's comments and concurrence on the objectives and design of Study CSL830_3001 (safety and efficacy) and CSL830_3002 (long term) overall clinical development plans in the prevention of HAE attacks.
- On July 8, 2013, the applicant submitted the protocol for phase 3 study CSL830_3001 which specified a primary endpoint not in keeping with advice given before and during the End-of-Phase 2 meeting. The applicant chose time-normalized number of HAE attacks during treatment with CSL830 compared to placebo (within-subject comparison). The FDA-recommended primary endpoint, proportion of responders (subject who have at least a 50% reduction in time-normalized HAE attacks compared to placebo) in the two CSL830 groups, was specified as one of two secondary endpoints.
- On December 18, 2014, FDA provided the written response for a Type C meeting seeking feedback regarding the acceptability of the proposed CSL830 program safety database, including long-term safety data, to be provided in the upcoming BLA planned for February 2016 as well as the proposed content for the 120 Day Safety Update following the BLA submission.
- On November 23, 2015, FDA provided written responses for a pre-BLA meeting. FDA stated that the decision on whether to include information on secondary endpoints in product labeling would be a review issue. For the proposed analysis method for the secondary efficacy endpoint of time normalized number of uses of rescue medication, FDA recommended the applicant use different values for each of the four treatment sequences instead of combining and using only two values and remove the separate testing of carryover effect.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

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

### 5.1 Review Strategy

The clinical development program of CSL830 consists of three completed (study 1001, 2001, 3001) and one on-going clinical studies (study 3002), assessing efficacy, safety, PK, PD, and QoL of CSL830 in adolescent and adult patients.

**Study 1001** was a phase 1, single-center study evaluated the safety, bioavailability, and PK of a single IV dose of 1500 IU CSL830 (500 IU/mL) relative to a single IV dose of 1500 IU Berinert (50 IU/mL) in healthy subjects.

Study 1001 is completed. The results of this study are not covered in this review and are deferred to the clinical pharmacologist.

**Study 2001** was a phase 1 / 2, multicenter, open-label, dose-ranging, crossover study evaluated the PK, PD, and safety of SC administration of three dosing regimens of CSL830 (1500 IU, 3000 IU, and 6000 IU twice per week for 4 weeks) in subjects with HAE type I or II.

Study 2001 is completed. The results of this study are not covered in this review and are deferred to the clinical pharmacologist.

**Study 3001** was a phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover study investigating the efficacy and safety of SC administration of CSL830 for routine prophylaxis to prevent HAE attacks in adolescent and adult subjects with HAE type I or II.

Study 3001 is completed and considered pivotal. The results of this study will be reviewed in detail in section 6.

**Study 3002** is a phase 3b, multicenter, randomized, open-label study to evaluate the long-term clinical safety and efficacy of SC administration of CSL830 in the prophylactic treatment of HAE.

At the time of BLA submission, enrollment in this study was completed, but study conduct is ongoing. Since the efficacy variable (time-normalized number of HAE attacks) in this study was considered exploratory, the study is not reviewed in this memo.

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

- Original submission under BLA 125606/0
  - Module 1.6: Meetings
  - Module 1.14: Labeling
  - Module 2.2: Introduction
  - Module 2.5: Clinical Overview
  - Module 2.7: Clinical Summary

- Module 5.3.5.1: Clinical Study Report (CSR) for CSL830_3001, Statistical Analysis Plans (SAPs) and tabulation data
  - The CSR (3005 pages), Version 1.0, dated May 2, 2016, with 193-page main text.
  - The Protocol (113 pages), Amendment 2, dated December 11, 2011.
  - The SAP (69 pages), Version 2, dated December 2, 2015.

### 5.3 Table of Studies/Clinical Trials

The clinical development program of CSL830 consists of four studies. An overview of these studies is provided in Table 1.

**Table 1. Overview of CSL830 Clinical Studies Contributing to the Clinical Development Program**

| Study; Status; Report Location | Type of Study | Phase; Study Design | Primary Objective(s) | Subject Population; Median Age (Range) | Treatment; Route; Dose; Duration | Location and Number of Study Centers |
|---|---|---|---|---|---|---|
| Study 1001<br><br>Completed | PK, safety | Phase 1, single-center, randomized, double-blind, crossover study | Assess the safety of IV CSL830, a (b) (4) presentation of Berinert | 16 healthy subjects (5 females / 11 males);<br><br>35 years (24 to 45 years) | Single IV bolus dose of 1500 IU CSL830 (500 IU/mL) and a single IV infused dose of 1500 IU Berinert (50 IU/mL) administered using a double-dummy approach | Germany (1) |
| Study 2001<br><br>Completed | PK, PD, safety | Phase 1/2, multicenter, open-label, dose-ranging, crossover study | Characterize the PK and PD of 3 different dosing regimens of SC CSL830 | 18 subjects with HAE type I or II (11 females / 7 males);<br><br>34 years (19 to 69 years) | Single IV dose of 20 IU/kg Berinert (50 IU/mL) followed by 2 treatment periods with CSL830 (500 IU/mL) administered SC twice per week for 4 weeks according to 1 of 6 treatment sequences:<br><br>• 1500 IU in TP1, 3000 IU in TP2<br>• 3000 IU in TP1, 1500 IU in TP2<br>• 3000 IU in TP1, 6000 IU in TP2<br>• 1500 IU in TP1, 6000 IU in TP2<br>• 6000 IU in TP1, 1500 IU in TP2<br>• 6000 IU in TP1, 3000 IU in TP2 | Germany (3)<br>United States (5) |

(Table 1 continues)

| Study; Status; Report Location | Type of Study | Phase; Study Design | Primary Objective(s) | Subject Population; Median Age (Range) | Treatment; Route; Dose; Duration | Location and Number of Study Centers |
|---|---|---|---|---|---|---|
| Study 3001<br><br>Completed | Efficacy, safety, PK, PD, and QoL | Phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover study | Demonstrate the clinical efficacy of SC CSL830 in the the prophylactic treatment of HAE and compare the clinical efficacy of 2 doses of SC CSL830 | 90 subjects with HAE type I or II (60 females / 30 males);<br><br>40 years (12 to 72 years) | Single SC injection of CSL830 or or placebo twice per week for 16 weeks in 2 consecutive treatment periods (according to 1 of 4 treatment sequences):<br>• High-volume placebo (0.12 mL/kg) in TP1 and 40 IU/kg CSL830 (0.08 mL/kg) in TP2<br>• 40 IU/kg CSL830 (0.08 mL/kg) in TP1 and high-volume placebo (0.12 mL/kg) in TP2<br>• Low-volume placebo (0.08 mL/kg) in TP1 and 60 IU/kg CSL830 (0.12 mL/kg) in TP2<br>• 60 IU/kg CSL830 (0.12 mL/kg) in TP1 and low-volume placebo (0.08 mL/kg) in TP2 | Australia (1)<br>Canada (6)<br>Czech Republic (2)<br>Hungary (1)<br>Israel (2)<br>Italy (2)<br>Romania (2)<br>Spain (4)<br>United Kingdom (2)<br>United States (19) |
| Study 3002<br><br>Ongoing<br><br>(Interim CSR; Data cut-off: 11 Feb 2016) | 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 | 126 subjects with HAE type I or II (76 females / 50 males);<br><br>41 years (8 to 72 years) | Single SC injection of 40 IU/kg or 60 IU/kg HAEGARDA twice per week for up to 140 weeks:<br>• TP1 (fixed dose period): 24 weeks<br>• TP2 (dose adjustment period): 28 weeks<br>• Extension Period (US subjects only): 88 weeks | Australia (1)<br>Canada (4)<br>Czech Republic (1)<br>Germany (4)<br>Hungary (1)<br>Israel (2)<br>Italy (2)<br>Romania (1)<br>Spain (3)<br>United Kingdom (1)<br>United States (12) |

CSR = clinical study report; TP1 / TP2 = Treatment Period 1 / Treatment Period 2.
Source: Original from BLA 125606/0; Module 2.5 Clinical overview, V1.0, Table 1.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study 3001

Study 3001 was titled "A double-blind, randomized, placebo-controlled, crossover study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema".

#### 6.1.1 Objectives (Primary, Secondary, etc.)

Primary objectives:

- To demonstrate the clinical efficacy of CSL830 in the prophylactic treatment of HAE.
- To compare the clinical efficacy of two doses of CSL830.

Secondary objectives:

- To further characterize the clinical efficacy of two doses of CSL830.
- To demonstrate the safety and tolerability of CSL830.

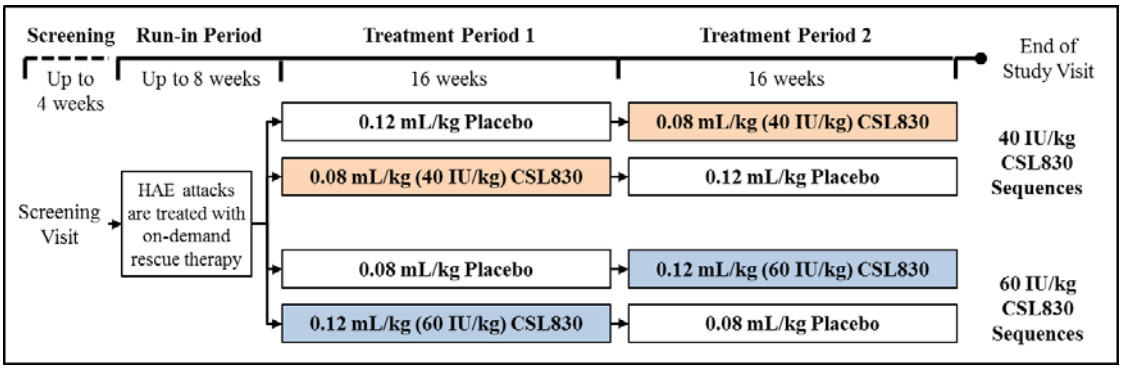
Other objectives:

- To evaluate the correlation between various biomarkers (PK and PD assessments) and clinical efficacy in the prophylactic treatment of HAE.
- To evaluate subject reported outcome measures:
  - European quality of life-5 dimensions (EQ-5D) questionnaire.
  - Work productivity and activity impairment (WPAI) questionnaire: general health.
  - Treatment satisfaction questionnaire for medication (TSQM).
  - Hospital anxiety and depression scale (HADS).

#### 6.1.2 Design Overview

This phase 3, multicenter, randomized, double-blind, placebo-controlled, incomplete crossover study investigated the efficacy and safety of prophylactic SC treatment with CSL830 in subjects with HAE. The study comprised four distinct parts (Screening Period, Run-in Period, Treatment Period 1 [TP1], and Treatment Period 2 [TP2]) as shown in Figure 1.

**Figure 1. Study Design Schematic**




Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Figure 9-1

After a Screening Period of up to 4 weeks, eligible subjects with HAE type I or II entered a Run-in Period of up to 8 weeks. During the Run-in Period, subjects and

study center staff monitored HAE attacks, adverse events (AEs), and the use of rescue medication and other medication. Eligible subjects who experienced ≥ 1 HAE attack during the first 2 weeks of the Run-in Period or ≥ 2 HAE attacks during any consecutive 4-week period of the Run-in Period were randomized into the study. Subjects who were not eligible to proceed beyond the Run-in Period were considered screen failures and could not be randomized into the study or rescreened.

To achieve the planned total of 72 completers, the study aimed to enter at least 100 subjects into the Run-in Period, and to randomize at least 80 subjects into TP1.

Randomized subjects were assigned with a ratio of 1:1:1:1 to the four treatment sequences described below.

- **40 IU/kg CSL830 sequences:**
  - Single SC injection of 0.12 mL/kg placebo (i.e., high-volume placebo) twice per week for 16 weeks, then a single SC injection of 40 IU/kg CSL830 (0.08 mL/kg) twice per week for 16 weeks; OR
  - Single SC injection of 40 IU/kg CSL830 (0.08 mL/kg) twice per week for 16 weeks, then a single SC injection of 0.12 mL/kg placebo twice per week for 16 weeks.
- **60 IU/kg CSL830 sequences:**
  - Single SC injection of 0.08 mL/kg placebo (i.e., low-volume placebo)twice per week for 16 weeks, then a single SC injection of 60 IU/kg CSL830 (0.12 mL/kg) twice per week for 16 weeks; OR
  - Single SC injection of 60 IU/kg CSL830 (0.12 mL/kg) twice per week for 16 weeks, then a single SC injection of 0.08 mL/kg placebo twice per week for 16 weeks.

The volume to be administered (planned volume) was based on treatment assignment, a subject's body weight, and rounding (i.e., up to the nearest whole mL).

An End of Study Visit occurred either 1 week after the end of TP2 or at the time that a subject was discontinued from the study.

This study contained no washout period between TP1 and TP2 (i.e., Week 16 of TP1 was immediately followed by Week 1 of TP2). To account for a wash-in / washout period of 2 weeks at the beginning of each treatment period, the evaluation period for efficacy assessments started at Week 3 of each treatment period (i.e., the total evaluation period was up to 14 weeks in duration). From a safety perspective, if placebo was given in TP1, no carryover effect in TP2 was possible. If active treatment was given in TP1, a carryover effect in unsolicited AEs was possible in TP2.

### 6.1.3 Population

Subjects who were screened under the original protocol (dated 07 June 2013) were not required to meet the updated eligibility criteria set forth in protocol amendment 1 (dated 20 February 2014) to continue participation in the study.

Subject eligibility criteria for entry into the Run-in Period:

1. Capable of providing written informed consent / assent (as appropriate) and willing and able to adhere to all protocol requirements, and / or the subject's

parent(s) or legally acceptable representative(s) was capable of providing written informed consent.
2. Male or female.
3. Aged 12 years or older at the time of providing written informed consent / assent (as appropriate).
4. Clinical diagnosis of HAE type I or II, which was confirmed by central laboratory testing before inclusion into TP1.
5. Experienced at least four HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period within the 3 months before the Screening Visit, as documented in the subject's medical records.
6. Original protocol:
   Willing to cease any preexisting medications for HAE prophylaxis (e.g., C1-INH, androgens, antifibrinolytics) after informed consent was obtained and was assessed by the investigator to be able to be adequately managed pharmacologically on acute treatments of HAE attacks alone.
   Protocol amendment 1:
   For subjects who had used oral medication for prophylaxis against HAE attacks (i.e., androgens, tranexamic acid, progestins) within 3 months before the Screening Visit: use of a stable regimen of oral prophylactic medication (i.e., dose and administration frequency) during the 3 months before the Screening Visit. Subjects who were using oral medication for prophylaxis against HAE attacks were expected to continue to use their stable regimen throughout the study (from the Screening Visit through the final study visit).
7. Investigator believed that the subject was willing and able to adhere to all protocol requirements.
8. Assessed by the investigator as able to appropriately store study medication (i.e., investigational product and rescue medicine) and was capable of being trained to administer study medication (by the subject or caretaker) outside of the study center setting.

<u>Subject eligibility criteria for randomization into the study and entry into TP1:</u>

1. HAE type I or II confirmed by central laboratory testing:
   - C1-INH functional activity of less than 50%, AND
   - C4 antigen concentration below the laboratory reference range.
2. Did not have any clinical abnormalities on hematology, biochemistry, thrombotic screen, coagulation profile, viral serology, or urinalysis performed during the Screening Visit and assessed as clinically significant by the investigator.
3. During their participation in the Run-in Period:
   - Experienced ≥ 2 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) within any consecutive 4-week period within the Run-in Period; OR
   - Experienced ≥ 1 HAE attack (requiring acute treatment, medical attention, or causing significant functional impairment) during the first 2 weeks of the Run-in Period.

### 6.1.4 Study Treatments

The study product was CSL830 and the comparator was placebo (see Table 2).

**Table 2. Study treatments**

| | Study product | Placebo |
|---|---|---|
| **Substance name** | CSL830 | Not applicable |
| **Active substance** | C1-esterase inhibitor (Human) | Excipients of CSL830 plus albumin |
| **Dosage form** | Lyophilized powder for reconstitution 1500 IU C1-INH per single-use vial | Lyophilized powder for reconstitution |
| **Dose** | 40 or 60 IU/kg | Not applicable |
| **Mode of administration** | Subcutaneous injection | Subcutaneous injection |

Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Tables 9-1, 9-2

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

In both crossover periods, subjects received CSL830 as a single SC injection twice per week for 16 weeks. After formal training, subjects self-administered CSL830 for the duration of the study. Caregivers could assist subjects in the administration of CSL830.

Two doses of CSL830 were evaluated in this study: 40 IU/kg (equivalent to a volume of 0.08 mL/kg) and 60 IU/kg (equivalent to a volume of 0.12 mL/kg). Subjects randomized to receive 40 IU/kg CSL830 (i.e., the lower volume) in one treatment period administered placebo at the higher volume in the other treatment period. Alternatively, subjects randomized to receive 60 IU/kg CSL830 (i.e., the higher volume) in one treatment period administered placebo at the lower volume in the other treatment period.

### 6.1.6 Sites and Centers

The study was conducted at 41 study centers in 10 countries (number of recruiting sites in parentheses): Australia (1), Canada (6), Czech Republic (2), Hungary (1), Israel (2), Italy (2), Romania (2), Spain (4), United Kingdom (2), US (19).

### 6.1.8 Endpoints and Criteria for Study Success

Primary efficacy variable:

- The time-normalized number of HAE attacks, which is calculated as:
  - The number of HAE attacks as reported by the investigator per subject and per treatment period/length of stay of subject in treatment period (days),

  where the length of stay of subject in treatment period is calculated as:
  - date of last day of subject in treatment period - date of first day of Week 3 of subject in the treatment period +1

Secondary efficacy variables:

- Percentage of responders, which is calculated as:

- 100%×[1 – (the time-normalized number of HAE attacks as reported by the investigator when treated with CSL830)/ (the time-normalized number of HAE attacks as reported by the investigator when treated with placebo)]

A subject is classified as a responder if he/she experiences a ≥ 50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830 compared with placebo. All other subjects are classed as non-responders. CSL830 is regarded as beneficial for subjects if the lower limit of the 95% Wilson CI for the observed percentage of responders for the combined active treatment groups (≥ 40 IU/kg CSL830) is greater than the predefined lower limit of 33 %.

- Time-normalized number of uses of rescue medication as recorded by the subject per subject, which is calculated as:
  - The number of uses of rescue medication as recorded by the subject per subject in treatment period/ length of stay of subject in treatment period (days)

Other efficacy variables:

- Average severity of HAE attacks.
- Reduction to less than one HAE attack per 4-week period.
- Investigator's global assessment of response to therapy.
- Percentage of subjects who did not fulfill the early escape criterion.
- Time-normalized number of days of HAE symptoms.
- Time-normalized sum of severity scores.
- Time-normalized sum of severity scores combined with rescue medication use.
- Subject's global assessment of response to therapy.

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

- **Intent-to-Treat (ITT) Population** – The ITT Population consisted of all subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.

- **Safety Population** – The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least one dose (or partial dose) of investigational product. Subjects in the Safety Population were analyzed "as treated" (i.e., subjects were classified according to the treatment actually received, regardless of the treatment assigned by randomization).

- **Per-protocol (PP) Population** – The PP Population consisted of all subjects in the ITT Population, excluding subjects who had a significant protocol violation. Protocol violations that led to exclusion from the PP Population were determined before unblinding.

Primary and secondary efficacy endpoints were to be analyzed using the ITT and PP Populations, with the ITT Population serving as the primary analysis. All other efficacy data were to be analyzed using the ITT Population.

*Reviewer comment: According to the applicant's protocol, they planned to use the ITT population for the efficacy analyses and to use the available data without imputation for the primary analyses in case of missing values. I have concerns regarding use of the term "ITT population" throughout the study report. Due to the specific study design (crossover with two treatment periods), and some subjects having missing data in one of the treatment periods because they discontinued prematurely from the study for various reasons, these subjects belong to the ITT population but were excluded from the efficacy analyses due to the missing values in one of their treatment periods. Ideally, the analytical plan would either have allowed for the inclusion of all members of the ITT population in efficacy analyses or would have specified a different analysis population for the efficacy analyses.*

Subgroup analyses

The subgroup analyses planned for the primary efficacy variable included:

- Region (US, non-US).
- Sex (Male, Female).
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other).
- Age class (12 to < 17 Years, 17 to < 65 Years, 65 Years or Older).
- HAE attack location (Facial, Peripheral, Laryngeal, Thoracic, Abdominal, Urogenital, Other).
- Mucosal (e.g., submucosal tissues of the respiratory, gastrointestinal, or genitourinary tracts) and non-mucosal HAE attack location (Mucosal, Non-Mucosal).
- Use of any oral prophylaxis for treatment of HAE during the study.
- Received the following medication for at least 1 month during the 3 months before Screening:
  - Plasma-derived C1-INH prophylaxis (Cinryze / Berinert / C1-INH not otherwise specified).
    - Cinryze prophylaxis.
    - Berinert prophylaxis.
  - Subjects with any oral prophylaxis.
    - Androgens or progestins.
    - Tranexamic acid or aminocaproic acid.
  - Subjects for whom no C1-INH or oral prophylaxis was reported.

Sample size determination

A total of 72 subjects were determined to provide:

- More than 80% power to detect an assumed 30% difference in the primary efficacy endpoint between the two CSL830 doses, at a two-sided significance level of 5%.
- Approximately 99% power to detect differences between 60 IU/kg CSL830 and low-volume placebo and between 40 IU/kg CSL830 and high-volume placebo, at a two-sided significance level of 5%.

The sample size estimation was based on the following a priori assumptions:

- 0.152 attacks per day in the placebo group, regardless of volume.

- A common standard deviation (SD) of 0.066 (which is also equal to the SD of the intra-subject differences between placebo and treatment, and is based upon the SDs from a prior study of IV C1-INH prophylaxis).
- The 40 IU/kg CSL830 dose has 50% of the number of attacks of high-volume placebo.
- The 60 IU/kg CSL830 dose has 20% of the number of attacks of low-volume placebo.

A secondary efficacy endpoint was the percentage of responders in the two CSL830 dose groups. Assuming that the population response rate $\pi$ is 0.50 for both active treatments, a sample size of N = 72 (both groups combined) yielded 80% power for the lower bound of a 95% CI to exceed 33% for the secondary percentage of responders endpoint.

In addition, assuming 72 subjects complete the study, an AE that occurs with a probability of at least 4% can be observed at least once with 95% probability.

To achieve a total of 72 completers, the study aimed to enter at least 100 subjects into the Run-in Period, and to randomize at least 80 subjects into TP1.

Handling of missing data

The primary and secondary efficacy analyses were based on the available data (i.e., the number of subjects with data) without imputed values. Analyses (based on imputing missing values by drop out reasons [i.e., the multiple imputation method], systematic approach, or complete-case analyses) were added as sensitivity analyses. The first imputation method among the sensitivity analyses was the multiple imputation method for the ITT Population.

A subject was considered to have missing values if he / she prematurely discontinued from the study. The fraction of non-missing data ($f$) and the time-normalized number of HAE attacks ($r_{observed}$) were determined per treatment period and subject as in Table 3.

**Table 3. Determination of the fraction of non-missing data and the time-normalized number of HAE attacks**

| Category | Description | Fraction of non-missing data (f) | Observed time-normalized number of HAE attacks ($r_{observed}$) |
|---|---|---|---|
| A | Subject was not discontinued from the study (including early escapes) | 1 | See primary efficacy variable definition in Section 6.1.8 |
| B | Subject was discontinued from the study with ≤ 2 weeks (14 days) participation in treatment period | 0 | Missing |
| C | Subject was discontinued from the study with > 2 weeks (14 days) participation in treatment period | Length of stay of subject in treatment period (days)[a] /schedule length of treatment period (days)[b] | See primary efficacy variable definition in Section 6.1.8 |

[a] Length of stay of subject in treatment period (days) was calculated as defined in Section 6.1.8.

[b] Scheduled length of treatment period was 98 days (i.e., 16 weeks minus 2 weeks not considered for analysis).

Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table on page 59

The time-normalized number of HAE attacks to be used for a sensitivity analysis ($r_{analyzed}$) was calculated based on the observed rate ($r_{observed}$) and the imputed rate ($r_{imputed}$) taking into account the fraction of non-missing data ($f$) as:

$r_{analyzed} = f \times r_{observed} + (1 - f) \times r_{imputed}$

Values for $r_{observed}$ were determined as outlined in Table 3. Values for $r_{imputed}$ were determined for each subject and period with missing data depending on the sensitivity analysis:

- Drop out reason:
  - Missing data were to be considered as missing at random if the dropout reasons were not related to the study drug and study termination by sponsor (subject moved away, work doesn't allow further participation, other personal reasons). The value $r_{imputed}$ was to be sampled from the time-normalized number of HAE attacks of all subjects within the same treatment with complete data.
  - Missing data due to dropout for the following reasons were to be considered as missing not at random: discontinued due to AEs, death or lack of efficacy. The median of the worst 25% observed data in that treatment group ($\tilde{x}$) was to be determined. The value of $r_{imputed}$ equals the subjects' maximum observed rate if the observed rate is > $\tilde{x}$, and $\tilde{x}$ otherwise
  - Missing data which were missing because of protocol violations, other, withdrawal by subject, or physician decision were to be reviewed, and a decision of classifying them into the categories as described in A or B was to be made and documented prior to unblinding.

- Systematic:
  For each treatment group, the range of the observed rates was to be determined and further subdivided into at least five increments. For the two comparisons of active treatment versus placebo, all possible combinations from the subdivided ranges were to be analyzed using the primary analysis model. Results were to be classified into negative (i.e. placebo significantly better), neutral (i.e. no significance achieved) and positive (i.e. active treatment significantly better) and depicted in a table and two graphs where the x-axis presents the subdivided range for placebo and the y-axis the subdivided range for the active treatment component. The different outcomes were to be distinguished by different symbols.
- Complete-case:
  No imputation was to be done. Subjects with missing data were to be excluded from the analysis and the primary analysis model was to be applied.

The data generated for the primary efficacy endpoint were also applied to the secondary percentage of responders endpoint. For this endpoint, the values of $r_{analyzed}$ for the primary endpoint were used to derive the response for each subject.

Statistical methodology

The primary endpoint was summarized by treatment, and by treatment and period using descriptive statistics. To detect a difference in the primary efficacy endpoint between the three treatments, the following pairwise comparisons were performed by testing a series of hypotheses using a 2-sided test at $\alpha = 0.05$,

- $H_{01}$: $r_1 = r_2$ vs $H_{11}$: $r_1 \neq r_2$ (60 IU/kg CSL830 tested against 0.08 mL/kg placebo),
- $H_{02}$: $r_3 = r_4$ vs $H_{12}$: $r_3 \neq r_4$ (40 IU/kg CSL830 tested against 0.12 mL/kg placebo),
- $H_{03}$: $r_2 = r_4$ vs $H_{13}$: $r_2 \neq r_4$ (60 IU/kg CSL830 tested against 40 IU/kg CSL830),

where $r_1$, $r_2$, $r_3$, and $r_4$ are the time-normalized number of HAE attacks for 0.08 mL/kg placebo, 60 IU/kg CSL830, 0.12 mL/kg placebo, and 40 IU/kg CSL830, respectively.

A hierarchical testing procedure was followed to control the total Type I error rate over the first two hypotheses: $H_{01}$ was first tested against $H_{11}$. If the null hypothesis $H_{01}$ was rejected at $\alpha = 0.05$, $H_{02}$ was tested against $H_{12}$ at $\alpha = 0.05$. If the null hypothesis $H_{01}$ was not rejected, the testing stopped. By using this hierarchical testing the overall alpha of 0.05 was to be preserved. The third hypothesis was considered exploratory. $H_{03}$ was tested against $H_{13}$ at $\alpha = 0.05$ for informational purposes, regardless of the test results for $H_{01}$ and $H_{02}$.

To test the first two hypotheses (comparison against placebo), a mixed model was used to analyze the effect of treatment on the time-normalized number of HAE attacks. The same mixed model was used separately for subjects who received the treatments in Sequences 3 and 4 and for subjects who received the treatments in Sequences 1 and 2. The model included fixed effect terms for period, sequence, and treatment (60 IU/kg CSL830 and 0.08 mL/kg [low-volume] placebo or 40 IU/kg CSL830 and 0.12 mL/kg [high-volume] placebo) and a repeated statement for subject. The correlated errors due to the repeated measurements were accounted for by

including a repeated statement with an unstructured covariance matrix. LS means for the treatment effect and the following treatment differences were estimated with 2-sided 95% CIs and the corresponding p-value was presented:

- 60 IU/kg CSL830 and low-volume placebo.
- 40 IU/kg CSL830 and high-volume placebo.

To test the third hypothesis, an additional mixed model for subjects who received the treatments in Sequences 1, 2, 3, and 4 was used to analyze the effect of treatment on the time-normalized number of HAE attacks between 60 IU/kg CSL830 and 40 IU/kg CSL830. The model included fixed effect terms for period, sequence, and treatment (60 IU/kg CSL830 or 40 IU/kg CSL830). To account for repeated measurements and the correlated errors, a repeated term was included in the model with an unstructured covariance matrix structure. LS means for the treatment effect and the treatment difference (60 IU/kg CSL830 vs 40 IU/kg CSL830) were estimated with 2-sided 95% CIs and the corresponding p-value was presented. No alpha-adjustment was done.

The number and percentage of responders and non-responders were to be presented for both CSL830 doses combined and for each CSL830 dose separately with corresponding Wilson Score 95% CI. The time-normalized number of uses of rescue medication was to be summarized using descriptive statistics (by treatment). The effect of treatment on the time-normalized number of uses of rescue medication was to be analyzed by using a mixed effect model, similar method as for the primary efficacy analyses.

Other efficacy variables and all safety variables were planned to be analyzed using summary statistics. The number of data available and missing data, mean, standard deviation, median, minimum and maximum values and other summary statistics were to be calculated for continuous data. Frequency tables were to be generated for categorical data.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

One hundred fifteen subjects provided informed consent and were screened (Screening Population, Table 4). A total of 90 subjects completed the Run-in Period and were randomized to 1 of the 4 treatment sequences and treated (ITT Population and Safety Population). One subject in the ITT Population was excluded from the PP Population due to a major protocol deviation (changes in hormonal contraceptive regimens between the 3 months before the screening visit until after the final study visit).

**Table 4. Analysis sets**

| | TP1: 40 IU/kg CSL830; TP2: High-volume Placebo n (%) | TP1: High-volume Placebo; TP2: 40 IU/kg CSL830 n (%) | TP1: 60 IU/kg CSL830; TP2: Low-volume Placebo n ( %) | TP1: Low-volume Placebo; TP2: 60 IU/kg CSL830 n (%) | Overall n (%) |
|---|---|---|---|---|---|
| **Screening Population** | | | | | 115 (100.0) |
| **Run-in Period Population** | | | | | 90 (78.3) |
| **ITT Population** | 23 (100.0) | 22 (100.0) | 22 (100.0) | 23 (100.0) | 90 (100.0) |
| **PP Population** | 23 (100.0) | 22 (100.0) | 22 (100.0) | 22 ( 95.7) | 89 ( 98.9) |
| **Safety Population** | 23 (100.0) | 22 (100.0) | 22 (100.0) | 23 (100.0) | 90 (100.0) |

Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.1.1

#### 6.1.10.1.1 Demographics

Of the 90 subjects in the ITT/Safety Population, 60 (66.7%) were female and 84 (93.3%) were White. The mean (± SD) age of the ITT population was 39.6 (± 14.9) years (median: 40.0 years). Six subjects (6.7%), with three each in the 40 IU/kg and 60 IU/kg sequences, were adolescents between 12 and 16 years. The mean (± SD) body mass index (BMI) of the ITT population was 28.6 (± 7.1) kg/m$^2$ (median: 27.3 kg/m$^2$). Mean age was higher in the 40 IU/kg than 60 IU/kg treatment sequences. There were no notable differences in terms of sex, race, weight, and BMI between the 40 IU/kg and 60 IU/kg treatment sequences. A summary of the demographic and other baseline characteristics is shown in Table 5.

**Table 5. Demographic and other baseline characteristics (ITT/Safety population)**

| Parameter | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | Overall (N = 90) |
|---|---|---|---|
| **Age (years)** | | | |
| n | 45 | 45 | 90 |
| Mean (SD) | 42.4 (14.41) | 36.8 (14.92) | 39.6 (14.85) |
| Min, Max | 12, 67 | 14, 72 | 12, 72 |
| Median | 43.0 | 35.0 | 40.0 |
| **Sex, n (%)** | | | |
| Female | 28 (62.2) | 32 (71.1) | 60 (66.7) |
| Male | 17 (37.8) | 13 (28.9) | 30 (33.3) |
| **Race, n (%)** | | | |
| White | 40 (88.9) | 44 (97.8) | 84 (93.3) |
| Black or African American | 3 (6.7) | 1 (2.2) | 4 (4.4) |
| Asian | 1 (2.2) | 0 | 1 (1.1) |
| Other | 1 (2.2) | 0 | 1 (1.1) |
| **Weight (kg)** | | | |
| n | 45 | 45 | 90 |
| Mean (SD) | 82.98 (23.035) | 80.15 (24.577) | 81.56 (23.727) |
| Min, Max | 50.0, 141.1 | 43.0, 156.8 | 43.0, 156.8 |
| Median | 80.20 | 78.00 | 78.10 |
| **BMI (kg/m$^2$)** | | | |
| n | 45 | 45 | 90 |
| Mean (SD) | 29.53 (7.309) | 27.65 (6.811) | 28.59 (7.088) |
| Min, Max | 19.7, 46.5 | 16.2, 55.7 | 16.2, 55.7 |
| Median | 28.12 | 26.12 | 27.30 |

BMI = body mass index; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with data; ITT = Intent-to-treat.

Note: Treatment sequences (ie, placebo → CSL830 and CSL830 → placebo) are combined.

Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-1

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All 90 subjects in the ITT Population had a biochemically confirmed diagnosis of HAE before randomization. The percentages of subjects with HAE type I and type II (as reported by the investigator) were similar in the 40 IU/kg and 60 IU/kg treatment sequences (Table 6). The mean (± SD) reported historic number of HAE attacks per subject in the 3 months before Screening was 10.8 (± 6.73) attacks (median: 10.0

attacks) in the 40 IU/kg treatment sequence and 8.8 (± 6.40) attacks (median: 7.0 attacks) in the 60 IU/kg treatment sequence (Table 6).

**Table 6. HAE History by Treatment Sequence (ITT population)**

| | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | Overall (N = 90) |
|---|---|---|---|
| **HAE Type, n (%)** | | | |
| Type I | 41 (91.1) | 37 (82.2) | 78 (86.7) |
| Type II | 4 (8.9) | 8 (17.8) | 12 (13.3) |
| **Number of HAE Attacks in the 3 Months Before Screening** | | | |
| n | 45 | 45 | 90 |
| Mean (SD) | 10.8 (6.73) | 8.8 (6.40) | 9.8 (6.61) |
| Min, Max | 0, 33 | 0, 37 | 0, 37 |
| Median | 10.0 | 7.0 | 8.0 |

HAE = hereditary angioedema; ITT = Intent-to-treat; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with data.

Note: Treatment sequences (ie, placebo → CSL830 and CSL830 → placebo) are combined.

Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-3

The applicant stated that the difference between treatment sequences in the historic number of HAE attacks may have been due to differences in the numbers of subjects receiving prior HAE prophylaxis (Table 7). Overall, 37/90 (41.1%) subjects in the ITT Population received HAE prophylaxis in the 3 months before Screening (Table 7). The percentage of subjects who received HAE prophylaxis overall and in each prophylaxis category (i.e., IV C1-INH and oral androgens) was higher in the 60 IU/kg treatment sequences than in the 40 IU/kg treatment sequences.

**Table 7. Prior HAE Prophylaxis by Treatment Sequence (ITT population)**

| | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | Overall (N = 90) |
|---|---|---|---|
| **Subjects who Received HAE Prophylaxis in the 3 Months Before Screening, n (%)** | 16 (35.6) | 21 (46.7) | 37 (41.1) |
| Plasma-derived C1-INH Prophylaxis | 9 (20.0) | 13 (28.9) | 22 (24.4) |
| Cinryze | 6 (13.3) | 9 (20.0) | 15 (16.7) |
| Berinert | 3 (6.7) | 3 (6.7) | 6 (6.7) |
| Not specified | 0 | 1 (2.2) | 1 (1.1) |
| Oral Prophylaxis | 8 (17.8) | 11 (24.4) | 19 (21.1) |
| Danazol | 6 (13.3) | 10 (22.2) | 16 (17.8) |
| Stanozolol | 2 (4.4) | 0 | 2 (2.2) |
| Oxandrolone | 0 | 1 (2.2) | 1 (1.1) |

Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-4

Overall, the mean (± SD) time-normalized number of HAE attacks during the Run-in Period was 0.14 (± 0.07) attacks per day (median: 0.13 attacks per day) (Table 8). The mean (± SD) time-normalized number of HAE attacks during the Run-in Period was

similar in the treatment sequences (40 IU/kg: 0.15 (±0.073) attacks per day; 60 IU/kg: 0.13 (± 0.066) attacks per day).

**Table 8. Time-normalized Number of HAE Attacks (Number/Day) During Run-in Period by Treatment Sequence (ITT population)**

| | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | Overall (N = 90) |
|---|---|---|---|
| Time-normalized Number of HAE Attacks | | | |
| n | 45 | 45 | 90 |
| Mean (SD) | 0.15 (0.073) | 0.13 (0.066) | 0.14 (0.070) |
| Min, Max | 0.0, 0.3 | 0.0, 0.3 | 0.0, 0.3 |
| Median | 0.14 | 0.13 | 0.13 |

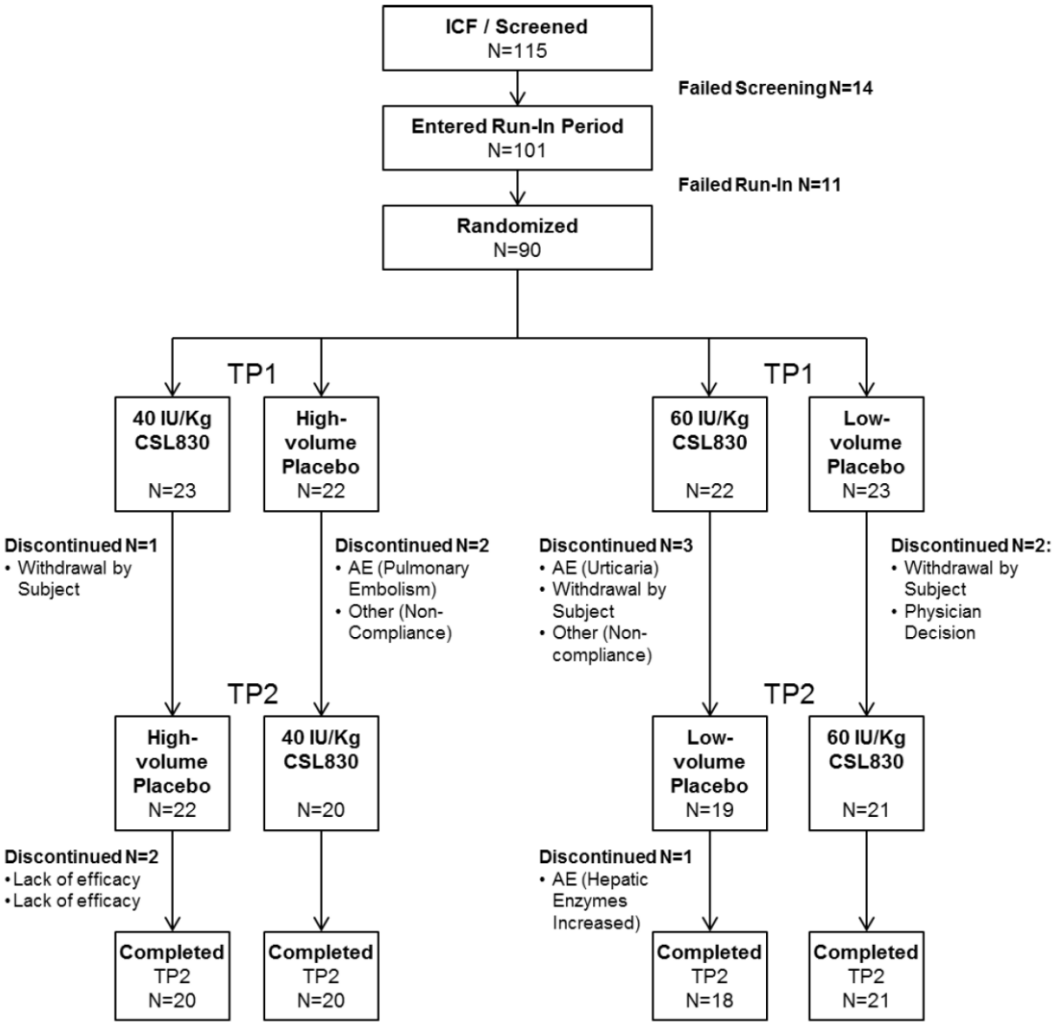
Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-5

### 6.1.10.1.3 Subject Disposition

Figure 2 gives an overview on the subject disposition in this study. Seventy-nine of the 90 (87.8%) randomized subjects completed the study: 20 subjects in both TP1 treatment sequences, and 18 and 21 subjects, respectively, in the CSL830-first and placebo-first TP2 sequences.

Eleven subjects discontinued from the study prematurely. Eight subjects discontinued in TP1 and did not cross over to TP2 (one subject during treatment with 40 IU/kg CSL830; two subjects during treatment with high-volume placebo; three subjects during treatment with 60 IU/kg CSL830; two subjects during treatment with low-volume placebo). Hence, not all the randomized subjects received both CSL830 and placebo in TP1 and TP2. Three subjects discontinued in TP2 (all during treatment with placebo).

**Figure 2. Subject disposition (all subjects)**




AE = Adverse event; ICF = Informed consent form; N = Number of subjects; TP1 = Treatment Period 1; TP2 = Treatment Period 2;
Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 10-1

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint

Treatment with CSL830 reduced the number of subjects with HAE attacks and the total number of HAE attacks relative to treatment with placebo.

Of the 45 subjects randomized to a 60 IU/kg treatment sequence, 43 subjects received 60 IU/kg CSL830, 42 subjects received low-volume placebo, and 40 subjects received both 60 IU/kg CSL830 and placebo. Twenty-five subjects had 71 attacks on 60 IU/kg CSL830, and 42 subjects had 472 attacks on low-volume placebo.
The LS mean (95% CI) time-normalized number of HAE attacks was 0.02 (0.00, 0.03) attacks per day on 60 IU/kg (median: 0.01 attacks per day) and 0.13 (0.12, 0.15) attacks per day on low-volume placebo (median: 0.12 attacks per day). Of the 40 subjects who received both 60 IU/kg CSL830 and low-volume placebo, the within-subject treatment difference was statistically significant ($p < 0.001$). Therefore, the

hypothesis testing of 40IU/kg CSL830 against high-volume placebo was performed next due to the hierarchical testing approach and the significant result of 60 IU/kg treatment sequence.

Of the 45 subjects randomized to a 40 IU/kg treatment sequence, 43 subjects received 40 IU/kg CSL830, 44 subjects received high-volume placebo, and 42 subjects received both 40 IU/kg CSL830 and placebo. Twenty-six subjects had 145 attacks on 40 IU/kg CSL830, and 40 subjects had 503 attacks on high-volume placebo. The LS mean (95% CI) time-normalized number of HAE attacks was 0.04 (0.02, 0.06) attacks per day on 40 IU/kg (median: 0.01 attacks per day) and 0.12 (0.10, 0.14) attacks per day on high-volume placebo (median: 0.13 attacks per day). Of the 42 subjects who received both 40 IU/kg CSL830 and high-volume placebo, the within-subject treatment difference was statistically significant ($p < 0.001$).

The between-subject comparison of doses showed that 60 IU/kg had a better treatment effect than 40 IU/kg. The difference between doses in the time-normalized number of HAE attacks (LS mean [95% CI]: -0.02 [-0.05, 0.01] attacks per day) was not statistically significant ($p = 0.114$).

Table 9 summarizes these data.

**Table 9. Time-normalized Number of HAE Attacks (Number/Day) by Treatment**

| | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | |
|---|---|---|---|---|
| | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| n | 43 | 44 | 43 | 42 |
| Mean (SD) | 0.04 (0.076) | 0.12 (0.069) | 0.02 (0.025) | 0.13 (0.076) |
| Min, Max | 0.0, 0.4 | 0.0, 0.3 | 0.0, 0.1 | 0.0, 0.4 |
| Median | 0.01 | 0.13 | 0.01 | 0.12 |
| LS Mean (SE) [a] | 0.04 (0.011) | 0.12 (0.011) | 0.02 (0.009) | 0.13 (0.009) |
| 95% CI for LS Mean [a] | (0.02, 0.06) | (0.10, 0.14) | (0.00, 0.03) | (0.12, 0.15) |
| **Treatment difference (within-subjects)** | **40 IU/kg CSL830 – High-volume Placebo** | | **60 IU/kg CSL830 – Low-volume Placebo** | |
| LS Mean [a] (95% CI) | -0.08 (-0.11, -0.05) | | -0.12 (-0.14, -0.09) | |
| p-value [a] | < 0.001 | | < 0.001 | |
| **Treatment difference (between-subjects)** | **60 IU/kg CSL830 – 40 IU/kg CSL830** | | | |
| LS Mean [a] (95% CI) | -0.02 (-0.05, 0.01) | | | |
| p-value [a] | 0.114 | | | |

CI = confidence interval; HAE = hereditary angioedema; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with data; LS = Least squares.
[a] From a mixed model.
Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-7

When expressed as the rate of attacks per month, the LS mean (95% CI) time-normalized number of HAE attacks was 1.19 (0.54, 1.85) attacks per month on 40 IU/kg (median: 0.29 attacks per month) and 3.61 (2.96, 4.26) attacks per month on high-volume placebo (median: 3.75 attacks per month). The LS mean (95% CI) time-normalized number of HAE attacks was 0.52 (0.00, 1.04) attacks per month on 60 IU/kg (median: 0.29 attacks per month) and 4.03 (3.51, 4.55) attacks per month on low-volume placebo (median: 3.81 attacks per month). The maximum rate of HAE

attacks per month was 3.1 on 60 IU/kg and 12.5 on 40 IU/kg. Table 10 summarizes these data.

**Table 10. Time-normalized Number of HAE Attacks (Number/Month) by Treatment**

| | 40 IU/kg CSL830 Treatment Sequences (N = 45) | | 60 IU/kg CSL830 Treatment Sequences (N = 45) | |
|---|---|---|---|---|
| | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| n | 43 | 44 | 43 | 42 |
| Mean (SD) | 1.22 (2.310) | 3.61 (2.088) | 0.53 (0.771) | 4.02 (2.308) |
| Min, Max | 0.0, 12.5 | 0.0, 8.9 | 0.0, 3.1 | 0.6, 11.3 |
| Median | 0.29 | 3.81 | 0.29 | 3.75 |
| LS Mean (SE)* | 1.19 (0.327) | 3.61 (0.327) | 0.52 (0.261) | 4.03 (0.263) |
| 95% CI for LS Mean* | (0.54, 1.85) | (2.96, 4.26) | (0.00, 1.04) | (3.51, 4.55) |
| **Treatment difference (within-subjects)** | **40 IU/kg CSL830 – Placebo** | | **60 IU/kg CSL830 – Placebo** | |
| LS Mean* (95% CI) | -2.42 (-3.38, -1.46) | | -3.51 (-4.21, -2.81) | |
| p-value* | < 0.001 | | < 0.001 | |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects; n = number of subjects with data; LS = Least squares.
* From a mixed model.
Source: Adapted from BLA 125606/0; Package insert, Table 4

*Reviewer comment: The applicant used the available data (i.e., the number of subjects with data) without imputed values for the efficacy analyses. Although the ITT population has 45 subjects for each dosing treatment sequence, only 42 subjects have both treatment and placebo data in the 40 IU/kg group and 40 subjects have both treatment and placebo data in the 60 IU/kg group. Therefore, the within-subject treatment differences between the treatment and the placebo were based on a reduced ITT population (42 subjects for the 40 IU/kg group and 40 subjects for 60 IU/kg). By checking the analyses with the imputed values using the method described in section 6.1.9, the results and the conclusions are similar to the results using the reduced ITT population (see section 6.1.11.4 for more details).*

### 6.1.11.2 Analyses of Secondary Endpoints

Percentage of Responders

The percentage of responders (95% CI) with a ≥ 50% reduction in the time-normalized number of HAE attacks on the combined active treatments (≥ 40 IU/kg CSL830) was 82.9% (73.4%, 89.5%) (Table 11). By treatment group, 76.2% of subjects on 40 IU/kg and 90% of subjects on 60 IU/kg responded to treatment.

**Table 11. Percentage Reduction of ≥ 50% in Time-normalized Number of HAE Attacks by Treatment**

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

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects with data; LS = Least squares.
Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-10

The percentages of subjects (95% CI) with ≥70% and ≥90% reductions in the time−normalized number of HAE attacks on CSL830 were 74.4% (64.0%, 82.6%) and 50.0% (39.4%, 60.6%), respectively. The percentages of subjects with ≥70% and ≥90% reductions were 82.5% and 57.5% on 60 IU/kg and 66.7% and 42.9% on 40 IU/kg.

Table 12 summarizes these data.

**Table 12. Percentage Reduction of ≥ 70% and ≥ 90% in Time-normalized Number of HAE Attacks by Treatment**

| Table 11–11 | Percentage Reduction of ≥ 70% and ≥ 90% in Time-normalized Number of HAE Attacks by Treatment (ITT Population) | | |
|---|---|---|---|
| | 40 IU/kg CSL830 (N = 45) | 60 IU/kg CSL830 (N = 45) | ≥ 40 IU/kg CSL830 (N = 90) |
| n | 42 | 40 | 82 |
| **Reduction of ≥ 70%** | | | |
| Responder, % (n) [a] | 66.7% (28) | 82.5% (33) | 74.4% (61) |
| 95% Wilson CI | (51.6, 79.0) | (68.1, 91.3) | (64.0, 82.6) |
| **Difference in % of Responders [b]** | | | |
| 60 IU/kg CSL830 – 40 IU/kg CSL830 (%) | 15.8% | | – |
| 95% Wilson CI | (-3.2, 33.3) | | – |
| **Reduction of ≥ 90%** | | | |
| Responder, % (n) [a] | 42.9% (18) | 57.5% (23) | 50.0% (41) |
| 95% Wilson CI | (29.1, 57.8) | (42.2, 71.5) | (39.4, 60.6) |
| **Difference in % of Responders [b]** | | | |
| 60 IU/kg CSL830 – 40 IU/kg CSL830 (%) | 14.6% | | – |
| 95% Wilson CI | (-6.7, 34.3) | | – |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects with data; LS = Least squares.
Note: The percentage reduction (%) in time-normalized number of HAE attacks per subject is calculated as: 100 x [1 – (the time-normalized number of HAE attacks when treated with CSL830) / (the time-normalized number of HAE attacks when treated with placebo)]. A subject is classified as a responder if the percentage reduction is ≥ 70% or ≥ 90%, respectively.
Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-11

*Reviewer comment: Similar to the reviewer comment in Section 6.1.11.1, the applicant used the modified ITT population (42 subjects for the 40 IU/kg group and 40 subjects for 60 IU/kg) in the secondary efficacy analyses for the percentage of responders endpoint. By checking the analyses with the imputed values using the method described in section 6.1.9, the results and the conclusions are similar to the results using the reduced ITT population (see section 6.1.11.4 for more details).*

Time-normalized Number of Uses of Rescue Medication

For subjects randomized to a 40 IU/kg CSL830 treatment sequence, the LS mean (95% CI) time-normalized number of uses of rescue medication was 0.04 (-0.05, 0.12) uses per day on 40 IU/kg CSL830 and 0.18 (0.10, 0.26) uses per day on high-volume placebo. For subjects randomized to a 60 IU/kg treatment sequence, the LS mean (95% CI) time-normalized number of uses of rescue medication was 0.01 (-0.01, 0.03) uses per day on 60 IU/kg and 0.13 (0.11, 0.15) uses per day on low-volume placebo.

A summary of the time-normalized number of uses of rescue medication is shown in Table 13.

**Table 13. Time-normalized Number of Uses of Rescue Medication (Number/Day) by Treatment**

| | 40 IU/kg CSL830 / High-volume Placebo Treatment Sequences (N = 45) | | 60 IU/kg CSL830 / Low-volume Placebo Treatment Sequences (N = 45) | |
|---|---|---|---|---|
| | CSL830 | Placebo | CSL830 | Placebo |
| n | 43 | 44 | 43 | 42 |
| Mean (SD) | 0.04 (0.084) | 0.18 (0.355) | 0.01 (0.018) | 0.13 (0.098) |
| Min, Max | 0.0, 0.4 | 0.0, 2.4 | 0.0, 0.1 | 0.0, 0.4 |
| Median | 0.01 | 0.13 | 0.00 | 0.10 |
| LS Mean (SE) [a] | 0.04 (0.042) | 0.18 (0.040) | 0.01 (0.011) | 0.13 (0.011) |
| 95% CI for LS Mean [a] | (-0.05, 0.12) | (0.10, 0.26) | (-0.01, 0.03) | (0.11, 0.15) |

CI = confidence interval; HAE = hereditary angioedema; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with data; LS = Least squares.
[a] From a mixed model.
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 11-12

When expressed as the rate of rescue medication use per month, the LS mean (95% CI) time-normalized number of uses of rescue medication was 1.13 (-1.44, 3.69) uses per month on 40 IU/kg and 5.55 (3.10, 8.00) uses per month on high-volume placebo. The LS mean (95% CI) time-normalized number of uses of rescue medication was 0.32 (-0.33, 0.97) uses per month on 60 IU/kg and 3.89 (3.23, 4.55) uses per month on low-volume placebo.

Other Efficacy Results (as presented in the package insert)

71.1% (32 out of 45) of subjects on 60 IU/kg and 53.3% (24 out of 45) of subjects on 40 IU/kg had ≥1 HAE attack per 4 week period on placebo and <1 HAE attack per 4 week period on HAEGARDA. A total of 40.0% (18 out of 45) of subjects on 60 IU/kg and 37.8% (17 out of 45) of subjects on 40 IU/kg were attack-free.

The median ($25^{th}$, $75^{th}$ percentile) percentage reduction in the time-normalized

number of HAE attacks relative to placebo was 88.6% (69.6%, 100.0%) on 40 IU/kg CSL830 and 95.1% (79.0%, 100.0%) on 60 IU/kg CSL830 among subjects with evaluable data in both treatment periods (Table 14).

**Table 14. Percentage Reduction in Time-normalized Number of HAE Attacks (%) by Treatment**

| | 40 IU/kg CSL830 (N=45) | 60 IU/kg CSL830 (N=45) | >=40 IU/kg CSL830 (N=90) |
|---|---|---|---|
| n | 38 | 40 | 78 |
| Number Missing | 7 | 5 | 12 |
| Mean (SD) | 55.16 (101.660) | 83.96 (26.219) | 69.93 (74.325) |
| Min, Max | -366.7, 100.0 | -27.6, 100.0 | -366.7, 100.0 |
| Median | 88.61 | 95.07 | 93.88 |
| 25th, 75th Percentile | 69.58, 100.00 | 78.98, 100.00 | 71.43, 100.00 |

Source: Original from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.1.14

### 6.1.11.3 Subpopulation Analyses

Subgroup analyses of the primary endpoint and the secondary percentage of responders endpoint were performed by region (US, non-US), sex, race, age groups (12 to < 17 years, 17 to < 65 years, ≥ 65 years), HAE attack location, use of oral prophylaxis during study, and use of IV C1-INH prophylaxis or oral prophylaxis for ≥ 1 month in the 3 months before Screening.

Subgroup results for the time-normalized number of HAE attacks were similar to the overall analysis results (i.e., the rate of attacks was lower on CSL830 than placebo, and 60 IU/kg had a numerically greater treatment effect than 40 IU/kg CSL830) except for laryngeal HAE attacks, in which placebo had a lower attack rate than CSL830. Specifically, the LS estimate (95% CI) for the within-subject treatment difference between 40 IU/kg and high-volume placebo was 0.02 (0.00, 0.03) with a p-value of 0.079 (see Table 15).

Subgroup results for the percentage of responders were similar to the overall analysis results (i.e., the percentages of responders were higher on 60 IU/kg than on 40 IU/kg CSL830; Table 16). There were other patterns noticed: more female responders than male in the 40 IU/kg CSL830 group (84.0% vs. 64.7%); more Type I HAE responders than Type II for both 40 IU/kg and 60 IU/kg CSL830 groups (85.7% vs. 66.7%). Of the six subjects on CSL830 with laryngeal HAE attacks, there were no responders.

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

## Table 15. Time-normalized Number of HAE Attacks (Number/Day) by Treatment for selected subgroups

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Region** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| USA (N) | 28 | 28 | 26 | 26 |
| n | 27 | 28 | 24 | 25 |
| Mean (SD) | 0.03 (0.038) | 0.11 (0.071) | 0.01 (0.016) | 0.11 (0.061) |
| Median | 0.01 | 0 10 | 0.01 | 0.11 |
| Min, Max | 0.0, 0.1 | 0.0, 0 3 | 0.0, 0.1 | 0.0, 0.2 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.08 (-0.11, -0.06), < 0.001 | | -0.10 (-0.13, -0.07), < 0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.01 (-0.04, 0.02), 0.368 | | | |
| Non-USA (N) | 17 | 17 | 19 | 19 |
| n | 16 | 16 | 19 | 17 |
| Mean (SD) | 0.06 (0.112) | 0.14 (0.064) | 0.02 (0.033) | 0.16 (0.090) |
| Median | 0.01 | 0 14 | 0.01 | 0.14 |
| Min, Max | 0.0, 0.4 | 0.0, 0 2 | 0.0, 0.1 | 0.1, 0.4 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.07 (-0.15, 0.01), 0.066 | | -0.13 (-0.18, -0.09), <0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.03 (-0.08, 0.02), 0.197 | | | |

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Sex** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| Male (N) | 17 | 17 | 13 | 13 |
| n | 17 | 17 | 13 | 13 |
| Mean (SD) | 0.04 (0.063) | 0.10 (0.056) | 0.01 (0.009) | 0.13 (0.084) |
| Median | 0.01 | 0 11 | 0.01 | 0.11 |
| Min, Max | 0.0, 0.2 | 0.0, 0 2 | 0.0, 0.0 | 0.0, 0.3 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.06 (-0.11, -0.02), 0.005 | | -0.12 (-0.18, -0.07), < 0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.03 (-0.08, 0.02), 0.183 | | | |
| Female (N) | 28 | 28 | 32 | 32 |
| n | 26 | 27 | 30 | 29 |
| Mean (SD) | 0.04 (0.084) | 0.13 (0.075) | 0.02 (0.029) | 0.13 (0.073) |
| Median | 0.01 | 0 14 | 0.01 | 0.13 |
| Min, Max | 0.0, 0.4 | 0.0, 0 3 | 0.0, 0.1 | 0.0, 0.4 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.09 (-0.13, -0.04), < 0.001 | | -0.11 (-0.14, -0.09), <0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.01 (-0.04, 0.02), 0.390 | | | |

(Table 15 continues)

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Race** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| White (N) | 40 | 40 | 44 | 44 |
| n | 38 | 39 | 42 | 41 |
| Mean (SD) | 0.04 (0.080) | 0.12 (0.072) | 0.02 (0.026) | 0.13 (0.077) |
| Median | 0.01 | 0 14 | 0.01 | 0 11 |
| Min, Max | 0.0, 0.4 | 0.0, 0 3 | 0.0, 0.1 | 0.0, 0.4 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.08 (-0.11, -0.04), < 0.001 | | -0.11 (-0.14, -0.09), < 0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.03 (-0.05, 0.00), 0.074 | | | |
| Asian (N) | 1 | 1 | 0 | 0 |
| Black or African American (N) | 3 | 3 | 1 | 1 |
| Other | 1 | 1 | 0 | 0 |

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Age** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| 12 to <17 Years (N) | 3 | 3 | 3 | 3 |
| n | 3 | 3 | 3 | 3 |
| Mean (SD) | 0.02 (0.020) | 0.04 (0.074) | 0.01 (0.012) | 0.12 (0.099) |
| Median | 0.01 | 0.00 | 0.02 | 0 10 |
| Min, Max | 0.0, 0.0 | 0.0, 0.1 | 0.0, 0.0 | 0.0, 0 2 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | N/A | | N/A | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | N/A | | | |
| 17 to <65 Years (N) | 38 | 38 | 39 | 39 |
| n | 36 | 37 | 37 | 36 |
| Mean (SD) | 0.04 (0.080) | 0.12 (0.059) | 0.02 (0.027) | 0.14 (0.077) |
| Median | 0.01 | 0.13 | 0.01 | 0 13 |
| Min, Max | 0.0, 0.4 | 0.0, 0 2 | 0.0, 0.1 | 0.0, 0.4 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.08 (-0.12, -0.05), < 0.001 | | -0.12 (-0.15, -0.10), <0.001 | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | -0.02 (-0.05, 0.01), 0.166 | | | |
| 65 Years or Older (N) | 4 | 4 | 3 | 3 |
| n | 4 | 4 | 3 | 3 |
| Mean (SD) | 0.05 (0.065) | 0.16 (0.120) | 0.03 (0.016) | 0.11 (0.040) |
| Median | 0.03 | 0.15 | 0.02 | 0 10 |
| Min, Max | 0.0, 0.1 | 0.0, 0.3 | 0.0, 0.0 | 0 1, 0 2 |
| Treatment difference | 40 IU/kg CSL830 – Placebo | | 60 IU/kg CSL830 – Placebo | |
| LS Mean (95% CI), p-value | -0.09 (-0.38, 0.19), 0.301 | | N/A | |
| Treatment difference | 60 IU/kg CSL830 – 40 IU/kg CSL830 | | | |
| LS Mean (95% CI), p-value | N/A | | | |

(Table 15 continues)

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **HAE Type** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| Type I (N) | 41 | 41 | 37 | 37 |
| n | 39 | 40 | 35 | 34 |
| Mean (SD) | 0.03 (0.051) | 0.12 (0.066) | 0.02 (0.028) | 0.14 (0.077) |
| Median | 0.01 | 0.13 | 0.01 | 0 13 |
| Min, Max | 0.0, 0.2 | 0.0, 0.3 | 0.0, 0 1 | 0.0, 0.4 |
| Treatment difference | 40 IU/kg **CSL830** – Placebo | | 60 IU/kg **CSL830** – Placebo | |
| LS Mean (95% CI), p-value | -0.09 (-0.11, -0.06), < 0.001 | | -0.12 (-0.14, -0.09), < 0.001 | |
| Treatment difference | 60 IU/kg **CSL830** – 40 IU/kg **CSL830** | | | |
| LS Mean (95% CI), p-value | -0.01 (-0.04, 0.01), 0.324 | | | |
| Type II (N) | 4 | 4 | 8 | 8 |
| n | 4 | 4 | 8 | 8 |
| Mean (SD) | 0.13 (0.189) | 0.10 (0.098) | 0.01 (0.012) | 0.12 (0.072) |
| Median | 0.05 | 0.09 | 0.01 | 0 10 |
| Min, Max | 0.0, 0.4 | 0.0, 0.2 | 0.0, 0.0 | 0.0, 0 2 |
| Treatment difference | 40 IU/kg **CSL830** – Placebo | | 60 IU/kg **CSL830** – Placebo | |
| LS Mean (95% CI), p-value | 0.02 (-0.79, 0.84), 0.922 | | -0.09 (-0.16, -0.03), 0.015 | |
| Treatment difference | 60 IU/kg **CSL830** – 40 IU/kg **CSL830** | | | |
| LS Mean (95% CI), p-value | -0.01 (-0.13, 0.10), 0.784 | | | |

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Non-USA Female** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| N | 10 | 10 | 13 | 13 |
| n | 9 | 9 | 13 | 13 |
| Mean (SD) | 0.06 (0.134) | 0.13 (0.077) | 0.03 (0.038) | 0.15 (0.093) |
| Median | 0.01 | 0.14 | 0.01 | 0 14 |
| Min, Max | 0.0, 0.4 | 0.0, 0.2 | 0.0, 0 1 | 0.1, 0.4 |
| Treatment difference | 40 IU/kg **CSL830** – Placebo | | 60 IU/kg **CSL830** – Placebo | |
| LS Mean (95% CI), p-value | -0.06 (-0 18, 0.06), 0.285 | | -0.11 (-0.16, -0.06), <0.001 | |
| Treatment difference | 60 IU/kg **CSL830** – 40 IU/kg **CSL830** | | | |
| LS Mean (95% CI), p-value | 0.00 (-0.05, 0.05), 1.000 | | | |

| | 40 IU/kg CSL830 Treatment Sequences | | 60 IU/kg CSL830 Treatment Sequences | |
|---|---|---|---|---|
| **Location: Laryngeal** | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| N | 6 | 12 | 0 | 8 |
| n | 6 | 12 | 0 | 8 |
| Mean (SD) | 0.03 (0.027) | 0.01 (0.007) | - | 0.01 (0.006) |
| Median | 0.01 | 0.01 | - | 0.01 |
| Min, Max | 0.0, 0.1 | 0.0, 0.0 | - | 0.0, 0.0 |
| Treatment difference | 40 IU/kg **CSL830** – Placebo | | 60 IU/kg **CSL830** – Placebo | |
| LS Mean (95% CI), p-value | 0.02 (0.00, 0.03), 0.079 | | N/A | |
| Treatment difference | 60 IU/kg **CSL830** – 40 IU/kg **CSL830** | | | |
| LS Mean (95% CI), p-value | N/A | | | |

N: number of subjects; n: number of subjects with data. For location subgroup, only subjects with HAE attacks were included.
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.1.5

## Table 16. Percentage of Responders by Treatment for selected subgroups

| **Region** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
|---|---|---|---|
| USA (N) | 28 | 26 | 54 |
| n | 27 | 23 | 50 |
| Responder, % (n) | 77.8% (21) | 87.0% (20) | 82.0% (41) |
| 95% Wilson CI | (59.2, 89.4) | (67.9, 95.5) | (69.2, 90.2) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 9.2% | - |
| 95% Wilson CI | | (-13.2, 29.6) | - |
| Non-USA (N) | 17 | 19 | 36 |
| n | 15 | 17 | 32 |
| Responder, % (n) | 73.3% (11) | 94.1% (16) | 84.4% (27) |
| 95% Wilson CI | (48.0, 89.1) | (73.0, 99.0) | (68.2, 93.1) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 20.8% | - |
| 95% Wilson CI | | (-5.6, 46.5) | - |
| **Sex** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
| Male (N) | 17 | 13 | 30 |
| n | 17 | 13 | 30 |
| Responder, % (n) | 64.7% (11) | 92.3% (12) | 76.7% (23) |
| 95% Wilson CI | (41.3, 82.7) | (66.7, 98.6) | (59.1, 88.2) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 27.6% | - |
| 95% Wilson CI | | (-3.7, 51.8) | - |
| Female (N) | 28 | 32 | 60 |
| n | 25 | 27 | 52 |
| Responder, % (n) | 84.0% (21) | 88.9% (24) | 86.5% (45) |
| 95% Wilson CI | (65.3, 93.6) | (71.9, 96.1) | (74.7, 93.3) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 4.9% | - |
| 95% Wilson CI | | (-14.6, 24.9) | - |
| **Race** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
| White (N) | 40 | 44 | 84 |
| n | 37 | 39 | 76 |
| Responder, % (n) | 73.0% (27) | 89.7% (35) | 81.6% (62) |
| 95% Wilson CI | (57.0, 84.6) | (76.4, 95.9) | (71.4, 88.7) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 16.8% | - |
| 95% Wilson CI | | (-0.9, 33.9) | - |
| Asian (N) | 1 | 0 | 1 |
| Black or African American (N) | 3 | 1 | 4 |
| Other (N) | 1 | 0 | 1 |

(Table 16 continues)

| **Age** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
|---|---|---|---|
| 12 to <17 Years (N) | 3 | 3 | 6 |
| n | 3 | 3 | 6 |
| Responder, % (n) | 33.3% (1) | 66.7% (2) | 50.0% (3) |
| 95% Wilson CI | (6.1, 79.2) | (20.8, 93.9) | (18.8, 81.2) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 33.3% | - |
| 95% Wilson CI | | (-31.6, 71.8) | - |
| 17 to <65 Years (N) | 38 | 39 | 77 |
| n | 35 | 34 | 69 |
| Responder, % (n) | 80.0% (28) | 91.2% (31) | 85.5% (59) |
| 95% Wilson CI | (64.1, 90.0) | (77.0, 97.0) | (75.3, 91.9) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 11.2% | - |
| 95% Wilson CI | | (-6.1, 28.1) | - |
| 65 Years or Older (N) | 4 | 3 | 7 |
| n | 4 | 3 | 7 |
| Responder, % (n) | 75.0% (3) | 100.0% (3) | 85.7% (6) |
| 95% Wilson CI | (30.1, 95.4) | (43.9, 100.0) | (48.7, 97.4) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 25.0% | - |
| 95% Wilson CI | | (-34.8, 69.9) | - |
| **HAE Type** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
| Type I (N) | 41 | 37 | 78 |
| n | 38 | 32 | 70 |
| Responder, % (n) | 78.9% (30) | 93.8% (30) | 85.7% (60) |
| 95% Wilson CI | (63.7, 88.9) | (79.9, 98.3) | (75.7, 92.1) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 14.8% | - |
| 95% Wilson CI | | (-2.3, 30.7) | - |
| Type II (N) | 4 | 8 | 12 |
| n | 4 | 8 | 12 |
| Responder, % (n) | 50.0% (2) | 75.0% (6) | 66.7% (8) |
| 95% Wilson CI | (15.0, 85.0) | (40.9, 92.9) | (39.1, 86.2) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 25.0% | - |
| 95% Wilson CI | | (-23.8, 64.3) | - |
| **Non-USA Female** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
| N | 10 | 13 | 23 |
| n | 8 | 11 | 19 |
| Responder, % (n) | 87.5% (7) | 90.9% (10) | 89.5% (17) |
| 95% Wilson CI | (52.9, 97.8) | (62.3, 98.4) | (68.6, 97.1) |
| Difference in % of Responders | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | | 3.4% | - |
| 95% Wilson CI | | (-27.0, 38.8) | - |
| **Location: Laryngeal** | **40 IU/kg CSL830** | **60 IU/kg CSL830** | **≥ 40 IU/kg CSL830** |
| N | 6 | 0 | 6 |
| n | 3 | 0 | 3 |
| Responder, % (n) | 0.0% (0) | 0 | 0.0% (0) |
| 95% Wilson CI | (0.0, 56.1) | 0 | (0.0, 56.1) |

N: number of subjects; n: number of subjects with data. For location subgroup, only subjects with HAE attacks were included.

Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.2.3

### 6.1.11.4 Dropouts and/or Discontinuations

Eleven 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 in section 6.1.10.1.3. To evaluate the impact of missing data due to the early discontinuation, the applicant conducted three sensitivity analyses (please see Handling of Missing Data in section 6.1.9). The results of all three sensitivity analyses (multiple imputation method, the systematic approach, and the complete-case analysis) were consistent with the results of the primary efficacy analysis and the secondary percentage of responders endpoint.

For the primary efficacy endpoint, Table 17 shows the results using the multiple imputation method and Table 18 shows the complete-case analysis results. For the secondary percentage of responders endpoint, Table 19 shows the results using the multiple imputation method and Table 20 shows the complete-case analysis results.

**Table 17. Time-normalized Number of HAE Attacks (Number/Day) by Treatment-Imputation Analysis Drop-Out Reason**

| | 40 IU/kg CSL830 Treatment Sequences (N = 45) | | 60 IU/kg CSL830 Treatment Sequences (N = 45) | |
|---|---|---|---|---|
| | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| n | 45 | 45 | 45 | 45 |
| LS Mean (SE)* | 0.04 (0.01) | 0.13 (0.01) | 0.02 (0.009) | 0.14 (0.009) |
| 95% CI for LS Mean* | (0.02, 0.06) | (0.11, 0.15) | (0.00, 0.03) | (0.12, 0.15) |
| **Treatment difference (within-subjects)** | **40 IU/kg CSL830 – Placebo** | | **60 IU/kg CSL830 – Placebo** | |
| LS Mean* (95% CI) | -0.09 (-0.11, -0.06) | | -0.12 (-0.14, -0.10) | |
| p-value* | < 0.001 | | < 0.001 | |
| **Treatment difference (between-subjects)** | **60 IU/kg CSL830 – 40 IU/kg CSL830** | | | |
| LS Mean* (95% CI) | -0.02 (-0.05, 0.00) | | | |
| p-value* | 0.093 | | | |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects with data (including the imputed missing data); LS = Least squares.
* From a mixed model.
Note: Missing values considered as missing at random - impute value from the observed values of subjects within the same treatment; missing values considered as missing not at random - impute median from 25% worst observations within the same treatment or subject´s worst value prior to drop-out (if available) whichever is worse (10 repeats).
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.1.6

**Table 18. Time-normalized Number of HAE Attacks (Number/Day) by Treatment-Complete Case Analysis**

| | 40 IU/kg CSL830 Treatment Sequences (N = 45) | | 60 IU/kg CSL830 Treatment Sequences (N = 45) | |
|---|---|---|---|---|
| | **CSL830** | **Placebo** | **CSL830** | **Placebo** |
| n | 40 | 40 | 39 | 39 |
| LS Mean (SE)* | 0.03 (0.009) | 0.12 (0.009) | 0.02 (0.009) | 0.14 (0.009) |
| 95% CI for LS Mean* | (0.01, 0.05) | (0.10, 0.14) | (0.00, 0.04) | (0.12, 0.15) |
| **Treatment difference (within-subjects)** | **40 IU/kg CSL830 – Placebo** | | **60 IU/kg CSL830 – Placebo** | |
| LS Mean* (95% CI) | -0.09 (-0.11, -0.07) | | -0.12 (-0.14, -0.09) | |
| p-value* | < 0.001 | | < 0.001 | |
| **Treatment difference (between-subjects)** | **60 IU/kg CSL830 – 40 IU/kg CSL830** | | | |
| LS Mean* (95% CI) | -0.02 (-0.04, 0.01) | | | |
| p-value* | 0.202 | | | |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects included in the analysis; LS = Least squares.
* From a mixed model.
Note: Complete Case - subjects with missing values and subjects who discontinued prematurely are excluded from the analysis.
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.1.8

**Table 19. Percentage Reduction of ≥ 50% in Time-normalized Number of HAE Attacks by Treatment - Imputation Analysis Drop-Out Reason**

| | 40 IU/kg CSL830 (N=45) | 60 IU/kg CSL830 (N=45) | ≥ 40 IU/kg CSL830 (N=90) |
|---|---|---|---|
| n | 45 | 45 | 90 |
| Responder, % | 79.6% | 90.0% | 84.8% |
| 95% Wilson CI | (67.6, 91.5) | (80.9, 99.1) | (77.3, 92.3) |
| **Difference in % of Responders** | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | 10.4% | | - |
| 95% Wilson CI | (-4.7, 25.6) | | - |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects with data (including the imputed missing data);
Note: Imputation - missing values for reduction in time-normalized HAE attacks are imputed; missing values considered as missing at random - impute value from the observed values of subjects within the same treatment; missing values considered as not missing at random - impute median from 25% worst observations within the same treatment or subject´s worst value prior to drop-out (if available) whichever is worse (10 repeats).
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.2.4

**Table 20. Percentage Reduction of ≥ 50% in Time-normalized Number of HAE Attacks by Treatment - Complete Case Analysis**

| | 40 IU/kg CSL830 (N=45) | 60 IU/kg CSL830 (N=45) | ≥ 40 IU/kg CSL830 (N=90) |
|---|---|---|---|
| n | 40 | 39 | 79 |
| Responder, % (n) | 82% (32) | 89.7% (35) | 84.8% (67) |
| 95% Wilson CI | (65.2, 89.5) | (76.4, 95.9) | (75.3, 91.1) |
| **Difference in % of Responders** | | | |
| 60 IU/kg CSL830-40 IU/kg CSL830 (%) | 9.7% | | - |
| 95% Wilson CI | (-6.6, 25.7) | | - |

CI = confidence interval; HAE = hereditary angioedema; N = number of subjects;
n = number of subjects included in the analysis.
Note: Complete Case - subjects with missing values and subjects who discontinued prematurely are excluded from the analysis.
Source: Adapted from BLA 125606/0; Clinical Study Report CSL830_3001, V1.0, Table 14.2.2.6

### 6.1.12 Safety Analyses

#### 6.1.12.3 Deaths

No subjects died during the study.

#### 6.1.12.4 Nonfatal Serious Adverse Events

Four SAEs occurred in three subjects during the study; of which, one SAE occurred during treatment with 40 IU/kg and three SAEs occurred during treatment with placebo. No SAEs occurred during treatment with 60 IU/kg. None of the SAEs were solicited AEs.

Subject (b) (6), a 50-year-old female, experienced an SAE of Pulmonary Embolism during treatment with high-volume placebo in TP1. The event was reported as related to blinded investigational product. The event led to study discontinuation, and the subject did not receive CSL830 during the study. The event was graded as severe. The outcome of the event was recovered / resolved. The subject had a family history of thromboembolic events and had a history of heavy smoking.

Subject (b) (6), a 19-year-old female, experienced concurrent SAEs of Hereditary Angioedema (reported terms: abdominal HAE attack and genital HAE attack) and Syncope during treatment with low-volume placebo in TP2. The events were reported as not related to blinded investigational product. The events did not lead to study discontinuation. The outcome of the events were recovered / resolved.

Subject (b) (6), a 66-year-old female, experienced an SAE of Urosepsis during treatment with 40 IU/kg in TP2, which was graded as severe. The event was reported as not related to blinded investigational product and did not lead to study discontinuation. The outcome of the event was recovered / resolved.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

I verified the primary and second efficacy results for the pivotal study 3001.

The efficacy and safety of CSL830 for routine prophylaxis to prevent HAE attacks were demonstrated in a multicenter, randomized, double blind, placebo controlled,

crossover study. The study assessed 90 adult and adolescent subjects with symptomatic HAE type I or II. The median (range) age of subjects was 40 (12 to 72) years old; 60 subjects were female and 30 subjects were male. Subjects were randomized to receive either 60 IU/kg or 40 IU/kg CSL830 in one 16 week treatment period and placebo in the other 16 week treatment period. Patients subcutaneously self-administered CSL830 or placebo 2 times per week. Efficacy was evaluated for the last 14 weeks of each treatment period.

The primary efficacy analysis of study 3001 demonstrated that twice per week SC doses of 40 IU/kg or 60 IU/kg CSL830 yielded statistically significant reductions in the time-normalized number of HAE attacks relative to placebo. For the 45 subjects randomized to a 60 IU/kg CSL830 treatment sequence, 43 subjects received 60 IU/kg CSL830, 42 subjects received low-volume placebo, and 40 subjects received both 60 IU/kg CSL830 and placebo. The 60 IU/kg dose reduced the mean rate of attacks to 0.52 attacks per month from 4.03 attacks per month on placebo ($p < 0.001$). Of the 45 subjects randomized to a 40 IU/kg treatment sequence, 43 subjects received 40 IU/kg CSL830, 44 subjects received high-volume placebo, and 42 subjects received both 40 IU/kg CSL830 and placebo. The 40 IU/kg dose reduced the mean rate of attacks to 1.19 attacks per month from 3.61 attacks per month on placebo ($p < 0.001$). The difference between 40 IU/kg and 60 IU/kg doses in the time-normalized number of HAE attacks was not statistically significant ($p = 0.114$).

The analysis of the secondary efficacy endpoint demonstrated that percentage of responders (95% CI) with a ≥50% reduction in the time−normalized number of HAE attacks on CSL830 relative to placebo was 82.9% (73.4%, 89.5%). Of the subjects on 60 IU/kg, 90% responded to treatment by this definition and 76.2% of subjects on 40 IU/kg responded to treatment. The percentages of subjects (95% CI) with ≥70% and ≥90% reductions in the time−normalized number of HAE attacks on CSL830 relative to placebo were 74.4% (64.0%, 82.6%) and 50.0% (39.4%, 60.6%), respectively. The percentages of subjects with ≥70% and ≥90% reductions were 82.5% and 57.5% on 60 IU/kg and 66.7% and 42.9% on 40 IU/kg.

The LS mean (95% CI) time-normalized number of uses of rescue medication was 1.13 (-1.44, 3.69) uses per month on 40 IU/kg and 5.55 (3.10, 8.00) uses per month on high-volume placebo. The LS mean (95% CI) time-normalized number of uses of rescue medication was 0.32 (-0.33, 0.97) uses per month on 60 IU/kg and 3.89 (3.23, 4.55) uses per month on low-volume placebo.

In general, subgroup analyses of the primary endpoint and the secondary percentage of responders endpoint were similar to the overall analysis results. Of the six subjects on CSL830 with laryngeal HAE attacks, there were no responders.

No subjects died during participation in the study.

**10.2 Conclusions and Recommendations**

Based on the results of pivotal study 3001, adequate statistical evidence supports the proposed indication of routine prophylaxis to prevent HAE attacks in adolescent and adult patients.