2 SYNOPSIS

Name of Sponsor: CSL Behring GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: CSL830 (C1-esterase inhibitor, human [subcutaneous])		
Name of Active Ingredient: C1-esterase inhibitor (human)		

Title of Study:
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

Coordinating Investigator: PPD
Università degli Studi di Milano,
Dipartimento di Scienze Biochimiche e Cliniche L. Sacco–Ospedale L. Sacco
Unità Operativa di Medicina Generale,
Via G.B. Grassi 74,
20157 Milano,
Italy

Publication (reference): Not applicable

Study Period: *First Subject Visit*: 18 December 2013 *Last Subject Visit*: 12 October 2015	**Phase of Development:** Phase 3

Primary and Secondary Objectives:

***Primary Objectives*:**

1. To demonstrate the clinical efficacy of subcutaneous (SC) CSL830 in the prophylactic treatment of hereditary angioedema (HAE).
2. To compare the clinical efficacy of 2 doses of SC CSL830.

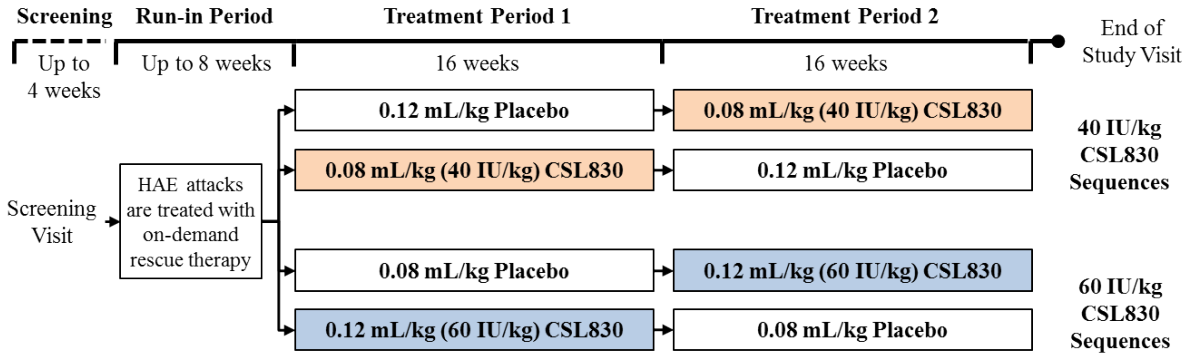
***Secondary Objectives*:**

1. To further characterize the clinical efficacy of 2 doses of SC CSL830.
2. To demonstrate the safety and tolerability of SC CSL830.

Methodology:

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 4 distinct parts (Screening Period, Run-in Period, Treatment Period 1 [TP1], and Treatment Period 2 [TP2]) (Figure 1).

Figure 1 Study Design Schematic



HAE = hereditary angioedema.

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. 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.

Randomized subjects were assigned to either a 40 IU/kg CSL830 treatment sequence or a 60 IU/kg CSL830 treatment sequence. Each sequence consisted of 2 consecutive treatment periods (TP1 and TP2) of up to 16 weeks each. 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.

Number of Subjects:

***Planned*:** 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.

***Actual*:** A total of 115 subjects were screened. 101 subjects entered the Run-in Period and 90 subjects were randomized into the study. A total of 79 subjects completed the study.

Diagnosis and Main Criteria for Inclusion:

1. Written informed consent / assent and willing and able to adhere to all protocol requirements.
2. Male or female, with ≥12 years of age.
3. Clinical diagnosis of HAE type I or II confirmed by central laboratory testing.
4. Experienced at least 4 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period within the 3 months before the Screening Visit, as documented in the subject's medical records.

Investigational Product, Dose and Mode of Administration, Batch Number:

The study product was CSL830 and the comparator was placebo.

In both crossover periods, subjects received CSL830 or placebo as a single SC injection twice per week for 16 weeks. After formal training, subjects self-administered investigational product for the duration of the study. Caregivers could assist subjects in the administration of investigational product. The abdomen was the preferred injection location in this study.

Two doses of CSL830 were evaluated: 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 (ie, the lower volume) in 1 treatment period, received high-volume placebo (0.12 mL/kg) in the other treatment period. Alternatively, subjects randomized to receive 60 IU/kg CSL830 (ie, the higher volume) in 1 treatment period received low-volume placebo (0.08 mL/kg) in the other treatment period. Investigators, study center staff, and subjects were blinded to subject treatment allocation and the order of active treatment and placebo within sequences.

Before use, each vial was to be reconstituted with 3 mL of water for injection, which for CSL830, resulted in a concentration of 500 IU/mL C1-esterase inhibitor (C1-INH). The batch numbers of CSL830 used in the study were: 00568811, 00668811, 00768811, 00768812, 00868811, 01068811, 01168811, 01268811, 01368811, 01468811, 01568811, and 01668811. The batch numbers of placebo used in the study were: 00266311, 00366311, 00466311, 00566311, 00666311, and 00766311.

Duration of Treatment:

The duration of the study for an individual subject was up to 45 weeks.

Criteria for Evaluation:

***Primary Endpoint*:**

Time-normalized number of HAE attacks.

***Secondary Endpoints*:**

- The percentage of responders in the 2 CSL830 dose groups, defined by a ≥ 50% relative reduction in the time-normalized number of HAE attacks during treatment with CSL830 compared with placebo (within individual subjects).
- The time-normalized number of uses of rescue medication.
- Adverse events (AEs) that began within 24 hours after the administration of investigational product.
- AEs, serious adverse events (SAEs), unsolicited AEs, suspected adverse drug reactions, thromboembolic events (TEEs), anaphylaxis events, sepsis and / or bacteremia events, increased risk scores for deep vein thrombosis and pulmonary embolism, inhibitory anti C1-INH antibodies, or clinically significant abnormalities in laboratory assessments.
- Solicited AEs (eg, pain, swelling, bruising, itching, or erythema at the investigational product injection site).

Statistical Methods:

A total of 72 subjects was determined to provide approximately 99% power to detect a difference between 60 IU/kg CSL830 and low-volume placebo and between 40 IU/kg CSL830 and high-volume placebo, for alpha equals 5% each, and more than 80% power to detect an assumed 30% difference in the primary efficacy endpoint between the 2 CSL830 doses, for alpha equals 5%. Assuming that the population response rate π is 0.50 for both active treatments, a sample size of 72 subjects (both groups combined) yielded 80% power for the lower bound of a 95% confidence interval to exceed 33% for the secondary percentage of responders endpoint.

Continuous variables were summarized using mean, standard deviation (SD), median, range, the 25^{th} and 75^{th} percentiles, and counts of missing and non-missing values. Categorical values were summarized using counts and percentages.

Primary Efficacy Analysis

The effect of the treatment on time-normalized number of HAE attacks was analyzed following a hierarchical testing procedure (first 60 IU/kg CSL830 tested against 0.08 mL/kg placebo, followed by 40 IU/kg CSL830 tested against 0.12 mL/kg placebo and subsequently 60 IU/kg CSL830 tested against 40 IU/kg CSL830) by using mixed effect models. Least squares means for the treatment effect and the treatment differences were estimated with 2-sided 95% confidence intervals (the corresponding p-value was presented).

Safety Analysis

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

Results:

Disposition and Demographics

Of the 90 subjects randomized in total, 45 subjects were randomized to a 40 IU/kg CSL830 treatment sequence, and 45 subjects were randomized to a 60 IU/kg CSL830 treatment sequence.

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

Of the 90 subjects in the Intent-to-treat Population, 60 (66.7%) were female and 84 (93.3%) were White. The mean (SD) age of the Intent-to-treat Population was 39.6 (14.85) years. Mean age (SD) was higher in the 40 IU/kg (42.4 [14.41] years) than in the 60 IU/kg CSL830 treatment sequences (36.8 [14.92] years). There were no notable differences in terms of sex, race, weight, and body mass index between the 40 IU/kg CSL830 and 60 IU/kg CSL830 treatment sequences.

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

Treatment Compliance and Exposure

Median treatment compliance was 100% for all treatments and mean compliance ranged from 99.4% to 106.2%. For subjects in the 40 IU/kg CSL830 treatment sequences, the mean duration of exposure to active treatment and placebo was 16.3 (1.56) weeks and 15.5 (3.33) weeks, respectively. For subjects in the 60 IU/kg CSL830 treatment sequences, the mean duration of exposure to active treatment and placebo was 16.0 (2.11) weeks and 15.1 (3.27) weeks, respectively.

Efficacy

The primary efficacy analysis demonstrated that CSL830 doses of 40 IU/kg and 60 IU/kg significantly reduced the time-normalized number of HAE attacks relative to placebo. Subjects on 60 IU/kg CSL830 experienced less than 1 attack per month on average and less than half the number of attacks as subjects on 40 IU/kg CSL830.

- 40 IU/kg CSL830 reduced the mean rate of attacks to 0.04 attacks per day (1.19 attacks per month) from 0.12 attacks per day (3.61 attacks per month) on high-volume placebo ($p < 0.001$).
- 60 IU/kg CSL830 reduced the mean rate of attacks to 0.02 attacks per day (0.52 attacks per month) from 0.13 attacks per day (4.03 attacks per month) on low-volume placebo ($p < 0.001$).
- Of the 45 subjects randomized to a 40 IU/kg treatment sequence, 26 subjects had 145 attacks on 40 IU/kg CSL830, and 40 subjects had 503 attacks on high-volume placebo. Of the 45 subjects randomized to a 60 IU/kg treatment sequence, 25 subjects had 71 attacks on 60 IU/kg CSL830, and 42 subjects had 472 attacks on low-volume placebo.

Treatment with CSL830 reduced the number of subjects with HAE attacks and the total number of HAE attacks at all anatomic locations relative to treatment with placebo. No subject on 60 IU/kg CSL830 experienced a laryngeal attack, compared with 8 subjects on low-volume placebo. Six subjects on 40 IU/kg CSL830 experienced a laryngeal attack, compared with 12 subjects on high-volume placebo.

The secondary percentage of responders analysis demonstrated that most subjects on 40 IU/kg (76.2%) and 60 IU/kg (90.0%) had a $\geq$ 50% reduction in the time-normalized number of HAE attacks on CSL830 relative to placebo. More than half of subjects (57.5%) on 60 IU/kg CSL830 had a $\geq$ 90% reduction.

CSL830 reduced the time-normalized use of rescue medication relative to placebo. The results of this analysis reflect the results of the time-normalized number of HAE attacks. Notably, the rate of rescue medication use was lower than the rate of HAE attacks on 60 IU/kg CSL830, suggesting that not all breakthrough attacks required "on demand" treatment.

- 40 IU/kg CSL830 reduced the mean rate of rescue use to 0.04 uses per day (1.13 uses per month) from 0.18 uses per day (5.55 uses per month) on high-volume placebo.
- 60 IU/kg CSL830 reduced the mean rate of rescue use to 0.01 uses per day (0.32 uses per month) from 0.13 uses per day (3.89 uses per month) on low-volume placebo.

Fewer subjects experienced at least 1 severe HAE attack on CSL830 than placebo.

- Of the 45 subjects randomized to a 40 IU/kg treatment sequence, 9 (20.0%) subjects experienced at least 1 severe attack on 40 IU/kg CSL830 compared with 33 (73.3%) subjects on high-volume placebo.
- Of the 45 subjects randomized to a 60 IU/kg treatment sequence, 4 (8.9%) subjects experienced at least 1 severe attack on 60 IU/kg CSL830 compared with 31 (68.9%) subjects on low-volume placebo.

The percentages of subjects with an "excellent" response to therapy based on the investigator's global assessment of response to therapy and subject's global assessment of response to therapy were higher on CSL830 than placebo.

The results of subject reported outcome measures provide evidence that routine prophylaxis with SC CSL830 was effective, enabled subjects with HAE to be more active and productive, and increased overall satisfaction with treatment. Thus, CSL830 may importantly reduce some of the burdens of HAE identified in the published literature.

Pharmacokinetics / Pharmacodynamics

Subcutaneous administration of CSL830 increased the C1-INH functional activity, C1-INH antigen concentrations, and C4 antigen concentrations in subjects with HAE. All 3 analytes increased in a dose-dependent manner from 40 IU/kg to 60 IU/kg CSL830. Steady-state appeared to be reached by Week 3, with consistent functional activity / antigen concentrations observed from Week 3 to Week 14.

Mean steady-state C1-INH functional activity ranged from 44.7 to 49.1% on 40 IU/kg CSL830, 63.4 to 69.0% on 60 IU/kg CSL830, and 26.9 to 30.6% on placebo. Mean steady-state C1-INH antigen concentrations ranged from 0.12 to 0.14 mg/mL on 40 IU/kg CSL830, 0.17 to 0.18 mg/mL on 60 IU/kg CSL830, and 0.09 to 0.10 mg/mL on placebo. Mean steady-state C4 antigen concentrations ranged from 13.5 to 14.8 mg/dL on 40 IU/kg CSL830, 17.8 to 18.7 mg/dL on 60 IU/kg CSL830, and 8.1 to 9.0 mg/dL on placebo.

Safety

Solicited Adverse Events

Solicited AEs (ie, injection site reactions) were the most common events reported during the study, occurring more frequently in subjects treated with CSL830 than placebo. Despite a higher number events occurring during treatment with CSL830 relative to placebo, there was no clear dose-relationship. The majority of solicited AEs were reported by 4 subjects, 3 in the 40 IU/kg CSL830 treatment sequences and 1 in the 60 IU/kg CSL830 treatment sequences. Three subjects contributed 193 solicited AEs to the events reported during treatment with 40 IU/kg CSL830 and 123 solicited AEs to the events reported during treatment with high-volume placebo. A single subject contributed 28 solicited AEs reported during treatment with 60 IU/kg and 41 solicited AEs reported during treatment with low-volume placebo.

Overall, the majority of solicited AEs were of mild severity, and were resolved within 1 day after injection (247/274 events with 40 IU/kg CSL830; 64/103 events with 60 IU/kg CSL830). There were no severe events occurring during treatment with CSL830, with a single severe event of Injection Site Pain occurring during treatment with placebo. All solicited AEs had an outcome of recovered / resolved. No solicited AEs were serious. The most common solicited AEs by preferred term were Injection Site Pain and Injection Site Erythema.

Unsolicited Adverse Events

Overall, there were fewer unsolicited AEs (122 events), when compared to solicited AEs (377 events) during treatment with CSL830. Unsolicited AEs were reported in the same percentage of subjects receiving combined active treatments and combined placebo (55.8% of subjects each). However, fewer unsolicited AEs were reported during treatment with combined active treatments (122 AEs) when compared to combined placebo (132 events). As with solicited AEs, there was no clear dose relationship. A greater number of unsolicited AEs were experienced by a smaller percentage of subjects receiving 40 IU/kg CSL830 (68 events, 53.5% of subjects) than with 60 IU/kg CSL830 (54 events, 58.1% of subjects). The majority of unsolicited AEs were of mild severity, and were reported as not related to investigational product.

Serious Adverse Events and Other Safety Events of Interest

There were 4 SAEs reported in 3 subjects. A single SAE of Pulmonary Embolism was reported as related to investigational product. The event was experienced during treatment with placebo. The subject had been treated with Berinert, but the subject did not receive CSL830. The subject had a family history of TEEs and had a history of heavy smoking. No other TEEs were reported. All other SAEs were reported as not related to investigational product. A single SAE of Urosepsis was reported during treatment with 40 IU/kg CSL830. No other sepsis or bacteremia events were reported. The remaining 2 SAEs occurred on placebo. All SAEs had an outcome of recovered / resolved.

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

No subjects died during the participation in the study.

Conclusions:

In conclusion, this study demonstrated the efficacy and safety of SC CSL830 for routine prophylaxis against HAE attacks in subjects with HAE type I or II. A dose-response was observed across efficacy endpoints, with 60 IU/kg consistently showing better efficacy than 40 IU/kg. Both doses of CSL830 (40 IU/kg and 60 IU/kg) were well tolerated and had favorable safety profiles, and there was no evidence of a dose-dependent safety concern.

Date of Report: 02 May 2016