CLINICAL PHARMACOLOGY BLA REVIEW

Division of Clinical Evaluation and Pharmacology/Toxicology Branch
Office of Tissues & Advance Therapies (OTAT)

STN 125606
Sponsor: CSL Behring
Product: C1 ESTERASE INHIBITOR SUBCUTANEOUS (HUMAN) (HAEGARDA)
Indication: For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients
Submission Date: June 30, 2016
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RPM: Cagungun Nannette
Through: Lei Xu, M. D.

TABLE OF CONTENTS

INTRODUCTION

C1-esterase inhibitor (C1-INH) (HAEGARDA) is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into (b) (4) . The heavy glycosylated molecule has an apparent molecular weight of (b) (4), of which the carbohydrate chains comprise (b) (4)

HAEGARDA is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1-INH to be reconstituted for subcutaneous administration. HAEGARDA is prepared from

large pools of human plasma from US donors. The potency of C1-INH is expressed in International Units (IU), which is related to the current WHO Standard for C1-INH products.

Each vial of reconstituted HAEGARDA contains 500 IU/mL of C1-INH, 65 mg total protein, 10 mg glycine, 8.5 mg sodium chloride and 2.5 mg sodium citrate. All plasma used in the manufacturing of C1-INH is obtained from US donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV.

The manufacturing process for HAEGARDA includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity consists of three steps:

- Pasteurization in aqueous solution at 60°C for 10 hours
- Hydrophobic interaction chromatography
- Virus filtration (also called nano-filtration) by two filters, 20 nm and 15 nm, in series.

This report is clinical pharmacology review of the BLA submission.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.1 Mechanism of Action

C1-INH is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha$_1$-protease inhibitor, alpha$_2$-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1-INH has an important inhibiting potential on several of the major cascade systems of the human body including the complement, fibrinolytic and coagulation systems. Regulation of these systems is performed through the formation of complexes between the protease and the inhibitor, resulting in inactivation of both and consumption of the C1-INH.

C1-INH, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1-INH is the only known inhibitor for the C1r and C1s subcomponents of complement component 1 (C1), coagulation factor XIIa, and plasma kallikrein. Additionally, C1-INH is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have absence or low levels of endogenous or functional C1-INH. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1-INH through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin. Administration of HAEGARDA replaces the missing or malfunctioning C1-INH protein in patients with HAE.

12.2 Pharmacodynamics

In untreated patients, insufficient levels of functional C1-INH lead to increased activation of C1, which results in decreased levels of complement component 4 (C4). The administration of HAEGARDA increases plasma levels of C1-INH in a dose-dependent manner and subsequently increases plasma concentrations of C4. The C4 plasma concentrations after S.C. administration of 60 IU/kg HAEGARDA were in the normal range (16 to 38 mg/dL).

1.1 12.3 Pharmacokinetics

The pharmacokinetic (PK) ~~characteristics~~ of C1-INH were ~~primarily~~ described using population PK ~~methods~~ on pooled data from 3 clinical trials in healthy subjects and HAE subjects.

The PK parameters of C1-INH following twice weekly subcutaneous dosing Please provide the dose given to the patients are shown in Table X.

~~Following twice weekly S.C. dosing, C1-INH is slowly absorbed, with a median (95% CI) time to peak concentration (t_{max}) of approximately 59 hours (23, 134 hours). Based on a median (95% CI) apparent plasma half-life of 69 hours (24, 250 hours), steady state for C1-INH is expected within 3 weeks of dosing. A mean (95% CI) steady-state trough functional C1-INH of 48% (25.1-102%) is expected after twice weekly S.C. administration of 60 IU/kg HAEGARDA. The mean (95% CI) relative bioavailability (F) of C1-INH after S.C. administration was approximately 43% (35.2, 50.2%).~~

~~The population mean (95% CI) clearance and apparent volume of distribution of C1-INH were estimated to be approximately 83 mL/hr (72.7, 94.2 mL/hr) and 4.33 L (3.51, 5.15 L). C1-INH clearance was found to be positively correlated with total body weight.~~

The steady state PK of S.C. of C1-INH was found to be independent of dose between 20-80 IU/kg in HAE subjects. Please provide PK parameters (Tmax, Cmax, CL, volume of distribution, and half-life) in a Tabulated form. The units of clearance should be in mL/hr per kg and volume of distribution in L/kg.

Studies have not been conducted to evaluate the PK of C1-INH in specific patient populations stratified by gender, race, age, or the presence of renal or hepatic impairment. ~~The population analysis, evaluating age (12 to 72 years), was found not to influence the PK of C1-INH.~~ The PK of C1-INH was not influenced at the age range of 12-72 years.

RECOMMENDATION

The pharmacokinetic study design and results are acceptable. The Sponsor should modify the clinical pharmacology labeling as suggested by the FDA.

Study #1

Study Title: A randomized, double-blind, single-center, cross-over study to evaluate the safety, bioavailability and pharmacokinetics of two formulations of C1-esterase inhibitor administered intravenously (CSL 830-1001).

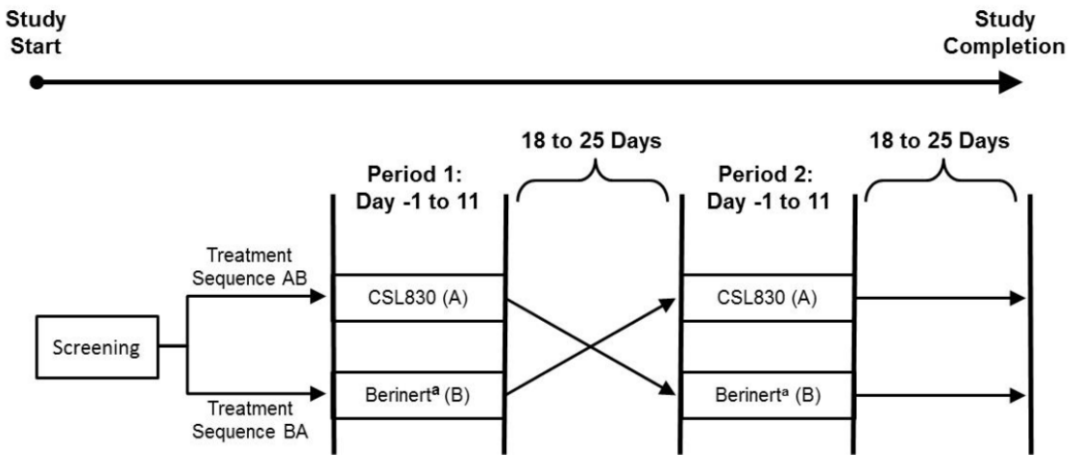
The primary objective of this study was to assess the safety of intravenous (IV) CSL830. The secondary objective of the study was to determine the bioavailability of IV CSL830 compared to IV Berinert (currently marketed product).

This was a phase 1, randomized, double-blind, single-center, cross-over study to evaluate the safety, relative bioavailability, and PK of two C1-esterase inhibitors (C1-INH) administered intravenously. A total of 16 healthy eligible male and female subjects were enrolled in the clinical study and then randomized to receive the following two formulations:

- CSL830: 1500 IU plasma-derived C1-INH reconstituted in 3 mL water for injection (test).
- Berinert (CE1145): 1500 IU plasma-derived C1-INH reconstituted in 30 mL water for injection (reference).

A wash out period of 18 to 25 days separated study period 1 and study period 2. Figure 1 highlights the overall study design.

Figure 1: Study design



[a]Berinert is the currently marketed presentation of CI-INH concentrate, CE1145
AB = CSL830 - Berinert; BA = Berinert - CSL830

There were 15 healthy subjects (male = 11; female =4) in the PK study (18 to 45 years of age). One subject was excluded because of a major protocol deviation (subject was erroneously

randomized and because she met the exclusion criteria). The body weight of the subjects ranged from 54 to 103 kg.

Blood samples for PK study were taken at time 0, 5, 10, 15, 30, and 60 minutes, 2, 4, 8, 12, and 24 hours, days 3, 5, 7, 9, and 11. All PK assessments were based on plasma concentrations of C1-INH antigen and CI-INH functional activity. Non-compartmental PK analysis was used to estimate the PK parameters with and without baseline correction. Baseline correction of C1-INH antigen concentration and C1-INH functional activity was done by subtracting the subject's baseline value from the value obtained at each time point after dosing. Mean baseline uncorrected and corrected C1-INH functional activity concentrations as a function of time are shown in Figures 2 and 3.

Figure 2: Mean baseline uncorrected C1-INH functional activity as a function of time

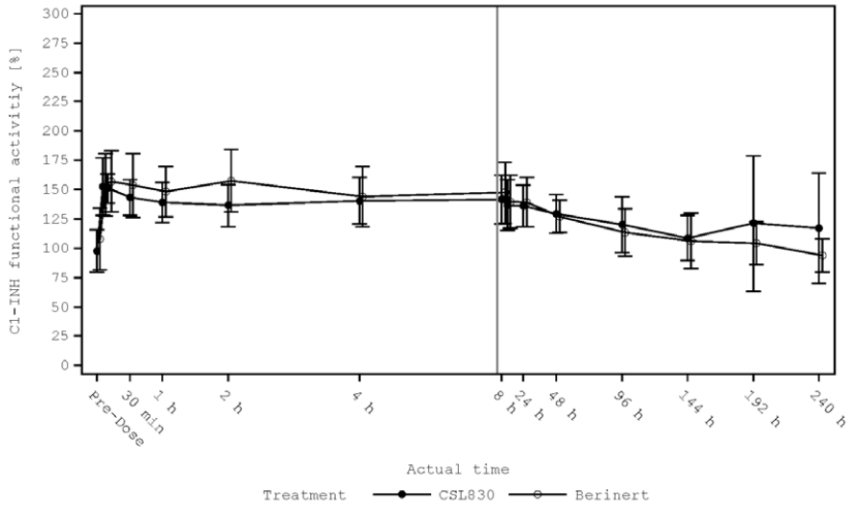
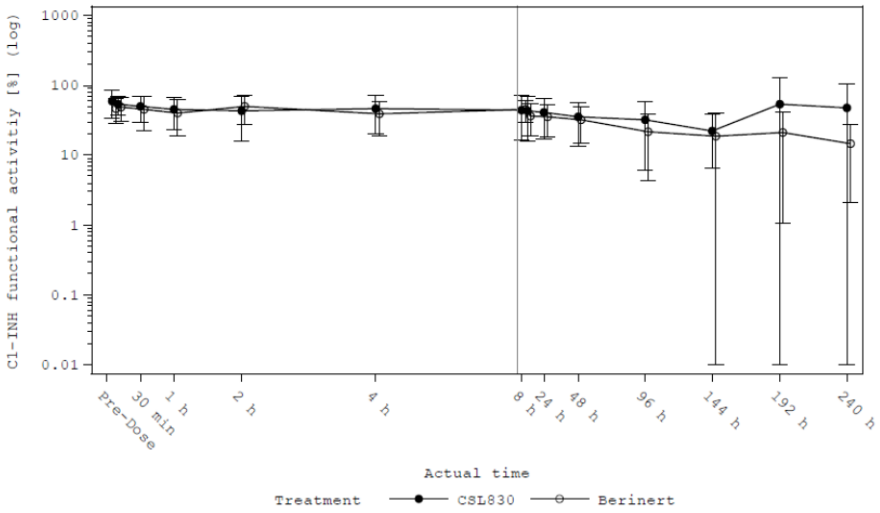


Figure 3: Mean baseline corrected C1-INH functional activity as a function of time



Mean pharmacokinetic parameters for C1-INH antigen and functional activity based on baseline-corrected values are shown in Table 1. In Tables 2 and 3, relative bioavailability of CSL830 and Berinert for C1-INH functional activity and antigen and is shown, respectively.

Table 1: Pharmacokinetic Parameters for C1-INH Antigen and Functional Activity based on Baseline-Corrected Values (PK Population)

Parameter	C1-INH Antigen			C1-INH Functional Activity		
	Units	CSL830 N = 15	Berinert[a] N = 15	Units	CSLS830 N = 15	Berinert[a] N = 15
C_{max}	mg/mL			%		
n		15	15		15	15
Mean (SD)		0.11 (0.027)	0.11 (0.019)		73.9 (46.74)	59.9 (16.60)
95% CI		0.09, 0.12	0.10, 0.12		48.0, 99.8	50.7, 69.1
Min, Max		0.04, 0.14	0.08, 0.14		35.0, 200.1	41.1, 96.9
AUC_{0-inf}	h*mg/mL			h*%		
n		6	5		3	4
Mean (SD)		10.1 (1.53)	7.34 (2.111)		5,233 (2,090.4)	3,193 (1,001.7)
95% CI		8.49, 11.7	4.72, 9.96		40.0, 10,425	1,600, 4,787
Min, Max		7.57, 11.2	3.98, 9.15		3,038, 7,200	2,227, 4,548
AUC_{0-last}	h*mg/mL			h*%		
n		15	15		15	15
Mean (SD)		7.87 (3.175)	7.33 (3.086)		6,702 (7,233.1)	3,839 (3,778.8)
95% CI		6.11, 9.63	5.62, 9.03		2,696, 10,707	1,746, 5,931
Min, Max		0.36, 12.5	2.88, 14.7		77.7, 22,474	129.3, 15,380
$T_{1/2}$	h			h		
n		7	7		5	9
Mean (SD)		87.7 (32.42)	91.4 (71.42)		64.3 (50.50)	89.7 (64.17)
95% CI		57.7, 117.7	25.4, 157.5		1.58, 127.0	40.3, 139.0
Min, Max		49.1, 150.4	27.9, 223.8		21.6, 151.3	22.7, 191.3
CL	IU/(h*mg/mL)			IU/(h*%)		
n		6	5		3	4
Mean (SD)		151.9 (26.57)	224.4 (88.56)		0.33 (0.150)	0.53 (0.170)
95% CI		124.0, 179.8	114.4, 334.4		-0.05, 0.71	0.25, 0.80
Min, Max		133.4, 198.3	163.9, 376.5		0.20, 0.50	0.30, 0.70
Vd	IU/(mg/mL)			IU/%		
n		6	5		3	4
Mean (SD)		16,748 (3,729.8)	15,313 (2,792.9)		22.1 (5.87)	27.2 (22.27)
95% CI		12,834, 20,662	11,845, 18,781		7.48, 36.7	-8.24, 62.6
Min, Max		9,447, 19,743	12,798, 20,021		16.5, 28.2	14.7, 60.5

[a] Berinert is the currently marketed presentation of CI-INH concentrate, CE1145.

AUC_{0-inf} = area under the plasma concentration-time curve (AUC) extrapolated to infinity; AUC_{0-last} = AUC to the last quantifiable concentration; CI = confidence interval; C1-INH = C1-esterase inhibitor; CL = clearance; C_{max} = maximum observed plasma concentration; h = hour(s); IU = international units; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; $T_{1/2}$ = apparent terminal elimination half-life; Vd = volume of distribution based on the terminal phase

Table 2: Relative Bioavailability of CSL830 and Berinert C1-INH functional activity

Parameter	Geometric Mean Ratio (90% CI)[b]
C_{max}	
Uncorrected	1.02 (0.92, 1.14)
Baseline-corrected	1.14 (0.88, 1.47)
$AUC_{0\text{-last}}$	
Uncorrected	1.05 (0.96, 1.16)
Baseline-corrected	1.41 (0.57, 3.50)

[a] Berinert is the currently marketed presentation of CI-INH concentrate, CE1145.

[b] n = 15 for both the CSL830 and Berinert treatments

$AUC_{0\text{-last}}$ = AUC to the last quantifiable concentration; C1-INH = C1-esterase inhibitor; CI = confidence interval; C_{max} = maximum observed plasma concentration; PK = pharmacokinetic

Table 3: Relative Bioavailability of CSL830 and Berinert C1-INH Antigen

Parameter	Geometric Mean Ratio (90% CI)[b]
C_{max}	
Uncorrected	1.02 (0.99, 1.04)
Baseline-corrected	0.97 (0.86, 1.09)
$AUC_{0\text{-inf}}$	
Baseline corrected[c]	1.42 (1.13, 1.79)
$AUC_{0\text{-last}}$	
Uncorrected	1.02 (0.99, 1.05)
Baseline-corrected	0.95 (0.66, 1.36)

[a] Berinert is the currently marketed presentation of CI-INH concentrate, CE1145.

[b] Unless otherwise stated, n = 15 for both CSL830 and Berinert treatments

[c] CSL830 treatment only, n = 3; CE1145 treatment, n = 2; Both CSL830 and CE1145 treatments, n = 3

$AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve (AUC) extrapolated to infinity; $AUC_{0\text{-last}}$ = AUC to the last quantifiable concentration; C1-INH = C1-esterase inhibitor; CI = confidence interval; C_{max} = maximum observed plasma concentration; PK = pharmacokinetic

Results and Conclusions:

C1-INH functional activity:

There was a substantial difference in C_{max}, $AUC_{(0\text{-last})}$, half-life, and clearance values between CSL830 and berinert (Table 1). The 90% confidence interval (CI) for C_{max} and $AUC_{(0\text{-last})}$ was within 80% to 125% for baseline uncorrected values. However, for baseline corrected values the 90% CI was outside the limits of 80-125% (Table 2).

C1-INH antigen concentrations:

Unlike C1-INH functional activity, C_{max}, $AUC_{(0\text{-}last)}$, half-life, and clearance between CSL830 and berinert were comparable by antigen concentrations (Table 1). The 90% confidence interval (CI) for C_{max} and $AUC_{(0\text{-}last)}$ was within 80% to 125% for baseline uncorrected values. However, for baseline corrected values the C_{max} was within the 90% CI but $AUC_{(0\text{-}last)}$ was outside the limits of 80-125% (Table 3).

Due to small size, it was difficult to assess the comparability between CSL830 and berinert. In terms of comparability, the two different analytical methods provided different results. The PK parameters estimated by C1-INH functional activity were substantially different between CSL830 and berinert whereas, based on antigen concentrations the PK parameters were comparable between the two products. However, a comparability study with berinert is not a requirement for the development of CSL830.

Study #2

Study Title: Population Pharmacokinetic Analysis of CSL830 in Patients with Hereditary Angioedema.

The objectives of the study were as follows:

• To characterize the population PK of C1-INH functional activity in patients with Hereditary Angioedema (HAE)

• To identify sources of variability in C1-INH functional activity PK

• To perform the simulations based on the final population model to support dosing of CSL830

• To perform exploratory evaluation of the correlation between C1-INH activity, C1-INH antigen concentrations and C4 antigen concentrations

Methodology: The population C1-INH functional activity data in the subjects treated with CSL830 (Studies 1001, 2001 and 3001) were analyzed by nonlinear mixed effects modeling using the NONMEM (version 7.2) (Table 1). The base model comprised of a one-compartment model with 2 separate baselines for patients and healthy volunteers. Absorption of CSL830 from the subcutaneous depot site in to the central compartment was modeled as a 1st-order process with absorption rate constant (Ka, $hour^{-1}$). One thousand individual profiles for the treatment-experienced population based on the distribution of individual weights were simulated to derive relevant PK parameters.

Table 1: Summary of Studies Included in the Population PK Analysis

Study	Population and No. Subjects	Dose/Treatment Duration	Planned PK Data
Study 1001 (Phase I)	16 Healthy Volunteers	Single dose of 1500IU CSL830 or Berinert (50IU/mL) given IV	C1-INH activity data after treatment with both CSL830 and Berinert was used in the analysis. Intense PK samples were collected up to 24 hrs after dosing followed by intermittent samples until Day 11 after dosing.
Study 2001 (Phase II)	18 HAE Patients	Single dose of 20IU/kg Berinert (50IU/mL) followed by 1500 IU, 3000 IU or 6000 IU of CSL830 given SC 2x per week for 4 weeks	C1-INH activity data after treatment with Berinert and various doses of CSL830 was used in the analysis. (Rescue C1-INH medication was also considered in the analysis). Intense PK samples were collected until 2 days after dosing followed by intermittent samples until the end of dosing at Week 4.
Study 3001 (Phase III)	90 HAE Patients	40 IU /kg or 60 IU/kg of CSL830 given SC 2x per week for 16 weeks	C1-INH activity data after treatment with various doses of CSL830 was used in the analysis. (Rescue C1-INH medication was also considered in the analysis). Sparse intermittent samples were collected throughout the study dosing at Week 16 in both periods of the study.

There were 124 subjects (108 HAE and 16 healthy volunteers) from Studies 1001, 2001, and 3001 in the PK analysis dataset. The dataset included 2103 C1-INH functional activity concentrations. In Table 2, the demography of the subjects included in the study is summarized.

Table 2: Subject Characteristics and Demographics by Study

Covariate	Statistic or category	Study 1001	Study 2001	Study 3001	Overall
Total Number					
Age (yrs) at baseline	Median [Min-Max]	35.0 [24-45]	33.5 [18-69]	40.0 [12-72]	38.5 [12-72]
Weight (kg) at baseline	Median [Min-Max]	73.7 [54-108]	78.9 [51-110]	78.1 [43-157]	77.6 [43-157]
Observed Baseline C1-INH functional activity	Mean [Min-Max]	99.8 [79-149]	17.9 [0-43]	28.6 [4.5-77]	36.5 [0-149]
Gender N	Male	11	7	30	48
	Female	5	11	60	76
Race N	Caucasian	16	14	84	114
	Asian	--	4	4	8
	Black	--	--	1	1
	Other	--	--	1	1
HAE Type N	Type 1	NA	16	78	94
	Type 2		2	12	14
Total No. of samples N		496	545	1062	2103

C1-INH functional activity was measured using a validated (b) (4) C1-Inhibitor assay (b) (4) , Marburg, Germany). The C1-INH functional activity, C1-INH antigen, and C4 antigen assays were validated with respect to accuracy, repeatability, precision, linearity, range, and robustness.

Model Building:

The population PK models were developed by comparing 1- and 2-compartment models with first order elimination. The parameters of the models were expressed in terms of volume of distribution (V) and CL. For the PK models, endogenous C1-INH functional activity was modeled as an estimated parameter with a random effect. The observed C1-INH functional activity was the sum of the baseline values and the exogenous drug administered.

Model selection was driven by the data and was based on evaluation of goodness-of-fit plots (observed vs. predicted concentration, conditional weighted residual vs. predicted concentration or time, histograms of individual random effects, etc.), successful convergence (with at least 3 significant digits in parameter estimates), plausibility and precision of parameter estimates, and the minimum objective function value (OFV). Distributions of individual parameters (*Pi*) were assumed to be log-normal and were described by an exponential error model. The covariate model included body weight, gender (male=0, female=1), age, HAE type, subject population (healthy or HAE patient), and region where the study was conducted. The base model comprised of a one-compartment model with 2 separate baselines for patients and healthy volunteers.

The predictive performance of the final model was assessed by applying a posterior visual predictive check (VPC). The final model was used to simulate 1000 datasets based on the covariates, sampling times and the dosing histories contained in the dataset. The original dataset was compared with the 5th, 10th, 90th, and 95th percentiles for the simulated data for each time. The number of observed concentrations that fell within 80% and 90% prediction intervals was determined by population type (HAE vs healthy). This comparison was used to evaluate whether the derived model and associated parameters were consistent with the observed data. In addition to the VPC, the final PK model was subjected to a nonparametric bootstrap analysis, generating 1000 datasets through random sampling with replacement from the original data using the individual as the sampling unit.

The final model was used to simulate plasma functional activity profiles for the treatment experienced population. C1-INH functional activity was predicted from first dose up to steady-state achieved following a 40IU/kg or 60IU/kg twice weekly dose of CSL830. In this procedure, parameters obtained from the population model were used to simulate 1000 individual profiles based on the distribution of individual weights from the population PK analysis.

Base model development

CSL830 functional activity was best described by a one-compartment model with first order absorption when administered SC with structural parameters for CL and V, first order absorption rate constant (k_a), and baseline C1-INH functional activity. A two-compartment model with first order absorption was also fitted to the data. Based on model diagnostics, the one-compartment model provided better description of the data. The baseline C1-INH functional activity was different between patients and healthy subjects due to the nature of the disease state. To account for this difference, separate baseline parameters were estimated for each population. The PK parameters estimated from the base model are shown in Table 3.

Table 3: Parameter Estimates of Base CSL830 Population PK Model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	IIV%	%RSE
CL [IU/hr·%]	0.839	6.71	30.6	19.8
Vd [IU/%]	43.5	9.00	40.7	31.1
Ka [hr^{-1}]	0.0142	12.6	80.4	13.9
BASE [%](Healthy volunteers)[hr]	106	3.18	11.0	18.3
BASE [%] (HAE patients)	23.3	3.62	29.7	10.0
F	0.427	FIX	54.0	12.1
Residual variability		**CV%**		**%RSE**
σ^2_{prop}		23.4		5.0

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, 95% , CL = clearance, Vd = volume of central compartment, Ka = absorption rate constant, CV = coefficient of variation of proportional error (=$[\sigma^2 prop]^{0.5}$*100), σ^2prop = proportional component of the residual error model. IIV=inter individual variability (=$[\sigma^2 prop]^{0.5}$*100)

Covariate Model Development:

The covariate model consisted of age, and body weight at baseline on CL and age and body weight at baseline on V being added simultaneously to form a full model. The reference covariate value used in the model was 80.7 kg for body weight (mean) and 38.5 years for age (median). Body weight on CL was the only covariate that was found to be statistically significant. In Table 4, summary of covariate model development is shown. Age and weight on CL and V reduced the objective function by 23.40 as compared with base model.

Table 4: Summary of Covariate Model Development

Run No	Model Description [a]	Reference Model	OFV	OFV Change	Minimization (Y/N)	Covariance (Y/N)
008	1 compartment model with Ka, CL, V, BASE for HAE and HV, F, eta (CL, V, Ka, BASE for HAE, BASE for HV, F), proportional residual error model; [Base model]	-	13355	--	Y	Y
010	**Add** Age and Wt on CL and V [Full model]	008	13332	-23.40	Y	Y
009	**Remove** Age on V	010	13332	0	Y	Y
011	**Remove** Age on CL	009	13332	0.075	Y	Y
*012	**Remove** Wt on V	011	13336	3.71	Y	Y
013	**Remove** Wt on CL [Base model]	012	13355	19.6	Y	Y
017	**Add** Study 2001 as covariate on CL	012	13315	-20.3	Y	Y
019	**Include** Rescue medication before start of study	012	13298	-37.5	N	N
040	2 compartment model with Ka, CL, V, BASE for HAE and HV, F, eta (CL, V, Ka, BASE for HAE, BASE for HV), proportional residual error model;	001	13484	-	Y	N

a. CSL830_1001_2001_3001_POPPK_24JAN2016.csv was used for all models
b. Abbreviations: CL = total clearance, BASE: Baseline C1-INH functional activity, V = Volume of distribution, Ka = absorption rate constant, WT: body weight
* Final model

Final Model:

The final population PK model had only one covariate effect: bodyweight on CL. The final CSL830 population PK model equation for CL:

CL = [redacted] (b) (4)

The PK parameters of CSL830 based on final population model are shown in Table 5.

Table 5: Parameter Estimates of Final CSL830 Population PK Model

Parameter [Units]	NONMEM Estimates			Bootstrap Estimates[a]		
	Point Estimate	%RSE	%IIV	%RSE	Median	95% CI
CL [IU/hr·%]	0.830	6.40	24.2	22.9	0.830	0.727-0.942
Vd [IU/%]	43.3	9.60	39.2	32.2	42.4	35.1-51.5
Ka [hr^{-1}]	0.0146	16.1	82.2	14.5	0.0143	0.0109-0.0194
BASE [%](Healthy volunteers)[hr]	105	3.20	11.03	17.8	105	98.7-113
BASE [%] (HAE patients)	23.2	3.68	29.5	9.76	23.3	21.5-24.9
F	0.427	FIX	49.1	12.6	0.427	NA
Effect of Body weight on CL	0.738	23.8			0.731	0.403-1.07
Inter-individual or inter-occasion variability						
ω^2_{CL}	0.0587				0.054	0.0148-0.134
ω^2_{V}	0.153				0.135	6.4E-07- 0.379
$\omega^2_{BASE\ HV}$	0.0122				0.0106	0.00304-0.0204
$\omega^2_{BASE\ HAE}$	0.0868				0.0862	0.0572-0.129
ω^2_{Ka}	0.675				0.635	0.0453-1.104
ω^2_{F}	0.241				0.243	0.130-0.374
Residual variability		**CV%**				**%RSE**
σ^2_{prop}		23.4				5.10

[a] From 1000 bootstrap runs.
Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, 95% CI= 95% confidence interval on the parameter, CL = clearance, V = volume of central compartment, Ka = absorption rate constant, ω^2_{CL}= variance of random effect of CL, CV = coefficient of variation of proportional error (=$[\sigma^2 prop]^{0.5}$*100), $\sigma^2 prop$ = proportional component of the residual error model, WT = baseline weight (kg).

Simulations:

C1-INH functional activity versus time profiles after 4 weeks of twice weekly dosing of 40 IU/kg or 60 IU/kg CSL830 (doses used in Phase 3; Study 3001) were simulated in 1000 HAE patients using the final model. In Table 6, the results of the simulation are shown. C_{max}, C_{avg} and C_{trough} are non-linear between 40 and 60 IU/kg dose, whereas AUC and half-life are within linear range. However, these parameters were simulated based on population PK modeling and carry some uncertainty.

Table 6: Summary of Steady-State PK parameters of CSL830 from the Simulated Population Stratified by Dose

Dose	C_{max} (%)	T_{max}* (hr)	$AUC_{0-\tau}$ (%·h)	Ctrough (%)	C_{avg}	Half-life* (hr)	Apparent Half-Life *† (hr)
40 IU/kg	48.7 (26.9-96.2)	58.7 (23-134)	1700 (558-5110)	40.2 (22.2-77.9)	44.6 (24.7-86.3)	36.9 (14.3-102)	68.7 (24.0-250)
60 IU/kg	60.7 (31.8-128)	58.7 (23-134)	2540 (837-7670)	48.0 (25.1-102)	54.8 (29.2-112)	36.9 (14.3-102)	68.7 (24.0-251)

Data presented as geometric mean (95% CI)
** Data presented as Median (95% CI)*
†Calculated using NCA module in (b) (4)

Conclusions:

- The C1-INH functional activity following administration of CSL830 was described by a one-compartment model with first-order absorption and first order elimination, with inter-individual variability in all parameters.
- The mean bioavailability of CSL830 was 0.427 (42.7%)
- Body weight effect on CL of C1-INH functional activity was included in the final model with the weight exponents on CL estimated to be 0.738.
- Simulations at 40 IU/kg and 60 IU/kg twice weekly dose of CSL830 resulted in a mean C_{trough} of 40.2 and 48.0 % C1-INH functional activity respectively.