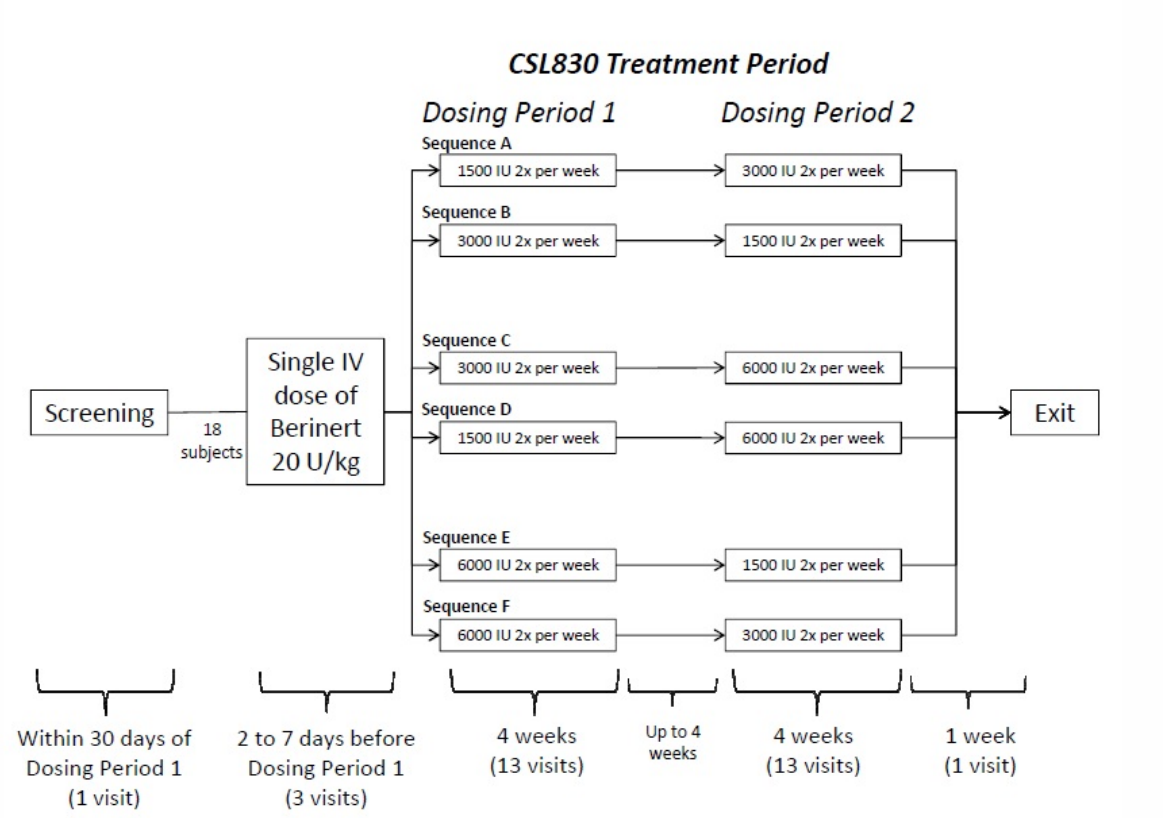
2 Synopsis

Name of Sponsor: CSL Behring GmbH **Name of Finished Product:** CSL830 (C1-esterase Inhibitor) **Name of Active Ingredient:** C1-esterase inhibitor	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority Use Only)*
Study Title: An Open-label, Cross-over, Dose-ranging Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of the Subcutaneous Administration of a Human Plasma-derived C1-esterase Inhibitor in Subjects with Hereditary Angioedema		
Study Number: CSL830_2001		
Coordinating Investigator: PPD University of California, San Diego, CA, USA		
Publication (reference): None		
Study Period: 30 April 2012 to 11 December 2012	**Phase of Development:** 1/2	
Objectives: ***Primary Objective:*** To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of the subcutaneous (SC) administration of 3 different dosing regimens of CSL830. ***Secondary Objective:*** To evaluate the safety, tolerability, and immunogenicity of the SC administration of 3 different dosing regimens of CSL830.		
Methodology: This was a prospective, international, multi-center, open-label, cross-over study to characterize the PK, PD, and safety, including tolerability, immunogenicity, of CSL830 administered SC to 18 subjects with hereditary angioedema (HAE). Following a screening period of up to 30 days, subjects were allocated sequentially to 1 of 6 possible CSL830 treatment sequences (Sequence A to Sequence F), which was preceded by a single intravenous (IV) dose of Berinert 20 U/kg administered 2 to 7 days before the first CSL830 dosing period (Figure 1). The 2 CSL830 dosing periods were run consecutively, unless an interval of up to 4 weeks was approved by the sponsor. One week after the completion of the study visits associated		

with the second dosing period, subjects had a follow-up assessment at the exit visit.

During the study, blood and urine samples were collected at specified times for safety, PK, or PD analyses. Safety and tolerability were evaluated by continuous observation of AEs and by other safety assessments that were conducted at specified times throughout the study (including infusion site tolerability, laboratory parameters, vital signs, body weight, physical examination, risk assessment for deep vein thrombosis, and concomitant medication usage). One week after the completion of the study visits, subjects had a follow-up assessment at the exit visit.

Figure 1. Study Schema



Number of Subjects

Planned: Maximum of 18 enrolled subjects.

Enrolled: 18 subjects.

Analysed: 18 subjects.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects with type I or II HAE aged 18 years or older weighing 50 to 110 kg, who had 5 or fewer HAE attacks within the 3 months prior to the screening visit, and who were able to provide written informed consent, were included in the study.

Investigational Product, Dose, and Mode of Administration:

CSL830 is a C1-esterase inhibitor (C1-INH), provided as a lyophilizate containing 1500 IU C1-INH to be reconstituted with 3 mL of water for injection. Each vial of CSL830 contained 150 to 240 mg protein, 25.5 to 34.5 mg glycine, 4.5 to 10.5 mg trisodium citrate dihydrate, and 21 to 30 mg sodium chloride. Subjects were allocated to receive 2 of the following 3 dosing regimens of CSL830 SC:

- 1500 IU administered 2 times weekly for 4 weeks.
- 3000 IU administered 2 times weekly for 4 weeks.
- 6000 IU administered 2 times weekly for 4 weeks

(CSL830 batch numbers: 00468811A and 00568811A)

Duration of Treatment:

The duration of the study treatment was up to 18 weeks which included a screening period of up to 30 days, Berinert administration 2 to 7 days before the first CSL830 dosing period, 2 CSL830 dosing periods of 4 weeks each run consecutively or with an interval of up to 4 weeks (if approved by the sponsor), and a 1-week follow-up period.

Reference Therapy, Dose and Mode of Administration:

Berinert is a C1-esterase inhibitor, provided as a lyophilizate containing 500 U C1-INH to be reconstituted with 10 mL of water for injection. Each vial of Berinert contained 50 to 80 mg protein, 85 to 115 mg glycine, 25 to 30 mg trisodium citrate dihydrate, and 70 to 100 mg sodium chloride. Subjects received a single IV dose of Berinert:

- 20 U/kg body weight administered as a slow IV infusion of approximately 4 mL/minute.

(Berinert batch numbers: 41261711B and 42661711C)

Criteria for Evaluation:

Primary Endpoint:

- Mean trough C1-INH functional activity at the fourth week of each dosing regimen of CSL830, based on modeling and simulation.

Secondary Endpoints:

- Mean trough C1-INH functional activity at the fourth week of each dosing regimen of CSL830, based on observed data.
- Mean trough C1-INH antigen level at the fourth week of each dosing regimen of CSL830, based on observed data.
- Mean trough C4 antigen level at the fourth week of each dosing regimen of CSL830, based on observed data.
- Mean change from baseline of C1-INH functional activity, C1-INH antigen level and C4 antigen levels to the mean trough level at the fourth week of each dosing regimen of CSL830, based on observed data.

Exploratory Endpoints:

- Modeling-derived PK/PD parameters (e.g., volume of distribution [V], clearance [CL], SC bioavailability) of C1-INH functional activity for IV Berinert and each CSL830 dosing regimen.

Additional safety and tolerability endpoints included:

- The frequency and intensity of adverse events (AEs).
- The intensity of solicited local AEs at the injection site (pain, swelling, bruising, and itching).

- Clinical laboratory tests and assessments including: hematology, blood chemistry, thrombotic screen, coagulation profile, D-dimer level, anti-C1-INH antibodies, viral safety, and urinalysis.
- Risk assessment for deep vein thrombosis.

Statistical Methods:

The data analysis for the study comprised descriptive statistics. C1-INH functional activity data were subjected to a population-based approach using nonlinear mixed-effects modeling using NONMEM version 7.2 or higher. The exploratory PK/PD parameters were derived from nonlinear mixed-effects modeling and simulation for each dosing regimen. All outputs were produced using SAS® version 9.2.

Results:

A total of 22 subjects provided informed consent and were screened for inclusion in this study. Of these, 18 eligible subjects were enrolled and allocated sequentially to receive 1 of 6 CSL830 treatment sequences. All 18 subjects received a single IV dose of Berinert prior to treatment with CSL830 to characterize their individual PK to IV C1-INH. All 18 randomized subjects received at least 1 dose of study product in each period and all 18 subjects completed the study.

Subject Demographics

Baseline characteristics were similar across the 3 dosing regimens. The majority of subjects (14/18; 77.8%) reported that they were of white race. Overall, the median age of subjects was 33.9 years and more females (11/18; 61.1%) than males (7/18; 38.9%) participated in the study. The median body weight of subjects was 78.9 kg and the median body mass index (BMI) was 25.4 kg/m^2.

Other baseline characteristics were similar across the 3 dosing regimens. The majority of subjects (16/18; 88.9%) had type I HAE and the median number of HAE attacks in the 3 months prior to screening was 2.0 in all 3 CSL830 dosing regimens. Overall, the median baseline as-observed C1-INH functional activity was 15.2%, the median baseline as-observed C1-INH antigen level was 0.050 mg/mL, and the median baseline as-observed C4 antigen level was 7.0 mg/mL.

CSL830 Doses Administered

The mean (SD) treatment compliance rate in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens were 100.0% (0.00), 101.0% (3.61), and 99.0% (3.61), respectively. One subject missed a CSL830 dose during dosing Period 1 and 1 subject had an incorrect dose administered; the missed and the incorrect dose administered were flagged as protocol deviations. The median duration of injection was 4, 6, and 12 minutes in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. There were a few outliers with longer administration times in the 3000 IU and 6000 IU regimens.

Pharmacokinetic Results

The mean modeling-derived steady-state trough C1-INH functional activity at the fourth week was 30.3%, 45.9%, and 80.6% in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. The mean as-observed steady-state trough C1-INH functional activity at the fourth week was 31.7%, 44.3%, and 80.5% in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. The mean as-observed C1-INH functional activity increased with the dose per body weight; the mean C1-INH functional activity at the fourth week was 26.8%, 39.3%, 63.4%, and 100.4% in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

The mean as-observed steady-state trough C1-INH antigen level at the fourth week was 0.06 mg/mL, 0.15 mg/mL, and 0.23 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. The mean as-observed increase in C1-INH antigen level from baseline at the fourth week trough was 0.02 mg/mL, 0.05 mg/mL, and 0.14 mg/mL in the CSL830 1500 IU, 3000 IU, and 6000 IU

dosing regimens, respectively. The mean as-observed C1-INH antigen level increased with the dose per body weight; the mean C1-INH antigen level at the fourth week was 0.05 mg/mL, 0.10 mg/mL, 0.20 mg/mL, and 0.28 mg/mL in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

The mean as-observed steady-state trough C4 antigen level at the fourth week was 11.1 mg/dL, 14.1 mg/dL, and 18.4 mg/dL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. The mean as-observed increase in C4 antigen level from baseline at the fourth week was 4.3 mg/dL, 5.6 mg/dL, and 9.1 mg/dL in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively. The mean as-observed C4 antigen level increased with the dose per body weight; the mean as-observed C4 antigen level at the fourth week was 11.3 mg/mL, 11.7 mg/mL, 18.0 mg/mL, and 18.2 mg/mL in the ≤ 20 IU/kg, > 20 to ≤ 45 IU/kg, > 45 to ≤ 90 IU/kg, and > 90 IU/kg planned dose per body weight categories, respectively.

Pharmacokinetic parameters are presented by study treatment (Berinert or CSL830 dosing regimens):

Table 1 Exploratory pharmacokinetic parameters

Parameter	Berinert 20 U/kg (all treated subjects) (N = 18)	CSL830 Dosing regimen		
		CSL830 1500 IU (N = 12)	CSL830 3000 IU (N = 12)	CSL830 6000 IU (N = 12)
$t_{1/2}$ (hr)				
Mean (SD)	52.8 (13.70)	50.6 (12.35)	51.5 (13.52)	56.2 (15.02)
95% CI	(46.0, 59.6)	(42.8, 58.5)	(42.9, 60.1)	(46.6, 65.7)
Median	52.2	51.7	51.7	54.8
Min, Max	33.1, 78.7	33.1, 78.7	34.9, 76.6	33.1, 78.7
$AUC_{(0\text{-}t)}$ (U.hr/mL)				
Mean (SD)	38.9 (8.93)	30.5 (11.31)	45.3 (11.98)	79.6 (25.36)
95% CI	(34.5, 43.3)	(23.3, 37.6)	(37.7, 52.9)	(63.5, 95.7)
Median	37.2	28.3	44.1	75.4
Min, Max	27.5, 57.5	16.9, 52.7	27.3, 64.0	41.4, 114.9
C_{max} (U/mL)				
Mean (SD)	0.67 (0.562)	0.38 (0.109)	0.59 (0.154)	1.09 (0.307)
95% CI	(0.64, 0.70)	(0.31, 0.45)	(0.49, 0.69)	(0.89, 1.28)
Median	0.67	0.39	0.61	1.07
Min, Max	0.60, 0.79	0.20, 0.56	0.33, 0.80	0.60, 1.49
C_{av} (U/mL)				
Mean (SD)	-	0.36 (0.135)	0.54 (0.142)	0.95 (0.303)
95% CI	-	(0.28, 0.45)	(0.45, 0.63)	(0.76, 1.14)
Median	-	0.34	0.53	0.90
Min, Max	-	0.20, 0.63	0.32, 0.76	0.49, 1.37
IR ([U/mL]/[U/kg])				
Mean (SD)	0.026 (0.0023)	0.011 (0.0024)	0.011 (0.0024)	0.012 (0.0027)
95% CI	(0.025, 0.027)	(0.010, 0.013)	(0.010, 0.013)	(0.010, 0.014)
Median	0.026	0.011	0.011	0.012
Min, Max	0.022, 0.030	0.008, 0.017	0.008, 0.015	0.008, 0.016

	Dose independent (N=18)
CL_{ss} (L/hr)	
Mean (SD)	0.043 (0.015)
95% CI	(0.036, 0.050)
Median	0.040
Min, Max	0.025, 0.077
V_{ss} (L)	
Mean (SD)	3.06 (0.598)
95% CI	(2.77, 3.36)
Median	3.06
Min, Max	2.06, 4.14
F	
Mean (SD)	0.44 (0.000)

$AUC_{(0-t)}$ = area under the plasma concentration time curve over a dosing interval; C_{av} = average C1-INH functional activity over a dosing interval; C_{max} = maximum drug concentration in plasma; CI = confidence interval, CL_{ss} = steady state clearance; F = bioavailability fraction; IR = incremental recovery; Min = minimum; Max = maximum; SD = standard deviation; $t_{1/2}$ = elimination half-life; V_{ss} = steady state volume of distribution.

Safety Results

Safety events were not related to either absolute CSL830 dose or dose per body weight. There was no evidence of a dose-response relationship between the administered dose of CSL830 and the intensity of treatment-emergent asdverse events (TEAEs).

During dosing Period 1, more TEAEs were reported in the CSL830 1500 IU and 3000 IU dosing regimens as opposed to dosing Period 2, where more TEAEs were reported in the CSL830 6000 IU dosing regimen. The most frequently reported TEAEs in either dosing regimen were in the System Organ Class (SOC) 'General disorders and administration site conditions' and were of mild or moderate intensity. Treatment-emergent AEs were assessed by the investigator as related to CSL830 in 41.7%, 8.3%, and 16.7% of subjects in the CSL830 1500 IU, 3000 IU, and 6000 IU dosing regimens, respectively.

No effect of CSL830 dose or dose per body weight was observed in the reported number of solicited local AEs. Most solicited local AEs were mild to moderate in intensity and most resolved within 3 days. More subjects reported moderate swelling at the injection site in the CSL830 6000 IU dosing regimen, which was not unexpected due to the administration of a higher volume of study drug; no other differences were observed across dosing regimens.

There were no deaths during the study. Serious AEs (SAEs) were reported in 1 subject in the Berinert treatment period and in 1 subject in the CSL830 6000 IU dosing. The 2 SAEs were not considered related to study treatment and subjects recovered on the same day. No other significant AEs were noted. No subject was withdrawn from the study because of a TEAE.

Table 2 Summary of treatment-emergent adverse events

	Dosing regimen				
	Berinert 20 U/kg (N = 18) n (%)	**CSL830 1500 IU (N = 12) n (%)**	**CSL830 3000 IU (N = 12) n (%)**	**CSL830 6000 IU (N = 12) n (%)**	**Overall (N = 18) n (%)**
TEAE[a]	4 (22.2)	10 (83.3)	8 (66.7)	9 (75.0)	17 (94.4)
TEAE within 24 hour of study drug[b]	1 (25.0)	8 (80.0)	6 (75.0)	6 (66.7)	14 (82.4)
Serious TEAEs[b]	1 (25.0)	0	0	1 (11.1)	2 (11.8)
Deaths[b]	0	0	0	0	0
TEAEs leading to DC[b]	0	0	0	0	0

[a] Percentages are calculated using the population N as the denominator.
[b] Percentages are calculated using the number of subjects with at least one TEAE as the denominator.
DC = discontinuation; n = number of subjets with at least 1 event; TEAE = treatment-emergent adverse event.

Table 3 Summary of treatment-emergent adverse events by intensity, causality, and hereditary angioedema events

	Dosing regimen				
	Berinert 20 U/kg (N = 18) n (%)	**CSL830 1500 IU (N = 12) n (%)**	**CSL830 3000 IU (N = 12) n (%)**	**CSL830 6000 IU (N = 12) n (%)**	**Overall (N = 18) n (%)**
TEAE intensity[a,b]					
Severe	0	3 (25.0)	1 (8.3)	1 (8.3)	5 (27.8)
Moderate	2 (11.1)	5 (41.7)	4 (33.3)	5 (41.7)	8 (44.4)
Mild	2 (11.1)	2 (16.7)	3 (25.0)	3 (25.0)	4 (22.2)
TEAE causality[a,b]					
Related	0	5 (41.7)	1 (8.3)	2 (16.7)	6 (33.3)
Not related	4 (22.2)	5 (41.7)	7 (58.3)	7 (58.3)	11 (61.1)
HAE events[a, c]					
Yes	1 (5.6)	2 (16.7)	2 (16.7)	1 (8.3)	5 (27.8)
Period 1	NA	1 (8.3)	0	0	NA
Period 2	NA	1 (8.3)	2 (16.7)	1 (8.3)	NA
No	17 (83.3)	10 (83.3)	10 (83.3)	11 (91.7)	13 (72.2)
Period 1	NA	5 (41.7)	6 (50.0)	6 (50.0)	NA
Period 2	NA	5 (41.7)	4 (33.3)	5 (41.7)	NA

[a] Percentages are calculated using the population N as the denominator.
[b] Worst intensity or causality most related to treatment recorded.
[c] Treatment-emergent HAE events are TEAEs with a preferred term recorded as 'Hereditary angioedema'.
HAE = hereditary angioedema; n = number of subjets with at least 1 event; NA = not applicable;
TEAE = treatment-emergent adverse event.

No safety issues were observed with laboratory parameters in the hematology, biochemistry, and

coagulation laboratory groups.

C1-INH antibodies were detected for 7/18 subjects during the study; however, the presence of C1-INH antibodies was not associated with inhibition of C1-INH activity. There was no apparent relationship between the dose of CSL830 administered and the presence of C1-INH antibodies.

No changes in serology results for human immunodeficiency virus (HIV), Hepatitis A virus (HAV), Hepatitis B surface (HBs) and Hepatitis B core (HBc), or Hepatitis C virus (HCV) from screening to exit were observed. Although a few positive results were detected at the exit visit and not baseline, based on all serology and polymerase chain reaction (PCR) results, there was no evidence of new viral infections.

No clinically significant abnormalities in vital signs and body temperature, and no differences related to dose were observed.

No risk for deep vein thrombosis was identified based on the clinical model scoring system, which resulted in risk assessment scores < 1 at all time points assessed.

Conclusions:

The SC administration of CSL830 increased plasma C1-INH functional activity to clinically relevant levels in a dose-dependent manner. The CSL830 6000 IU dosing regimen achieved trough activity levels that were within the normal range for C1-INH functional activity. Similar changes to C1-INH functional activity were observed for C1-INH antigen levels. For C4 antigen levels, all 3 CSL830 dosing regimens resulted in levels that were within the normal range.

The influence of body weight was investigated and the C1-INH functional activity, C1-INH antigen level, and C4 antigen level increased with the CSL830 dose per body weight.

Subcutaneous administration of CSL830 up to 6000 IU was tolerated with local site events. Adverse events were not related to either absolute dose or dose per body weight. There were no deaths, no withdrawals due to AEs, no thromboembolic event (TEEs), and no SAEs related to CSL830. Inhibitory auto-antibodies to C1-INH did not develop in any of the subjects in the study.

Subcutaneous administration of the 3 CSL830 dosing regimens was safe and well tolerated. Functional levels of C1-INH activity and levels of C1-INH antigen and C4 antigen were achieved with each dosing regimen.

Date of the report: 27 June 2013