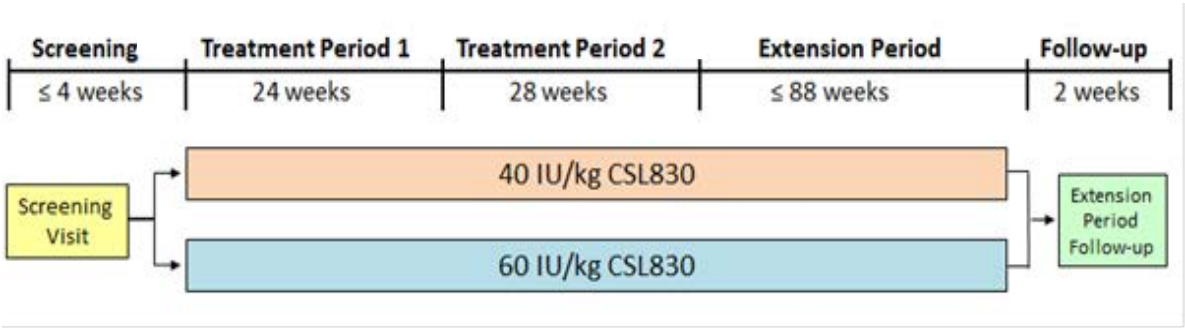
2 SYNOPSIS

<table>
<tr><td>Name of Sponsor: CSL Behring GmbH</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
CSL830 (C1-esterase inhibitor, human [subcutaneous])</td></tr>
<tr><td>Name of Active Ingredient:
C1-esterase inhibitor (human)</td></tr>
<tr><td colspan="3">Title of Study: An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema</td></tr>
<tr><td colspan="3">Coordinating Investigator: PPD</td></tr>
<tr><td>Current Address of Coordinating Investigator:</td><td colspan="2">Addenbrooke’s Hospital
Hills Rd
Cambridge, CB2 0QQ
United Kingdom</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable</td></tr>
<tr><td>Study Period:
First Subject Visit: 31 December 2014
Last Subject Visit: 21 September 2017</td><td colspan="2">Phase of Development: Phase 3b</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective: To assess the clinical safety of subcutaneously (SC) administered CSL830 in the long-term (ie, routine) prophylactic treatment of hereditary angioedema (HAE).
Secondary Objectives:
1. To further characterize the clinical safety of SC administered CSL830 in the long-term (ie, routine) prophylactic treatment of HAE.
2. To characterize the clinical efficacy of SC administered CSL830 in the long-term (ie, routine) prophylactic treatment of HAE.</td></tr>
<tr><td colspan="3">Methodology:
This multicenter, randomized, open-label, parallel-arm, phase 3b study investigated the clinical safety and efficacy of SC administered CSL830 in the prophylactic treatment of</td></tr>
</table>

HAE. An overview of the study is depicted in Figure 1. The study was conducted globally under the Original Protocol where subjects could receive CSL830 for up to 52 weeks or for up to 140 weeks in the United States, following a Country-specific Protocol Amendment.

Figure 1 Study Design Schematic



Subjects belonged to the following categories:

- "CSL830-Naïve" Subjects (subjects who did not participate in the preceding Study 3001 or subjects who participated in Study 3001 but did not receive investigational product as a part Study 3001).
- "CSL830-Interrupted" Subjects (subjects who completed participation in Study 3001, but who delayed entry into the current study [ie, > 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 (ie, Screening Visit)]).
- "CSL830-Continuation" Subjects (subjects who completed participation in Study 3001 and who continued directly on to participate in the current study [ie, ≤ 1 week between the End of Study Visit of Study 3001 and the first visit of Study 3002 Treatment Period 1 (TP1)]).

Eligibility for all subjects was assessed at a Screening Visit ("CSL830-Naïve" and "CSL830-Interrupted" Subjects) or from assessments conducted during participation in Study 3001 ("CSL830-Continuation" Subjects). Eligible subjects were randomized to either 40 IU/kg or 60 IU/kg CSL830 in the 24-week fixed-dose TP1. During TP1, subjects who experienced frequent HAE attacks (ie, ≥ 12 attacks within a 4-week evaluation period) were eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). Treatment Period 2 (TP2) was a dose-adjustment period to allow for individual optimization of routine prophylaxis, beginning at Week 25. Subjects who experienced ≥ 3 HAE attacks within an 8-week evaluation period during TP2 were eligible for CSL830 dose increases in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). TP2 ended at Week 53.

Additionally, a Country-specific Protocol Amendment included an optional Extension Period (88 weeks followed by 2-weeks' follow-up) to allow subjects from the United States who completed TP2 according to the protocol to then continue receiving treatment with open-label CSL830. The Extension Period followed TP2, with the last visit of TP2 serving

as the first visit of the Extension Period (except for subjects who elected to take a rest period of up to 30 days between TP2 and the Extension Period).

Subjects attended a Follow-up Visit occurring 14 days (± 3 days) after the final visit in TP2 or the Extension Period (if applicable), or any visit resulting in study discontinuation, unless informed consent / assent was withdrawn

Number of Subjects:

Planned: It was planned that 100 subjects would complete the study.

Actual: A total of 131 subjects provided informed consent / assent and were assessed for eligibility; 126 subjects were randomized into the study (63 to the 40 IU/kg dose and 63 to the 60 IU/kg dose).

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, ≥ 6 years of age.
3. Clinical diagnosis of HAE type I or II, as determined by a clinical history consistent with HAE ***and*** C1-esterase inhibitor (C1-INH) functional activity < 50%, concurrent with C4 antigen concentrations below normal limits.
4. Experienced at least 4 HAE attacks (requiring acute treatment, medical attention, or causing significant functional impairment) over a consecutive 2-month period before the Study 3002 Screening Visit and before start of treatment with intravenous (IV) C1-INH prophylaxis (for "CSL830-Naïve" Subjects using IV C1-INH prophylaxis).
5. Subjects who used oral medication for prophylaxis against HAE attacks (ie, androgens, tranexamic acid, progestins): use of a *stable* regimen of oral prophylactic medication during the 3 months before their first study visit and willingness to continue the stable regimen for at least 25 weeks.

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

The investigational product was CSL830.

During all treatment periods, subjects administered their randomized dose of CSL830 (40 IU/kg or 60 IU/kg) via a single SC injection, twice per week. The randomized dose of CSL830 could be increased in increments of 20 IU/kg up to a maximum dose of 80 IU/kg in subjects meeting the prespecified criteria for up-titration of their dose.

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.

Duration of Treatment:

The study duration for an individual subject participating in TP1 and TP2 was up to

58 weeks (including assessment of eligibility and follow-up). The study duration for an individual subject participating in TP1, TP2, and the Extension Period was up to 146 weeks (including assessment of eligibility and follow-up).

Criteria for Evaluation:

Primary Endpoints:

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

- Adverse events (AEs) leading to premature study discontinuation.
- Thromboembolic event (TEEs).
- Anaphylaxis.
- HAE attacks resulting in in-patient hospitalization (where hospitalization was the consequence of the need for emergent medical care).
- Solicited AEs (injection site reactions at the CSL830 injection site) graded as severe by the investigator.
- Related serious adverse events (SAEs), other than events specified above.
- Anti-C1-INH antibodies (inhibitory or non-inhibitory).

***Secondary Safety Endpoints*:**

- AEs, SAEs, solicited AEs (ie, injection site reactions), unsolicited AEs, AEs that began within 24 hours after CSL830 administration, and suspected adverse drug reactions (ADRs; defined as AEs that began within 24 hours after CSL830 administration, AEs at least possibly related to CSL830 administration, and AEs with no causality assessment).
- AEs of special interest (TEEs, anaphylaxis events), sepsis and bacteremia events.
- Clinical laboratory assessments, including hematology, biochemistry, urinalysis, coagulation profile, viral serology, and anti-C1-INH antibodies.
- Vital signs (including body weight) and physical examination.
- Risk scores for deep vein thrombosis (DVT) and pulmonary embolism.

Secondary Efficacy Endpoints:

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

Statistical Methods:

It was planned that 100 subjects would complete the study. The sample size was determined considering International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E1 guidelines on the extent of population exposure to assess clinical safety. This allowed observation of any AE that occurred at least once with a probability of 3% at 95% confidence. Continuous variables were described using means and respective 95% confidence intervals (CIs), as applicable; standard deviation (SD); ranges; 25^{th}, 50^{th} (median), and 75^{th} percentiles; and counts of missing and non-missing values. Categorical values were described using counts and percentages.

For subjects who did not participate in the Extension Period, the End of Study Visit was at Week 53. For subjects who participated in the Extension Period, the End of Study Visit was at Week 88.

Primary Safety Analyses

The primary safety analyses were performed on data from all subjects who received CSL830. The PTIRs for each primary endpoint safety event were calculated as follows:

- Subject-based analysis for PTIR = (the total number of subjects who experienced the respective safety event during the respective treatment) / (the sum of the date each subject experienced the first safety event – the subject's start date + 1 day) / (365.25 days). Subjects without the respective event were not included in the numerator, but were included in the time at risk with their entire study participation time.
- Event-based analysis for PTIR = (the total number of respective safety events documented during the respective treatment) / (the sum of each subject's end date – the subject's start date + 1 day) / (365.25 days). Subjects with or without the respective event were included in the time at risk with their entire study participation time.

Secondary Safety Analyses

The secondary safety analyses were performed on data from all subjects who received CSL830. AEs, solicited AEs, and unsolicited AEs were described by severity, relationship to investigational product, outcome, and seriousness by treatment. All solicited AEs were additionally summarized by duration. The percentage of subjects with AEs beginning during or within 24 hours of administration was summarized by treatment. Risk scores for DVT and pulmonary embolism, TEE events, events of Sepsis or Bacteraemia, potential cases of Anaphylaxis, and suspected ADRs were also assessed.

Secondary Efficacy Analysis

Every day, subjects had to enter HAE symptoms into their electronic diary, including the severity and location of the HAE symptom. Investigator-reported HAE attacks were based upon review of subject diaries and review of relevant interim medical history. The investigator was to determine the occurrence of an HAE attack and report its start and stop

dates, its severity, and its location(s). Each HAE attack was to be preceded and followed by an attack-free day. The investigator-reported HAE attacks that were not preceded and followed by an attack-free day were merged into 1 HAE attack with the earliest start date, the latest end date, and the most severe severity of the individual HAE attacks. If the start date of a merged HAE attack fell in the first 2 weeks of a treatment period, the merged HAE attack was not included in the analyses. If the investigator entered the individual HAE attacks during the same time frame but in different attack locations, the corresponding merged HAE attack location was classified as "multiple".

All efficacy endpoints which included HAE attacks were analyzed using the merged HAE attacks as the primary analysis approach.

The time-normalized number of HAE attacks was summarized descriptively by treatment, and was calculated per subject as the number of HAE attacks divided by the length of stay of the subject in the actual treatment.

The number and percentage of responders and non-responders and the difference in the percentage of responder between the 60 IU/kg CSL830 and 40 IU/kg CSL830 treatments was summarized and 95% Wilson CIs were calculated for all percentages.

Results:

Disposition and Demographics

A total of 126 subjects were randomized, 63 subjects to the 40 IU/kg CSL830 treatment arm and 63 subjects to the 60 IU/kg CSL830 treatment arm. Each treatment arm comprised 6 (9.5%) "CSL830-Continuation" Subjects, 26 (41.3%) "CSL830-Interrupted" Subjects, and 31 (49.2%) "CSL830-Naïve" Subjects.

Two (3.2%) subjects randomized to the 60 IU/kg CSL830 treatment arm were up-titrated to 80 IU/kg. Seven (11.1%) subjects randomized to the 40 IU/kg CSL830 treatment arm were up-titrated. Five of these 7 subjects were up-titrated once from 40 → 60 IU/kg and 2 subjects were up-titrated twice from 40 → 60 → 80 IU/kg.

A total of 16 (12.7%) subjects discontinued from the study and 110 (87.3%) subjects completed the study. Nine subjects discontinued in TP1 (5 [7.9%] subjects in the 40 IU/kg treatment arm and 4 [6.3%] subjects in the 60 IU/kg treatment arm), 6 subjects discontinued in TP2 (3 [4.8%] subjects in the 40 IU/kg treatment arm and 3 [4.8%] subjects in the 60 IU/kg treatment arm), and 1 (1.6%) subject discontinued in the Extension Period (in the 60 IU/kg treatment arm). Reasons for study discontinuation included AEs (4 subjects), withdrawal by subject (8 subjects), and pregnancy (4 subjects).

Of the 126 randomized subjects, 76 (60.3%) were female and 121 (96.0%) were White. The mean age of the study population was 40.5 years. The 40 IU/kg and 60 IU/kg treatment arms were similar in terms of age, sex, race, weight, and body mass index.

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 arms and consistent with what is seen

in the general HAE population. The mean (SD) reported historic number of HAE attacks per subject in the 3 months before Screening was 12.8 (8.42) attacks in the 40 IU/kg treatment arm and 13.3 (10.12) attacks in the 60 IU/kg treatment arm. The percentages of "CSL830-Naïve" Subjects who used any prior HAE prophylaxis (ie, IV C1-INH and / or oral androgens) in the 3 months before Screening were the same in the 40 IU/kg treatment arm (7 [22.6%] subjects) and the 60 IU/kg treatment arm (8 [22.9%] subjects).

Treatment Compliance and Exposure

Treatment compliance was high in both treatment arms, with a mean compliance of 100.2% (range: 94% to 108%) in the 40 IU/kg treatment arm and 100.0% (range: 95% to 105%) in the 60 IU/kg treatment arm. The median duration of exposure (regardless of any dose increase) was 52.4 weeks in the 40 IU/kg treatment arm and 52.6 weeks in the 60 IU/kg treatment arm. The maximum duration of exposure was > 2.5 years in both the 40 IU/kg and 60 IU/kg treatment arms.

Safety

Primary Safety Analyses

The sum of all subjects' exposure in each treatment was similar for each of the 7 primary endpoint safety events. The main findings of the primary safety analyses were:

- Four AEs (1 SAE and 3 non-serious AEs) led to study discontinuation of 4 subjects during the study. The event-based analysis PTIRs (rate / year) were low and similar in both treatments (40 IU/kg: 0.01 [95% CI: < 0.005, 0.07]; 60 IU/kg: 0.03 [95% CI: 0.01, 0.09]).
- One TEE (SAE of Myocardial Infarction, assessed as not related) was experienced by a subject on 60 IU/kg (event-based analysis PTIR: 0.01 [95% CI: < 0.005, 0.06]), and led to study discontinuation.
- There were no cases of anaphylaxis in either treatment.
- One subject, who had up-titrated to 80 IU/kg in the Extension Period, had an HAE attack (laryngeal, assessed as not related) during the Extension Period that resulted in hospitalization.
- No solicited AEs were graded as severe.
- No SAEs were reported as related to CSL830.
- Ten subjects who tested negative for non-inhibitory antibodies to C1-INH at Baseline then tested positive at a subsequent visit: 5 subjects treated with 40 IU/kg (including 1 subject who was up-titrated to 60 IU/kg) and 5 subjects treated with 60 IU/kg. Of these 10 subjects, 6 subjects were negative for non-inhibitory antibodies to C1-INH at the End of Study Visit (Week 53 / Week 88) and 3 subjects were positive at the End of Study Visit. One subject prematurely discontinued from the study due to pregnancy and was positive for non-inhibitory antibodies to C1-INH at the last assessment (Week 25).

No subjects had positive results for inhibitory antibodies to C1-INH at Baseline or at any Post-baseline Visit. The event-based analysis PTIRs (rate / year) were low and similar in both treatments (40 IU/kg: 0.06 [95% CI: 0.02, 0.14]; 60 IU/kg: 0.09 [95% CI: 0.04, 0.17]).

Adverse Events

AEs were reported in a similar percentage of subjects during treatment with 40 IU/kg and with 60 IU/kg, with a total of 18,699 CSL830 injections analyzed. AEs were reported in 56 (88.9%) subjects on 40 IU/kg and in 58 (82.9%) subjects on 60 IU/kg. Solicited AEs (ie, injection site reactions) were the most common events reported during the study, with no clear dose relationship.

Solicited AEs were reported in 35 (55.6%) subjects during treatment with 40 IU/kg (692 events; 0.08 events / injection), and in 32 (45.7%) subjects during treatment with 60 IU/kg (554 events; 0.06 events / injection). A disproportionately large number of events were reported by a small number of subjects. Across the study, 4 subjects contributed 675 of 1251 solicited AEs. This included 3 subjects randomized to treatment with 40 IU/kg (of which 1 subject was up-titrated to 60 IU/kg during TP2) and 1 subject randomized to treatment with 60 IU/kg who did not up-titrate to a higher dose. No specific safety concern was identified on review of the data for these subjects. None of these subjects discontinued their participation.

The solicited AEs reported for the highest percentage of subjects were Injection Site Pain (40 IU/kg: 17 [27.0%] subjects; 60 IU/kg: 10 [14.3%] subjects), Injection Site Erythema (40 IU/kg: 10 [15.9%] subjects; 60 IU/kg: 12 [17.1%] subjects), and Injection Site Bruising (40 IU/kg: 9 [14.3%] subjects; 60 IU/kg: 7 [10.0%] subjects). The majority of solicited AEs were assessed as related (692 / 692 events with 40 IU/kg; 552 / 554 events with 60 IU/kg), mild in severity (688 / 692 events with 40 IU/kg; 541 / 554 events with 60 IU/kg), and were resolved within 1 day after injection (468 / 692 events with 40 IU/kg; 487 / 554 events with 60 IU/kg). No severe solicited AEs occurred during treatment with either dose of CSL830. None of the solicited AEs were serious or resulted in discontinuation from the study.

Unsolicited AEs were reported in similar percentages of subjects during treatment with 40 IU/kg and with 60 IU/kg. Unsolicited AEs were reported in 50 (79.4%) subjects (256 events) during treatment with 40 IU/kg and in 56 (80.0%) subjects (295 events) during treatment with 60 IU/kg.

The most frequently reported unsolicited AEs were Nasopharyngitis (40 IU/kg: 12 [19.0%] subjects; 60 IU/kg: 21 [30.0%] subjects), Headache (40 IU/kg: 10 [15.9%] subjects; 60 IU/kg: 10 [14.3%] subjects), and Upper Respiratory Tract Infection (40 IU/kg: 8 [12.7%] subjects; 60 IU/kg: 8 [11.4%] subjects). The majority of solicited AEs were reported as not related (251 / 256 events with 40 IU/kg; 291 / 295 events with 60 IU/kg), mild in severity (151 / 256 events with 40 IU/kg; 184 / 295 events with 60 IU/kg), and had an outcome of recovered / resolved (237 / 256 events with 40 IU/kg; 263 / 295 events with 60 IU/kg).

Serious Adverse Events and Other Safety Events of Interest

No deaths were reported during the study. Twelve SAEs were experienced by 9 subjects during treatment with CSL830. Five SAEs occurred in 4 subjects on 40 IU/kg, 6 SAEs occurred in 5 subjects on 60 IU/kg, and 1 SAE occurred in 1 subject on 80 IU/kg. The majority of SAEs were graded as moderate or severe and had an outcome of recovered / resolved. No SAEs were solicited AEs and no SAEs were assessed as related.

A single TEE was reported during the study (Acute Myocardial Infarction during treatment with 60 IU/kg; assessed as not related to CSL830). The event was graded as severe, had an outcome of recovered / resolved, and resulted in discontinuation. The cardiologist's evaluation concluded that the cause of the Acute Myocardial Infarction was likely due to a spontaneous plaque rupture of an atherosclerotic plaque with associated mild clot formation, "rather than a spontaneous coronary thrombosis". The subject also had multiple cardiac risk factors including being PPD (body mass index of PPD kg/m^2), being a PPD (PPD / day for years), PPD, and PPD.

No cases of anaphylaxis, sepsis, or bacteremia were identified.

No seroconversions for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus were identified.

No inhibitory antibodies were detected. No apparent association was identified between treatment with CSL830 and detection of non-inhibitory antibodies to C1-INH, and the presence of these antibodies varied over time.

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

Secondary Efficacy Endpoints

The percentage of responders (95% Wilson CI) was 93.5% (84.6%, 97.5%) on 40 IU/kg and 91.7% (81.9%, 96.4%) on 60 IU/kg.

The proportion of subjects with a time-normalized HAE attack frequency of < 1 HAE attack per 4-week period was 79.4% in the 40 IU/kg treatment arm and 85.7% in the 60 IU/kg treatment arm. The difference in the number of HAE attacks experienced following treatment with CSL830 as compared with the number of attacks experienced pre-study, showed a mean (SD) reduction of -6.82 attacks (11.809) in the 40 IU/kg treatment arm and -6.83 attacks (16.346) in the 60 IU/kg treatment arm.

Conclusions:

The results of demonstrated that 40 IU/kg and 60 IU/kg CSL830 both have favorable long-term safety and tolerability when administered SC twice per week for prophylaxis in subjects with HAE type I and II. There were no dose dependent safety concerns. In addition, the secondary and exploratory efficacy results support the efficacy of SC CSL830 for routine prophylaxis against HAE attacks, and demonstrated that the effect is maintained over time periods in excess of 2 years.

Date of Report: 15 March 2018