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Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate

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Berinert; C1-esterase inhibitor; hereditary angioedema; long-term prophylaxis; subcutaneous treatment.

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Abstract

Background: Hereditary angioedema (HAE) due to C1 inhibitor deficiency manifests as recurrent swelling attacks that can be disabling and sometimes fatal. Long-term prophylaxis with twice-weekly intravenous injections of plasma-derived C1-inhibitor (pdC1-INH) has been established as an effective treatment. Subcutaneous (SC) administration of pdC1-INH has not been studied in patients with HAE.
Methods: This open-label, dose-ranging, crossover study (COMPACT Phase II) was conducted in 18 patients with type I or II HAE who received two of twice-weekly 1500, 3000, or 6000 IU SC doses of highly concentrated volume-reduced CSL830 for 4 weeks each. The mean trough plasma levels of C1-INH functional activity, C1-INH and C4 antigen levels during Week 4, and overall safety and tolerability were evaluated. The primary outcome was model-derived steady-state trough C1-INH functional activity.
Results: After SC CSL830 administration, a dose-dependent increase in trough functional C1-INH activity was observed. C1-INH and C4 levels both increased. The two highest dose groups (3000 and 6000 IU) achieved constant C1-INH activity levels above 40% values, a threshold that was assumed to provide clinical protection against angioedema attacks. Compared with intravenous injection, pdC1-INH SC injection with CSL830 showed a lower peak-to-trough ratio and more consistent exposures. All doses were well tolerated. Mild-to-moderate local site reactions were noted with pain and swelling being the most common adverse event.
Conclusions: Subcutaneous volume-reduced CSL830 was well tolerated and led to a dose-dependent increase in physiologically relevant functional C1-INH plasma levels. A clinical outcome study of SC CSL830 in patients with HAE warrants further investigation.

Abbreviations
AE, adverse event; $AUC_{(0-t)}$, area under the plasma concentration–time curve over a dosing interval; C1-INH, C1-inhibitor; C_{av}, average C1-INH functional activity over dosing interval; CI, confidence interval; CL, clearance; CL_{SS}, steady-state clearance; C_{max}, maximum drug concentration in plasma; CSL830, volume-reduced C1-INH concentrate; *F*, bioavailability; HAE, hereditary angioedema due to C1 inhibitor deficiency; IU, international unit; IV, intravenous; K_a, absorption rate constant; kDa, kiloDalton; pd, plasma-derived; PD, pharmacodynamic; PK, pharmacokinetic; pnf, pasteurized, nanofiltered; SC, subcutaneous; SD, standard deviation; $t_{1/2}$, half-life; TEAE, treatment-emergent adverse event; U, unit; *V*, volume of distribution; V_{SS}, steady-state volume of distribution; WT, body weight.

Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by C1 inhibitor deficiency and is associated with significant morbidity and mortality (1–4), which has been substantially reduced with the advent of effective on-demand therapies (5). However, patients continue to have impaired quality of life and in some cases require hospitalization for angioedema attacks. To minimize the number and severity of attacks, many patients choose to use prophylactic treatment.

Consensus guidelines conclude that long-term prophylaxis is appropriate for HAE patients with frequent attacks or who do not achieve sufficient benefit from on-demand treatment (4, 6–11). Before 2009, the most commonly utilized prophylactic drugs were anabolic androgens and to a lesser extent antifibrinolytics. Subsequently, long-term prophylaxis with C1 inhibitor concentrates (C1-INH) has become available and found to be safe and effective (12). The concept of routine prophylaxis with continuous intravenous C1-INH is based on correcting the deficiency of C1-INH activity, the fundamental abnormality in HAE. The efficacy of this approach was shown in two placebo-controlled studies; the efficacy of a vapor-heated C1-INH concentrate (25 U/kg body weight) was established for long-term prophylaxis in patients who did not respond adequately to androgens or antifibrinolytics (13), and the C1-INH concentrate (Cinryze, 1000 IU twice a week) demonstrated a reduction in the number of HAE attacks (12). However, none of the previous studies on C1-INH replacement therapy were specifically designed to achieve a constant level of biologically relevant activity C1-INH levels. Thus, most patients on intravenous C1-INH long-term prophylaxis continue to experience breakthrough attacks, likely related to the relatively short period of time that functional C1-INH plasma levels remain near the normal range (13).

Theoretically, maintaining plasma C1-INH functional levels above a certain threshold should prevent all attacks. However, this threshold value has not yet been defined. Hereditary angioedema is diagnosed based on functional C1-INH levels <50% of normal, but patients typically have C1-INH functional levels <40% of normal (14, 15). Enhanced activation of the complement system has been observed with C1-INH functional levels <38% of normal, suggesting a critical threshold of C1-INH function (16). Logistical and technical problems of repeated intravenous (IV) injections and the pharmacokinetic (PK) profile make it challenging to maintain the C1-INH level above a threshold value.

Subcutaneous (SC) administration of C1-INH offers several potential advantages including easier access for self-administration and more consistent PKs. The feasibility of SC administration of an IV C1-INH concentrate (1000 IU in 20 ml) was previously demonstrated in a pilot study in patients with HAE (17). Herein, the PK, pharmacodynamic (PD), and preliminary safety of an investigational, volume-reduced C1-INH concentrate (CSL830; CSL Behring, Marburg, Germany) developed for SC injection is reported.

Methods

Study medication

CSL830 is a volume-reduced formulation of the pasteurized, nanofiltered C1-INH concentrate (pnf C1-INH; Berinert®, Marburg, Germany). The manufacturing process of CSL830 is almost identical to that of pnf C1-INH, the major difference being the concentration after reconstitution. The final concentration of CSL830 is 500 IU/ml, whereas the final concentration of Berinert is 50 IU/ml.

Study design

This was a prospective, multicenter, open-label, crossover phase II study to characterize the PKs, PDs, and safety of CSL830 administered subcutaneously to 18 subjects with HAE (COMPACT phase II study). The study period spanned April 2012 to December 2012. Data were collected at three sites in Germany and five in the USA. For organizational details of the study setup, please refer to the Appendix S1.

Following a screening period of up to 30 days, subjects were sequentially allocated to one of six CSL830 treatment sequences by predetermined computer-generated assignment (Fig. 1A). A single dose of Berinert 20 U/kg was administered IV 2–7 days prior to the first CSL830 dosing period. Each subject received two of three possible CSL830 doses (1500, 3000, or 6000 IU administered as a short SC injection twice-weekly) for two 4-week treatment periods with a washout period of up to 4 weeks between periods. Administration of rescue medication (IV C1-INH) was permitted for breakthrough attacks.

The study protocol and all amendments were approved by the independent ethics committees of the participating sites. The study was carried out in accordance with the principles of the current International Conference on Harmonization Good Clinical Practice.

Study population

Male or female subjects aged ≥18 with HAE with type I or type II HAE, based on clinical history and confirmed by central laboratory testing at screening (C1-INH functional activity <50% or a C1-INH antigen level below the laboratory reference range), were eligible for the study. Subjects were required to have a body weight ≥50 and ≤110 kg at screening and have experienced ≤5 HAE attacks within the 3 months prior to the screening visit, of which ≤1 occurred within 30 days prior to the screening visit. The relatively low attack rate for the inclusion criteria was chosen to minimize the need for rescue therapy with C1-INH concentrate which would interfere with the PK measurements.

Key exclusion criteria included current C1-INH prophylactic therapy, androgen therapy within 30 days of screening, and any HAE-specific treatment within 7 days of screening (for full inclusion and exclusion criteria, see Appendix S1).

Endpoints

The primary endpoint was the mean trough C1-INH functional activity at the fourth week, based on modeling and simulation. Model-derived rather than observed trough levels were chosen to account for the confounding nature of possible rescue IV C1-INH use during the study.

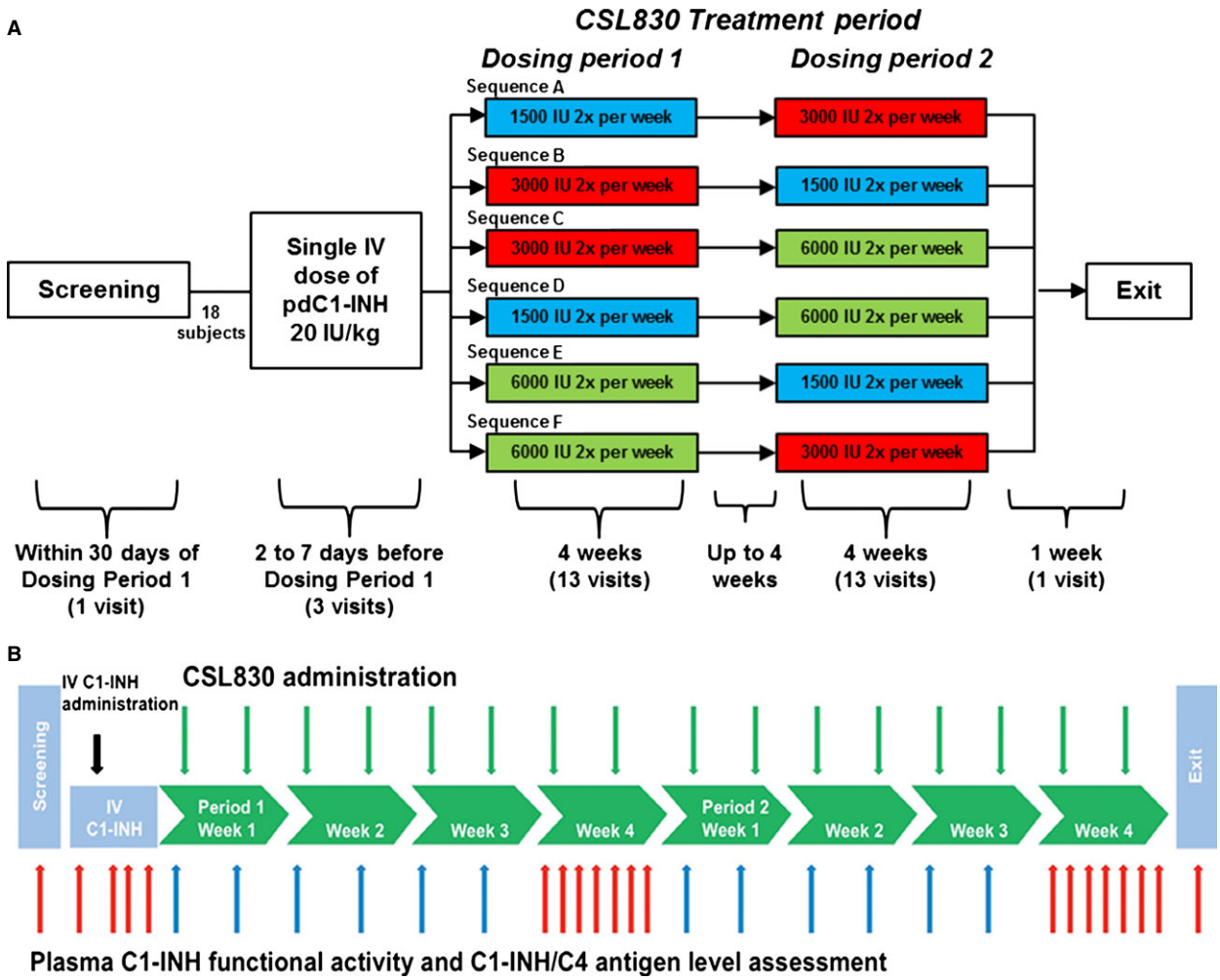

Figure 1 Study schema. (A) Dosing scheme and sample collection during the study, (B) ⬇ = single dose of IV C1-INH; ⬇ = single dose of subcutaneous (SC) CSL830; ⬆ = assessment of C1-INH functional activity and plasma C1-INH and C4 antigen concentrations; ⬆ = additional assessments of plasma C1-INH functional activity.

The secondary endpoints were the mean and mean change from baseline in trough C1-INH functional activity, C1-INH antigen level, and C4 antigen levels at the fourth week of each dosing regimen, based on observed data.

The dosing scheme and sample collection is illustrated in Fig. 1B. The initial single IV dose of C1-INH was administered to aid the PK model in accounting for any administration of IV C1-INH rescue doses and to enable a within-study estimate of bioavailability of SC CSL830. C1-INH functional activity, C1-INH plasma concentrations, and C4 antigen levels were assessed at several time points throughout each dosing period. Plasma C1-INH functional activity was additionally assessed immediately before CSL830 administration.

PK and PD measurements

Plasma C1-INH functional activity was assessed by a validated chromogenic assay (Berichrom C1-Inhibitor, Siemens; reference range: 70–130% of norm). Plasma C1-INH antigen (C1 reagent N-Antisera; Siemens Healthcare Diagnostics (Eschbom, Germany); reference range: 0.18–0.32 mg/l) and C4 antigen levels were assessed by nephelometry (C4 reagent, Beckman Coulter (Krefeld, Germany); reference range: 0.1–0.4 g/l). All measurements were performed at a central laboratory using a validated assay (CSL Behring GmbH).

C4 antigen levels were defined as a PD parameter as C4 activity occurs downstream from C1-INH; C1-INH replacement would therefore affect C4 levels. Levels of C4 antigen have been shown to rise slowly over time following IV pdC1-INH administration.

PK and PD analysis

The complete analysis set (18 patients who received ≥1 dose of CSL830 and provided ≥1 C1-INH functional measurement) was used for the primary endpoint analysis and to determine modeling-derived C1-INH functional activity.

Twelve subjects per dosing regimen were sufficient to provide an estimate of C1-INH activity, based on PK modeling of previous study results. The data for each treatment were summarized using descriptive statistics and a mixed model.

Subcutaneous and IV C1-INH functional activity data were collectively subjected to a population-based approach using nonlinear mixed-effects modeling (NONMEM version 7.2). Exploratory PK characteristics of CSL830 were assessed by estimating typical and individual values for parameters such as clearance (CL) and volume of distribution (V) along with associated interindividual variability. The influence of subject baseline characteristics was also investigated. Pharmacokinetic parameters such as CL, V, bioavailability (F), absorption rate constant (K_a), half-life ($t_{1/2}$), and incremental recovery were estimated with the final population PK model.

Pharmacokinetic simulations were conducted to examine whether steady-state trough levels of C1-INH functional activity were dependent on body weight. The body weight effect was evaluated by examining the distributions of model-predicted steady-state trough serum C1-INH functional activity at doses of 40 and 60 IU/kg and fixed doses of 3000 and 4500 IU, for baseline body weight ranges of <60, 60–100, and >100 kg. For the as-observed endpoint analysis, the fourth-week trough levels and increase in trough levels from baseline were summarized for C1-INH functional activity, C1-INH antigen levels, and C4 antigen levels for each CSL830 dosing regimen using descriptive statistics.

Safety assessment

Safety and tolerability were evaluated by continuous observation of adverse events (AEs) and by safety assessments that were conducted at specified times throughout the study. These assessments included infusion site tolerability, laboratory parameters, vital signs, body weight, physical examination, and concomitant medication usage. Local side-effects (pain, swelling, bruising, and itching at the injection site) were assessed by the investigator and intensity graded from mild (grade 1: present, but no interference with activity) to severe (grade 3: prevents daily activity and/or requires use of pain relievers). A risk assessment for deep vein thrombosis was also implemented based on earlier case reports on side-effects of thromboembolism in patients with HAE using C1-INH concentrate (18, 19).

Results

Study subjects

A total of 22 subjects from eight study sites signed the informed consent. Of these, 18 patients were assigned to treatment by a computer-generated list and received study drug. Four subjects signed the consent form but were not randomized, two because they did not meet the inclusion/exclusion criteria and two because the study had already reached the target of 18 subjects by the time they were found to be eligible. The demographics of the subjects are summarized in Table 1.

PK results after SC CSL830

The mean as-observed steady-state trough C1-INH functional activity at the fourth week increased with CSL830 dose (Fig. 2); increase from baseline was 16.4%, 33.2%, and 63.3% for the 1500, 3000, and 6000 IU doses, respectively. C1-INH antigen levels also increased with CSL830 dose; increase from baseline in C1-INH antigen at the fourth week was 0.02, 0.05, and 0.14 mg/ml for the three dosing regimens, respectively.

Population PK model

C1-INH functional activity was described by a linear one-compartmental PK model with first-order absorption. The relationships between model parameters and the following baseline covariates were examined: age, gender, body weight, body mass index, ideal body weight, lean body mass, creatinine CL, and C1-INH functional activity. The only statistically significant covariate effect on a model parameter identified was the effect of body weight on CL and V, which was described by the following relationships:

$$\mathrm{CL}_i = 0.398 \cdot \left(\frac{\mathrm{WT}_i(\mathrm{kg})}{78.9(\mathrm{kg})}\right)^{0.879} \cdot \exp^{\eta_{\mathrm{CL}}},$$

$$V_i = 30.8 \cdot \left(\frac{\mathrm{WT}_i(\mathrm{kg})}{78.9(\mathrm{kg})}\right)^{0.669} \cdot \exp^{\eta_V},$$

where CL_i is the individual value of clearance; V_i, the individual volume of distribution; and WT_i, the body weight of subject i.

Goodness-of-fit plots of the model (Fig. 3) reveal that the model prediction was consistent with the observed data, as the points are uniformly distributed around the line of identity. Therefore, no systematic bias was evident.

Model-derived C1-INH trough levels and PK parameters

The primary endpoint was the mean trough C1-INH functional level at the fourth week, based on modeling and simulation (Fig. 2). A dose-dependent increase in mean C1-INH functional activity was observed, increasing from 14.6% at baseline to 31.7%, 44.3%, and 80.5% for the 1500, 3000, and 6000 IU doses, respectively. The modeled steady-state trough C1-INH functional activity at the fourth week was similar to the as-observed C1-INH functional activity.

The model was also used to derive other exploratory PK parameters such as area under the activity–time curve from zero to end of dosing interval at steady state ($\mathrm{AUC}_{(0-t)}$), maximum plasma C1-INH functional activity levels ($C_{\max}$), average plasma activity at steady state (C_{avg}), incremental recovery, and elimination half-life. Table 2 summarizes the modeled PK parameters for functional C1-INH activity following IV and SC C1-INH administration. The bioavailability of SC CSL830 was 44%, with similar elimination half-life compared with IV C1-INH. As the CSL830 doses used were not weight based, body weight, body mass index, and ideal

Table 1 Demographic and baseline characteristics (complete analysis set)

Demographic characteristics	Dosing regimen			
	Berinert (N = 18)	CSL830 1500 IU (N = 12)	CSL830 3000 IU (N = 12)	CSL830 6000 IU (N = 12)
Age, years				
Mean (SD)	36.4 (13.07)	33.6 (11.83)	37.8 (14.69)	37.8 (12.65)
Median (min, max)	33.9 (19, 69)	30.3 (19, 53)	36.9 (19, 69)	35.2 (24, 69)
Sex, male : female, *n* (%)	7 : 11 (38.9 : 61.1)	4 : 8 (33.3 : 67.7)	5 : 7 (41.7 : 58.3)	5 : 7 (41.7 : 58.3)
Weight, kg				
Mean (SD)	80.0 (20.2)	79.9 (23.4)	78.5 (17.0)	81.6 (20.6)
Median (min, max)	78.9 (51.0, 110.0)	71.2 (51.0, 110.0)	78.9 (57.6, 106.5)	83.3 (51.0, 110.0)
Body mass index, kg/m^2				
Mean (SD)	27.3 (6.57)	27.5 (7.22)	26.8 (5.14)	27.6 (7.37)
Median (min, max)	25.4 (18.1, 40.9)	25.4 (18.1, 40.9)	25.4 (19.1, 34.5)	27.5 (18.1, 40.9)
HAE type, *n* (%)				
Type I	16 (88.9)	12 (100)	10 (83.3)	10 (83.3)
Type II	2 (11.1)	0 (0)	2 (16.7)	2 (16.7)
Number of HAE attacks in the preceding 3 months, *n*				
Mean (SD)	2.5 (1.42)	2.3 (1.50)	2.4 (1.51)	2.8 (1.29)
Median (min, max)	2.0 (0, 5)	2.0 (0, 5)	2.0 (0, 5)	2.0 (1, 5)
Baseline as-observed C1-INH functional activity, %				
Mean (SD)	14.6 (8.02)	15.4 (8.02)	11.3 (7.10)	17.1 (8.05)
Median (min, max)	15.2 (1.3, 26.7)	15.2 (4.3, 26.7)	9.9 (1.3, 22.7)	19.3 (1.3, 26.7)
Baseline as-observed C1 antigen level (mg/ml)*				
n	13	8	9	9
Mean (SD)	0.10 (0.126)	0.05 (0.009)	0.12 (0.149)	0.12 (0.147)
Median (min, max)	0.050 (0.02, 0.44)	0.047 (0.03, 0.05)	0.050 (0.02, 0.44)	0.053 (0.02, 0.44)
Baseline as-observed C4 antigen level (mg/dl)*				
n	17	12	11	11
Mean (SD)	8.6 (9.51)	6.8 (3.10)	9.2 (11.7)	9.9 (11.7)
Median (min, max)	7.0 (2.2, 43.8)	6.9 (2.2, 10.8)	7.0 (2.2, 43.8)	7.0 (2.4, 43.8)

HAE, hereditary angioedema.

*In some patients, the values for baseline as-observed C1 and C4 antigen were below the limits of detection of 0.022 mg/ml and 1.67 mg/dl, respectively. Complete analysis set: 18 patients who received ≥1 dose of CSL830 and provided ≥1 C1-INH functional measurement.

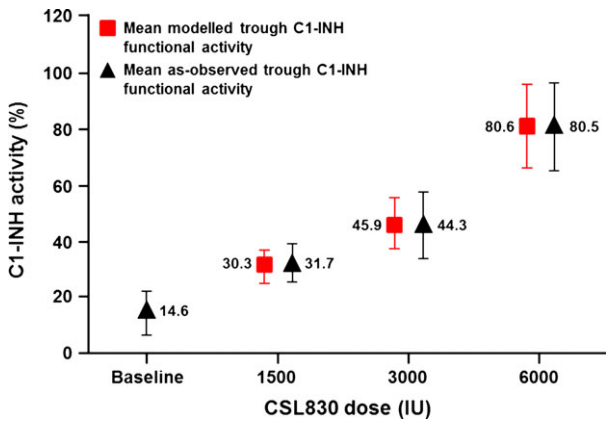

Figure 2 Pharmacokinetic (PK) results. Modeled steady-state trough C1-INH functional activity (primary endpoint; red rectangles) and as-observed C1-INH functional activity (black triangles). Data points show the mean and 95% CI.

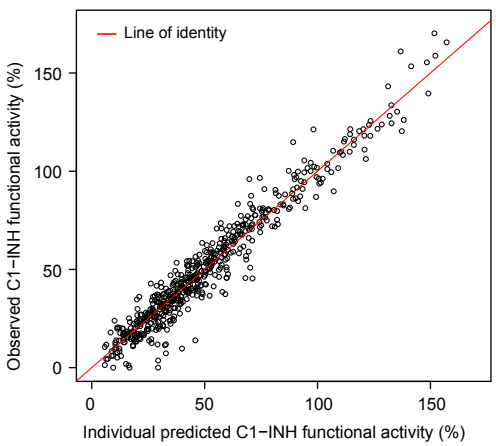

Figure 3 Final population pharmacokinetic (PK) model of as-observed C1-INH functional activity *vs* individual predictions of C1-INH functional activity. The line of identity (solid red) is included as a reference.

Table 2 Modeled pharmacokinetic parameters for C1-INH activity

	Berinert 20 IU/kg (N = 18)	CSL830 1500 IU (N = 12)	CSL830 3000 IU (N = 12)	CSL830 6000 IU (N = 12)
C_{max}, U/ml	0.67 (0.562)	0.38 (0.109)	0.59 (0.154)	1.09 (0.307)
$AUC_{(0-t)}$, U h/ml	38.9 (8.93)	30.5 (11.31)	45.3 (11.98)	79.6 (25.36)
C_{av}, U/ml	–	0.36 (0.135)	0.54 (0.142)	0.95 (0.303)
Incremental recovery ([U/ml]/[U/kg])	0.026 (0.0023)	0.011 (0.0024)	0.011 (0.0024)	0.012 (0.0027)
$t_{1/2}$ (h)	52.8 (13.70)	50.6 (12.35)	51.5 (13.52)	56.2 (15.02)
				Dose independent (n = 18)
CL_{SS}, l/h				0.043 (0.015)
V_{SS}, l				3.06 (0.598)
Bioavailability				0.44

$AUC_{(0-t)}$, area under the plasma concentration–time curve over a dosing interval; C_{av}, average C1-INH functional activity over a dosing interval; $t_{1/2}$, elimination half-life; C_{max}, maximum drug concentration in plasma; CL_{SS}, steady-state clearance; V_{SS}, steady-state volume of distribution.
Data are mean (SD).

body weight were assessed to determine their influence on median functional C1-INH levels. Not unexpectedly, we found a small negative relationship between body weight and steady-state trough levels for each dose regimen. Patients with a low body weight administered a fixed dose are predicted to achieve a relatively high functional C1-INH level compared with patients with a higher body weight. Therefore, a body weight-adjusted dosing is predicted to achieve the same level of activity across the range of body weights (see Fig. S1).

Pharmacodynamics

C4 antigen levels were also measured during the fourth week of each dose regimen. C4 antigen levels increased in a dose-dependent manner and normalized with all doses of CSL830. C4 levels of 11.1, 14.1, and 18.4 mg/dl for the 1500, 3000, and 6000 IU doses of CSL830, respectively, were observed. C4 antigen levels increased from baseline at the fourth week by 4.3, 5.6, and 9.1 mg/dl (normal level is 14 mg/dl) for the 1500, 3000, and 6000 IU doses, respectively.

When the fixed dose of CSL830 was calculated as a dose per body weight, the mean C4 antigen level increased with the dose per body weight; the mean as-observed C4 antigen level at the fourth week was 11.3, 11.7, 18.0, and 18.2 mg/ml in the ≤20, >20 to ≤45, >45 to ≤90, and >90 IU/kg categories, respectively.

Modeled twice-per-week CSL830 *vs* IV pdC1-INH over 4 weeks

The effect of dosing SC CSL830 *vs* IV 1000 IU pdC1-INH concentrate on C1-INH functional activity was examined in a *post hoc* analysis by simulating three different SC regimens of 1500, 3000, and 6000 IU twice-weekly for 4 weeks (Fig. 4). The simulated C1-INH functional activity time profiles showed a lower peak-to-trough ratio and more consistent exposures after SC administration compared with the current standard prophylactic treatment regimen of a twice-weekly injection of 1000 IU pdC1-INH concentrate.

Safety

There were no CSL830-related serious AEs or deaths, or withdrawals due to AEs throughout the study. No thromboembolic events were observed. Two serious AEs unrelated to CSL830 were reported, an episode of transient syncope 2 days after IV pdC1-INH administration in a 23-year-old woman and hypovolemic shock in a 27-year-old woman on the first dosing day of CSL830 during an abdominal attack that started before study drug administration. Laboratory surveillance did not reveal any safety signals, and there was no evidence of inhibitory auto-antibody development.

Adverse events are summarized in Table 3. The most common treatment-emergent adverse events were local site reactions reported as pain, swelling, bruising, and itching at the injection sites.

Most local site reactions were mild-to-moderate in intensity and resolved within 3 days. Moderate swellings at the injection site was reported in more subjects in the 6000 IU dose group (5/12 subjects) compared with the two other lower dose groups (2/12 in the 1500 IU and 1/12 in the 3000 IU dose group), which were likely related to the volume of injection. There was no apparent dose relationship for other local site reactions.

Hereditary angioedema-related symptoms occurring during the study were reported as AEs. Overall, 29 HAE-related AEs were reported in seven patients during the course of the study. Of those 29 HAE events occurring after study enrollment, 11 were reported during the 4-week dosing intervals with SC CSL830 and 18 HAE events were reported during times in the study with no exposure to the investigational drug. In the 1500 IU dose group, two of 12 patients had two and five HAE attacks, respectively. In the 3000 IU dose group, two patients had one and three attacks, respectively. No patient in the 6000 IU dose group experienced any HAE symptoms during the 4-week SC dosing period.

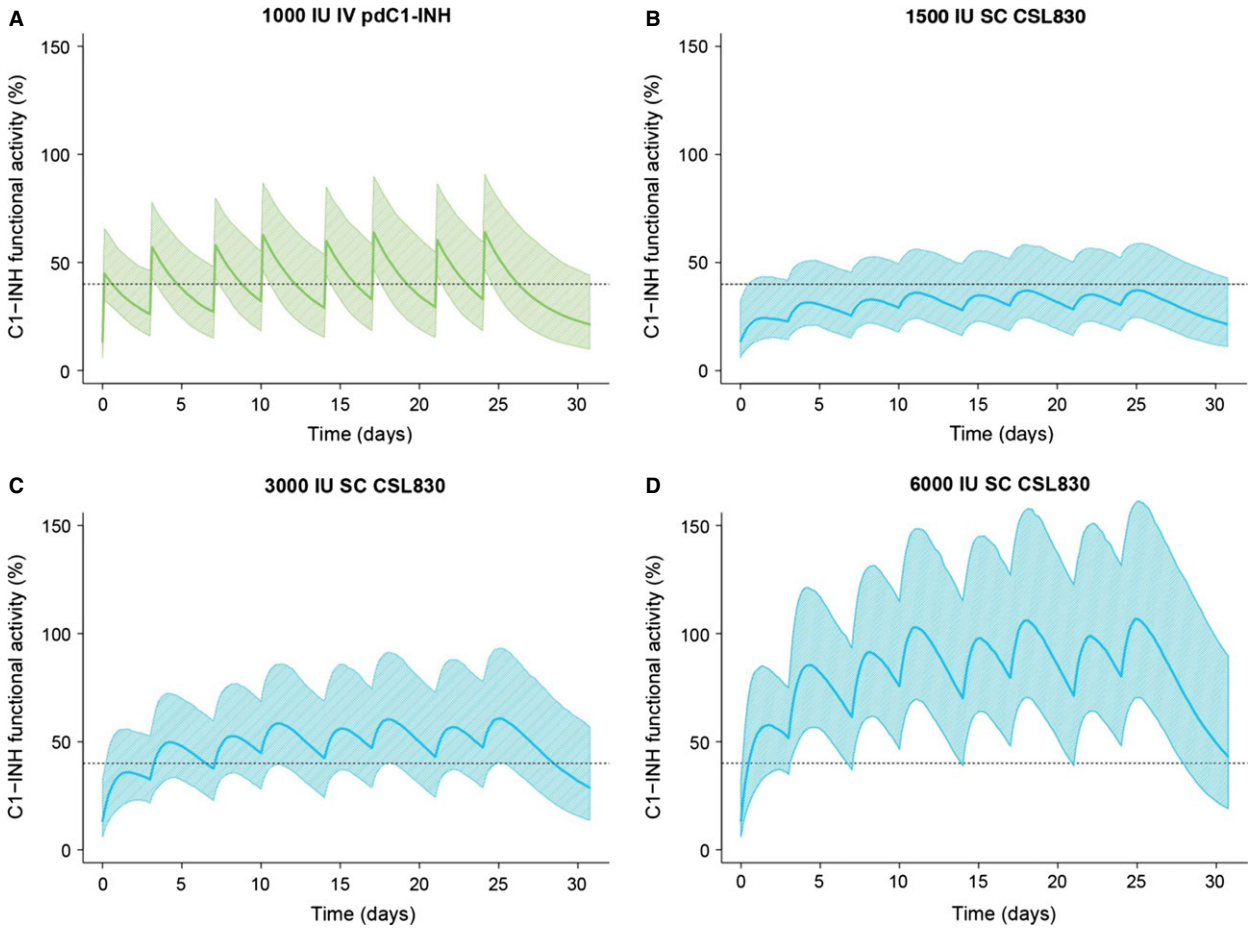

Figure 4 Modeled biweekly C1-INH functional activity after IV administration of (A) a therapeutic dose of 1000 IU pdC1-INH concentrate, or subcutaneous (SC) administration of (B) 1500 IU, (C) 3000 IU, or (D) 6000 IU of CSL830. Median functional activity (solid lines), 5th and 95th percentiles (shaded areas) and 40% C1-INH functional activity (dashed black line) are shown.

Table 3 Treatment-emergent adverse events (TEAEs) by dose group

	Dosing regimen			
	All treated subjects (N = 18)	CSL830 1500 IU (N = 12)	CSL830 3000 IU (N = 12)	CSL830 6000 IU (N = 12)
Subjects who reported any CSL830 TEAE, *n* (%)	17 (94.4)	10 (83.3)	8 (66.7)	9 (75.0)
Maximum reported event intensity of severe, *n* (%)	5 (27.8)	3 (25.0)	1 (8.3)	1 (8.3)
Maximum reported event intensity of moderate, *n* (%)	8 (44.4)	5 (41.7)	4 (33.3)	5 (41.7)
Assessed by investigator as related to CSL830, *n* (%)	6 (33.3)	5 (41.7)	1 (8.3)	2 (16.7)
Subjects with solicited local site reactions, *n* (%)	17 (94.4)	11 (91.7)	8 (66.7)	11 (91.7)
Pain	14 (82.4)	9 (72.7)	8 (100.0)	7 (63.6)
Swelling	14 (82.4)	8 (72.7)	7 (87.5)	9 (81.8)
Bruising	7 (41.2)	5 (45.5)	1 (12.5)	4 (36.4)
Itching	2 (11.8)	2 (18.2)	0 (0.0)	0 (0.0)

Discussion

Long-term prophylaxis of HAE aims to prevent or minimize the number and severity of angioedema attacks; however, the medications currently available for long-term prophylaxis are in many cases suboptimal. Oral antifibrinolytics requiring multiple daily doses are relatively ineffective and frequently associated with significant side-effects (20, 21). Anabolic androgens are convenient to take and often effective at doses <200 mg/day but can be associated with significant risk of

serious side-effects (22–25). Currently available formulations of pdC1-INH require IV access, imposing a burden on the patient or healthcare provider. Maintenance of IV access has required many patients to have ports implanted, which are associated with increased risks of infection and thrombosis (18, 19). Plasma levels of functional C1-INH fall rapidly following IV administration of therapeutic dosages of C1-INH concentrates, reaching near basal levels within 3 days (13). The failure to achieve therapeutic steady-state functional C1-INH levels during pdC1-INH prophylaxis may explain the occurrence of breakthrough attacks for many patients. Replacement of pdC1-INH subcutaneously may potentially address the above limitations.

Based on earlier observations, it was suggested (16) that C1-INH antigen levels above 0.075 g/l, approximately 40% of the plasma level in a healthy person, would have a clinically meaningful effect in preventing HAE attacks. The C1-INH concentrations below 0.075 g/l found in blood samples analyzed after an attack and the increase in frequency of attacks when C1-INH levels were below 0.035 g/l (18% of normal) support this suggestion.

Our study demonstrates that SC CSL830 administered twice-weekly for 4 weeks leads to a dose-dependent increase in functional C1-INH activity and C4 levels, with the 3000 and 6000 IU doses achieving constant C1-INH activity levels above 40%. C1-INH functional levels approached the range of normal C1-INH values of healthy subjects with the 6000 IU dose.

Compared with a standard IV prophylactic dose regimen of 1000 IU twice-weekly, our PK model predicted C1-INH functional activity time profiles with a considerably lower peak-to-trough ratio and more consistent exposures after SC administration. The lower peak-to-trough fluctuations are the expected consequence of SC dosing.

The size of a protein transported within the body, whether via the capillaries or lymphatics, affects its bioavailability. The 105 kDa C1-INH protein is taken up by the lymphatics (26, 27). The 44% bioavailability of SC CSL830 was similar to that observed in a pilot study using the IV pdC1-INH concentrate, Berinert (17). Reasons for the relatively low bioavailability could be attributed, in part, to degradation or consumption at the injection site or during lymphatic transport. It is known that C1-INH can be metabolized quickly in patients with C1-INH deficiency, as evidenced by reduced serum concentrations of 5–31% in patients with type I HAE; this is in contrast to most other inherited plasma protein deficiencies in which heterozygous carries have 50% of normal protein levels (27, 28). In addition, the half-life of exogenous C1-INH has been shown to be influenced by the severity of HAE as well as by whether the assessment was made in patients during an attack or not (17).

Overall, CSL830 was well tolerated, with no serious drug-related AEs. The most common AEs were mild-to-moderate local site reactions. Although this study was not designed to test efficacy, a trend of fewer HAE attacks occurring with the 3000 and 6000 IU doses was observed compared with the 1500 IU dose and the treatment-free period. A placebo-controlled study would be required to ascertain whether this effect was significant; however, the possibility that an efficacy signal in this preliminary study was observed is encouraging.

In conclusion, C1-INH replacement through repeated SC dosing of a volume-reduced C1-INH concentrate (CSL830) led to a predictable dose-dependent increase in functional C1-INH levels in patients with mild-to-moderate HAE. Furthermore, consistent and sustained steady-state C1-INH levels reached values that are predicted to be efficacious in preventing angioedema attacks. Subcutaneous CSL830 also appears to be safe and well tolerated. These results support the pursuit of studies to address the safety and efficacy of SC C1-INH for long-term prophylaxis in HAE patients with severe disease.

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Conflicts of interest

BZ: Research funding: Shire; Consultant: CSL Behring, Dyax, Isis, BioCryst; Speaker: Dyax, RMEI. MC: Consultant for CSL Behring, Viropharma, Dyax, SOBI, Pharming, BioCryst, Sigma Tau; Research/educational grant from Shire, CSL Behring. HL: Educational grants, Speaker, donations to her departmental fund, clinical trial investigator: Biocryst, CSL Behring, SOBI Biovitrum, Shire, Dyax, ViroPharma. JAB: Principal Investigator, Consultant, Speaker: Viropharma, CSL Behring, Dyax, and Shire; Editorial Board: Journal of Angioedema; Medical Advisory Board: HAEA organization. HH Li: Research grant support, Speaker, Consultant: CSL Behring, Dyax, GLG Pharma, Shire, Pharming NV, ViroPharma; member of the HAEA medical advisory board. MM: Consultant: Shire, Viropharma, CSL Behring, and Sobi. IMS: Research funding, Consultant, Speaker: CSL Behring, Shire, and ViroPharma. SMMR: Clinical trial investigator, Consultant: Shire, CSL Behring, Viropharma. PS: Clinical trial investigator: Shire, CSL Behring; Consultant: CSL Behring. HF, RP, JS and JE are employees of CSL Behring, the sponsor of this study. TC: Consultant: CSL Behring, Dyax, Viropharma, Shire, Biocryst; Research funding: Viropharma, CSL Behring, Shire, Dyax, Pharming, Speaker: CSL Behring, Dyax, Shire.

Author contribution

B. Zuraw, M. Cicardi, H. Longhurst, T. Craig, I. Martinez-Saguer, H. Feuersenger, and J. Edelmann were involved in the development of the study protocol and contributed to the interpretation of the data. B. Zuraw wrote the first manuscript draft and further versions. R. Parasrampuria and J. Sidhu conducted the PK analysis and described the PK findings. J. Bernstein, H.Li, M. Magerl, S. Maseehur Rehman and P. Staubach contributed to the data presentation, provided comments and reviewed the manuscript versions. All authors contributed to the review of the manuscript and provided final approval of the manuscript before submission.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Relationship between body weight and C1-INH functional activity after fixed-dosing or body-weight adjusted dosing of CSL830. Median (solid lines) and 95% CI (shaded areas) of the prediction.

Appendix S1. COMPACT STUDY GROUP (Clinical Studies for Optimal Management of Preventing Angioedema with low-volume subcutaneous C1-Inhbitor Replacement Therapy).

Table S1. Local site reactions are injection site events which were specifically sought for and recorded in our trial (so called 'solicited local adverse events').

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