2 SYNOPSIS

Name of Sponsor: CSL Behring K.K.	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: An open-label, single-arm, non-randomized phase 3 study to evaluate clinical efficacy, safety, and pharmacokinetics of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema in Japanese subjects		
Coordinating Investigator: PPD PPD, Saiyu Soka Hospital 1-7-22, Matsubara, Soka Saitama 340-0041 Japan		
Publication (reference): Not Applicable		
Study Period: *First Subject Visit*: 17 June 2020 *Last Subject Visit*: 22 February 2021	**Phase of Development:** Phase 3	

Objectives:

Primary Objectives:

1. To evaluate the clinical efficacy and pharmacokinetics (PK) of subcutaneous (SC) CSL830 in the prophylactic treatment of hereditary angioedema (HAE) in Japanese subjects.

Secondary Objectives:

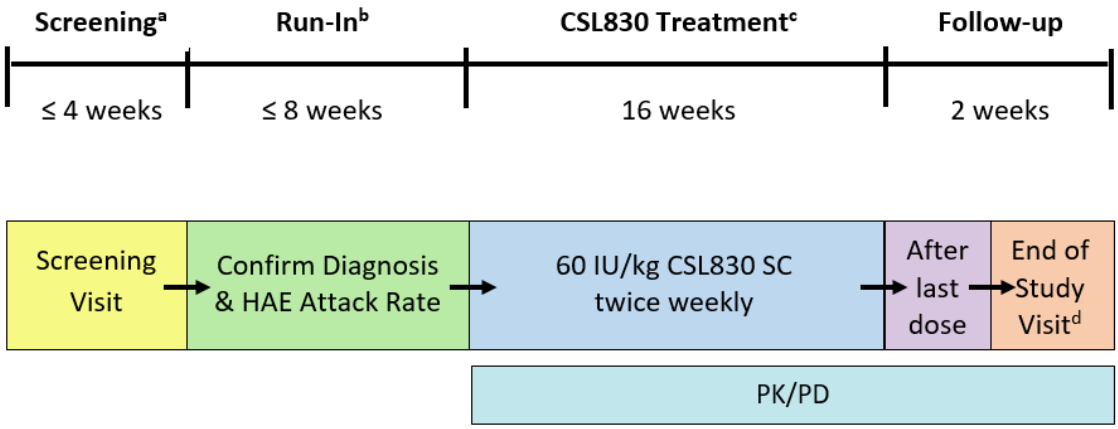
1. To further characterize the clinical efficacy of the SC CSL830
2. To demonstrate the safety and tolerability of SC CSL830
3. To evaluate C1-esterase inhibitor (C1-INH) functional activity and C1-INH antigen (PK), and C4 antigen (pharmacodynamics [PD]) during CSL830 treatment

4. To evaluate subject reported Angioedema quality-of-life (Angioedema Quality-of-Life [AEQoL] questionnaire) outcomes and subject and investigator global assessments of response to therapy (SGART and IGART)

Methodology:

This was a prospective, open-label, multicenter, non-randomized, single-arm phase 3 study to investigate the clinical efficacy, PK / PD and safety of SC CSL830 in the prophylactic treatment of HAE type I or II in Japanese subjects. The study was conducted in Japan and consists of 4 parts (a ≤ 4-week Screening Period, up to 8-week Run-in Period, a 16-week CSL830 Treatment Period, and a 2-week Follow-up Period after the last dose for PK / PD sample collection) as depicted in Figure 1.

Figure 1 Study Design



CSL830 = plasma-derived human C1-esterase inhibitor; HAE = hereditary angioedema; IU = international units; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous(ly)

[a] Subjects completed Screening if their medical record indicated they experienced ≥ 4 HAE attacks over a consecutive 2 months during the 3 months immediately preceding Screening (or prior to beginning oral prophylaxis) and if they met other inclusion criteria subjects entered into the Run-in Period.

[b] Only if a subject experienced ≥ 1 HAE attack during the first 2 weeks OR ≥ 2 HAE attacks within any consecutive 4-week period during the Run-in Period, and had a confirmed HAE type I or II diagnosis, he or she could enter the CSL830 Treatment Period.

[c] A single SC injection of CSL830 60 IU/kg was administered twice-weekly. Administration occurred at the study center on Day 1 and at the Week 16 study center visit, where a blood sample was collected before administration. All other administrations of CSL830 SC could occur at home, either self-administered or administered by a caregiver who had been trained by study personnel.

[d] The End of Study Visit occurred approximately 2 weeks after the end of the CSL830 Treatment or whenever a subject was withdrawn from the study.

Number of Subjects:

Planned: Approximately 10 subjects with HAE type I or II were planned to enroll to target ≥ 8 subjects complete at least 12 weeks of treatment with CSL830 during the study.

Actual: A total of 10 subjects were screened. All 10 subjects were eligible and entered the Run-in Period. One subject failed to meet the eligibility criteria to enter the CSL830 Treatment Period during the Run-in Period. A total of 9 subjects entered the CSL830 Treatment Period and completed the study.

Diagnosis and Main Criteria for Inclusion:

Screening / Run-in Period:

1. Male or female, aged 12 years or older at the time of providing written informed consent / assent
2. Japanese (race to be determined by investigator), with clinical diagnosis of HAE type I or II
3. At least 4 HAE attacks over a consecutive 2-month period as documented in the subject's medical records in the 3 months before the Screening Visit or before initiation of prophylactic therapy

CSL830 Treatment Period:

1. Documented laboratory (local or central) testing results of:
    a. C1-INH functional activity less than 50% norm, AND
    b. C4 antigen concentration below the laboratory reference range
2. During their participation in the Run-in Period:
    a. Experienced ≥ 2 HAE attacks within any consecutive 4-week period, OR
    b. Experienced ≥ 1 HAE attack during the first 2 weeks

Investigational Product, Dose and Mode of Administration, Batch Number(s):

The study product was CSL830 and there was no comparator. During the CSL830 Treatment Period, subjects received CSL830 as a single 60 IU/kg SC injection (abdomen), twice-weekly, 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.

Before use, each 2000 IU vial of CSL830 was reconstituted with 4 mL water for injection; 60 IU/kg CSL830 was equivalent to a volume of 0.12 mL/kg.

The batch number of CSL830 used in the study was: P100198693.

Duration of Treatment:

The duration of the study for an individual subject was up to 30 weeks.

Criteria for Evaluation:

Primary Endpoints:

- The time-normalized number (per month) of HAE attacks during treatment with 60 IU/kg CSL830 and during the Run-in Period
- C1-INH functional activity (PK) after the last dose at Week 16 of the CSL830 Treatment Period

Secondary Endpoints:

- The percentage of subjects who achieved ≥ 90%, ≥ 70%, ≥ 50% relative reduction of monthly HAE attack rate during treatment with CSL830 compared to the monthly attack rate during the Run-in Period
- Relative reduction of the HAE attack rate of moderate or severe HAE attacks during treatment with CSL830 compared to the monthly HAE attack rate of moderate or severe HAE attacks during the Run-in Period
- The relative reduction in the time-normalized number of rescue medication uses during treatment with CSL830 compared with that during the Run-in Period
- Safety and tolerability of CSL830 as measured by number and rates of reported adverse events (AEs)
- Mean trough C1-INH functional activity, C1-INH, and C4 antigens during 3rd, 7th, 11th, and 16th week of CSL830 treatment, C1-INH activity and C1-INH and C4 antigens after last dose of CSL830 treatment
- Subject reported AEQoL measure
- SGART and IGART

Statistical Methods:

The planned sample size was not based on a power calculation but on practical considerations. Approximately 10 subjects with HAE type I or II were planned to enroll to target ≥ 8 subjects complete at least 12 weeks of treatment with CSL830 during the study.

Continuous variables were summarized in terms of the number of observations (n), mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum. Other descriptive statistics (eg, standard error [SE], coefficient of variation percentage [CV%]) could be reported when appropriate. For repeated assessments of continuous variables, the change from Baseline was also summarized. Categorical variables were summarized using frequency counts and percentages.

Statistical tests were of exploratory nature and were performed 2-sided at an alpha level of 5% unless otherwise stated.

Primary Efficacy Analysis

The primary efficacy analysis was based on the investigator reported HAE attacks as entered in the HAE attack case report form. Each HAE attack was (generally) preceded and followed by an attack-free day.

Descriptive statistics were presented for the time-normalized number of HAE attacks per month for the Efficacy Evaluation Period during treatment with CSL830 and the Run-in Period. A within-subject comparison of the difference between the attack rate in the Efficacy Evaluation Period compared to the Run-in Period was tested exploratorily using a 2-sided Wilcoxon signed rank test at an alpha level of 5%.

Pharmacokinetics / Pharmacodynamics Analysis

Pharmacokinetic parameters were derived based on C1-INH functional activity after the last dose at Week 16 of the CSL830 Treatment Period. In addition, descriptive statistics were provided for the C1-INH functional activity, C1-INH antigen concentrations, and C4 antigen concentrations at Week 1 predose, Week 3, 7, 11, and 16 of the CSL830 Treatment Period, and after the last dose.

Safety Analysis

The analysis of safety comprised all subjects who entered the CSL830 Treatment Period received at least 1 dose of CSL830.

Adverse events were summarized by the number of subjects who experienced the event of interest, the percentage of subjects, and the number of events. In addition, injection and exposure-adjusted incidence rates were presented. The following information was summarized: AE, AEs related to study treatment, injection site reactions (ISRs), AEs occurring within 24 hours of CSL830 administration, AEs leading to study discontinuation, thromboembolic events (TEEs), sepsis, bacteremia, viremia, and fungemia AEs, anaphylactic reaction AEs, hypersensitivity AEs, serious adverse events (SAEs), SAEs related to study treatment, fatal AEs, fatal AEs related to study treatment, AEs by intensity, AEs by outcome.

Clinical laboratory evaluation results were summarized at scheduled visits using descriptive statistics for observed values and change from Baseline. The number and percentage of subjects with clinically significant laboratory results were presented by scheduled visit.

Results:

Subject Disposition and Demographics

Ten subjects provided informed consent / assent and were screened; all 10 subjects were eligible and entered the Run-in Period. One subject failed to meet the eligibility criteria to enter the CSL830 Treatment Period during the Run-in Period and 9 subjects entered the CSL830 Treatment Period. All the 9 subjects were treated during the CSL830 Treatment Period and completed the study.

All subjects in the study were Japanese, 67% were female, the mean (SD) age was 37.9 (11.43) years. Most subjects had diagnosis of HAE type I (89%). In the 3 months

before Screening or initiation of oral HAE prophylaxis subjects experienced a mean (SD) of 11.2 (10.97) HAE attacks.

Treatment Compliance and Exposure

All subjects had 100% treatment compliance. The median duration of exposure to CSL830 was 15.714 weeks (range 15.29 to 15.86 weeks), with an overall 2.70 subject-years of exposure.

Efficacy

The primary efficacy analysis demonstrated that CSL830 reduced the time-normalized number of HAE attacks relative to the Run-in Period.

- The mean time-normalized number of HAE attacks during the CSL830 Treatment Period was 0.295 attacks per month, compared with 3.691 attacks per month during the Run-in Period.
- The mean or median absolute reductions in attack rate during the CSL830 Treatment Period were 3.396 or 3.581 attacks per month, indicating mean or median relative reductions of 89% and 100%, respectively, compared with the Run-in Period.

The responder analysis demonstrated that all subjects were responders who had a relative reduction of ≥ 50% in the time-normalized number of HAE attacks during the CSL830 Treatment Period compared with the Run-in Period. Most subjects also had a relative reduction in the time-normalized number of HAE attacks ≥ 70% (78%) and ≥ 90% (67%). Importantly, 67% of subjects were attack-free during the CSL830 Treatment Period.

Time-normalized numbers of moderate or severe HAE attacks were reduced by a mean of 89% or a median of 100% during the CSL830 Treatment Period when compared with the Run-in Period. No subjects had severe attacks during the CSL830 Treatment Period.

CSL830 reduced the time-normalized number of uses of rescue medication relative to the Run-in Period. The mean time-normalized number of uses of rescue medication per month was reduced from 4.602 during the Run-in Period to 0.295 during the CSL830 Treatment Period, with a mean reduction of 4.307 uses per month. The mean or median relative reductions were 85% and 100%, respectively.

A clinically meaningful improvement (decrease of at least 6 points) was seen in all 4 domains of the AEQoL questionnaire, with decreases in domain scores ranging from 11 to 36 points and a decrease in total score of 24 points at the end of the CSL830 Treatment Period compared with the Baseline.

“Good or excellent” response to therapy was reported by all subjects (SGART) and investigators (IGART) and the majority reported “Excellent” response to therapy.

Pharmacokinetics / Pharmacodynamics

Following the last dose of CSL830 60 IU/kg SC twice-weekly for 16 weeks, the mean trough concentration (C_{trough}) was 59.77% and the mean area under the plasma

concentration-time curve to the end of the dosing period ($AUC_{0\text{-}tau}$) and area under the plasma concentration-time curve until last sample ($AUC_{0\text{-}last}$) were 5317.1164 and 13091.4870 h*%, respectively.

The administration of CSL830 increased C1-INH functional activity during the CSL830 Treatment Period. C1-INH functional activity appeared to reach steady-state at Week 3, with consistent C1-INH functional activity observed from Week 3 to Week 16 and appeared to approach the lower limit of normal (70%). At the End of Study Visit, C1-INH functional activity appeared to decrease toward the Baseline level. Similar increases were observed in C1-INH antigen and C4 antigen concentrations following SC administration of CSL830. C1-INH antigen and C4 antigen concentrations appeared to reach steady-state at Week 3, with consistent antigen concentrations observed from Week 3 to Week 16. At the End of Study Visit, both C1-INH antigen and C4 antigen appeared to decrease toward the Baseline level.

Safety

The results of Study 3003 demonstrated that CSL830 60 IU/kg SC twice-weekly was safe and were well tolerated.

- There were no deaths, SAEs, or AEs leading to study discontinuation. A total of 109 AEs were reported in 7 of 9 subjects and 62 AEs in 3 subjects were related to CSL830 treatment. A total of 44 ISRs were reported in 3 subjects.
- The majority of AEs were mild in severity (101 of 109) and had an outcome of recovered / resolved (107 of 109).

The AEs reported in at least 2 subjects were Injection Site Pain, Abdominal Distension, Contusion, and Nasopharyngitis, in 2 subjects each.

Injection site reactions comprised a major category of AEs, with a large number of events reported in a relatively small number of subjects. A total of 44 ISRs were reported in 3 subjects and 43 ISRs in 2 subjects were related to CSL830 treatment. The majority (36 of 44 events) of ISRs were of mild severity. All ISRs had an outcome of recovered / resolved.

Treatment-related AEs were reported in 3 subjects and consisted of ISRs or Malaise.

There were no notable findings related to clinical laboratory or vital sign parameters.

There were no TEEs or events of sepsis. No systemic anaphylaxis or hypersensitivity events were identified. No antibodies to C1-INH were detected.

Conclusions:

In conclusion, this study demonstrated the efficacy of CSL830 60 IU/kg SC twice-weekly for routine prophylaxis against HAE attacks in Japanese subjects with HAE, which was supported by the increased and maintained C1-INH functional activity. CSL830 was well tolerated and had a favorable safety profile in Japanese subjects. Overall, the results of Study 3003 in Japanese subjects confirm the efficacy, PK, and safety profile of CSL830 observed in the pivotal Study 3001.

Date of Report: 12 Aug 2021