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Population pharmacokinetics of subcutaneous C1-inhibitor for prevention of attacks in patients with hereditary angioedema

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Summary

Background: Long-term prophylaxis with subcutaneous (SC) administration of a highly concentrated plasma-derived C1-esterase inhibitor (C1-INH) formulation was recently approved by the Food and Drug Administration for hereditary angioedema (HAE) attack prevention.

Objective: To characterize the population pharmacokinetics of C1-INH (SC) (HAEGARDA®; CSL Behring) in healthy volunteers and HAE patients, and assess the variability and influence of covariates on pharmacokinetics.

Methods: C1-INH functional activity data obtained after administration of various C1-INH (intravenous; IV) and C1-INH (SC) doses from 1 study in healthy volunteers (n = 16) and 2 studies in subjects with HAE (n = 108) were pooled to develop a

population pharmacokinetic model (NONMEM v7.2). Pharmacokinetic parameters derived from steady-state simulations based on the final model were also evaluated.

Results: C1-INH functional activity following C1-INH (SC) administration was described by a linear one-compartment model with first-order absorption and elimination, with inter-individual variability in all parameters tested. The mean population bioavailability of C1-INH (SC), and pharmacokinetic parameters for clearance (CL), volume of distribution, and absorption rate were estimated to be ~43%, 1.03 mL/hour/kg, 0.05 L/kg and 0.0146 hour^{-1}, respectively. The effect of bodyweight on CL of C1-INH functional activity was included in the final model, estimated to be 0.74. Steady-state simulations of C1-INH functional activity vs time profiles in 1000 virtual HAE patients revealed higher minimum functional activity (C_{trough}) levels after twice-weekly dosing with 40 IU/kg (~40%) and 60 IU/kg (~48%) compared with 1000 IU IV (~30%). Based on the population pharmacokinetic model, the median time to peak concentration was ~59 hours and the median apparent plasma half-life was ~69 hours.

Conclusions and Clinical Relevance: Twice-weekly bodyweight-adjusted dosing of C1-INH (SC) exhibits linear pharmacokinetics and dose-dependent increases in C_{trough} levels at each dosing interval. In this analysis, SC dosing led to maintenance of higher C_{trough} levels than IV dosing.

KEYWORDS
angioedema, clinical immunology, prevention

1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by clinical symptoms including angioedema without urticaria or pruritus, generally affecting the subcutaneous (SC) tissues of the trunk, limbs or face, or the submucosal tissues of the respiratory, gastrointestinal or genitourinary tracts.[1-4] Without treatment, acute attacks can be life-threatening and may require hospitalization; moreover, many patients experience impaired quality of life.[1,2,5-7] Management of HAE involves the treatment of acute attacks, as well as short- and long-term prophylaxis in many patients.

Mutations on the *SERPING1* gene encoding the C1-esterase inhibitor (C1-INH) are responsible for the 2 most common types of HAE, type I (hereditary angioedema with deficient C1-INH; 85% of patients) and type II (hereditary angioedema with dysfunctional C1-_INH; 15% of patients).[1,5,8,9] In healthy individuals, C1-INH acts on the plasma kallikrein-bradykinin system to prevent excess generation of bradykinin and thus spontaneous activation of inflammatory reactions.[1,5,10] An absence in or dysfunction of C1-INH is the primary abnormality in patients with HAE, and a plasma-derived C1-INH twice-weekly intravenous (IV) injection provides a safe and generally effective treatment to reduce attacks of angioedema.[1,5,11,12] Consensus guidelines recommend C1-INH prophylaxis in patients who do not achieve sufficient benefit from on-demand treatment.[9,13-16]

Prior to the development of C1-INH (SC), the pharmacokinetics (PK) of C1-INH IV (Berinert®, CSL Behring, Marburg, Germany; 50 IU C1-INH/mL) were compared to a highly concentrated IV formulation (1500 IU C1-INH) in a phase I study of 16 healthy volunteers (NCT01760343). The bioavailability of the 2 formulations was found to be comparable, and the highly concentrated formulation safe to use in patients. The safety, efficacy and PK characteristics of C1-INH (SC) (HAEGARDA®; CSL Behring), were then subsequently demonstrated in 2 randomized trials; in the COMPACT phase II study, twice-weekly SC administration of a highly concentrated formulation of C1-INH for 4 weeks in patients with HAE demonstrated increased trough C1-INH functional activity in a dose-dependent manner, and was generally well tolerated.[17] The results of the COMPACT phase III study evaluating the efficacy and safety of C1-INH (SC) showed that twice-weekly 40 and 60 IU/kg significantly reduced the rate of HAE attacks compared with placebo ($P < 0.0001$ for both).[18] In 2017, the US Food and Drug Administration (FDA) approved C1-INH (SC) (HAEGARDA®) for the routine prophylaxis of HAE attacks in adolescent and adult patients.

The aim of the present analysis was to characterize the population PK of C1-INH (SC) (HAEGARDA®) in healthy volunteers and patients with HAE and to identify demographic and clinical factors that are potential determinants of PK variability. Simulations based on the final population PK model to support dosing of C1-INH (SC) were evaluated.

2 | METHODS

2.1 | Study medication

C1-INH (SC) (HAEGARDA®, CSL Behring; CSL830) is a highly concentrated formulation of a human, plasma-derived C1-INH.[17] C1-INH is a soluble single-chain glycoprotein with 478 amino acid residues and an apparent molecular weight of approximately 105 kDa—around 50% of the total molecular mass results from post-translational glycosylation of the protein. C1-INH is present in normal human plasma at concentrations of approximately 0.2 mg/mL, which is equivalent to 1 unit/mL plasma.[19-21] After reconstitution, the final concentration of C1-INH (SC) is 500 IU/mL, whereas that of the IV formulation (Berinert) is 50 IU/mL.

2.2 | Study populations, dose regimens and pharmacokinetic sampling

Data were obtained and pooled from 3 clinical studies: 1 study in healthy volunteers and 2 studies in patients with HAE following either IV or SC administration of C1-INH.

2.2.1 | Study 1 (Healthy volunteers; NCT01760343)

This was a randomized, double-blind, single-centre, cross-over phase I study to evaluate the safety, bioavailability and PK of 2 formulations of C1-INH. A cohort of 16 healthy volunteers aged 18-45 years with body mass index (BMI) 18-29 kg/m^2 received a single dose of the concentrated 1500 IU C1-INH formulation or the established C1-INH (IV) formulation (Berinert; 50 IU/mL). Blood samples were collected for the determination of C1-INH functional activity in plasma up to 24 hours post-dose and then intermittently until Day 11 after dosing.

2.2.2 | Study 2 (Patients with HAE; NCT01576523)

This was an open-label, dose-ranging, cross-over phase II study to characterize the PK, pharmacodynamics (PD) and safety of C1-INH (SC) in patients with HAE (COMPACT phase II study). The study included 18 patients with HAE who were allocated sequentially to a single dose of C1-INH (IV) followed by a dose of either 1500, 3000, or 6000 IU C1-INH (SC) twice-weekly for 4 weeks. After a washout period of up to 4 weeks, patients were allocated to another 4-week dosing period, such that each patient received 2 of the 3 doses. Full details of the study design have been reported previously.[17] Blood samples were collected for the determination of C1-INH functional activity in plasma up to 48 hours post-dose and then every day in Week 4 until the end of dosing.

2.2.3 | Study 3 (Patients with HAE; NCT01912456)

This was a double-blind, randomized, placebo-controlled, cross-over study to evaluate the clinical efficacy and safety of C1-INH (SC) (COMPACT phase III study). Ninety patients aged ≥ 12 years with a clinical diagnosis of HAE type I or II were randomly assigned (1:1:1:1) to one of the 40 IU/kg C1-INH (SC) (sequences 1, 2) or 60 IU/kg C1-INH (SC) (sequences 3, 4) treatment sequences. Each sequence consisted of 2 consecutive periods (Treatment Period 1 and Treatment Period 2) of up to 16 weeks each. During the treatment periods, subjects administered C1-INH or placebo via SC injection twice a week in a double-blind cross-over manner. Blood samples were collected in weeks 3, 5, 8, 11 and 14, and at the end of each period of the study to determine C1-INH functional activity in plasma. Available dosing information for the administration of on-demand rescue medication in patients was accounted for in the model.

2.3 | PK measurements

Plasma C1-INH functional activity was assessed by a validated chromogenic assay (Berichrom C1-inhibitor, Siemens Eschborn, Germany; reference range: 70%-130% of norm). All measurements were performed at a central laboratory (CSL Behring GmbH). Plasma C1-INH functional activity and C1-INH antigen were assessed in all 3 clinical studies.

2.4 | PK analysis

2.4.1 | Model development

The PK population included subjects who received C1-INH either as an IV or SC dose, and contributed at least 1 measurable PK concentration. C1-INH functional activity data following C1-INH (SC) administration in the 3 studies were analyzed by nonlinear mixed effects modelling using the software package NONMEM version 7.2 (ICON Development Solutions, Ellicot City, MD, USA), with the prediction of population pharmacokinetics (PREDPP) model library and NM-TRAN subroutines.

Various PK models, including 1- and 2-compartment models with first-order elimination, were evaluated to arrive at the model that best characterized the measured data. PK parameters such as clearance (CL), volume of distribution (V_d), bioavailability (F), absorption rate constant (K_a) and baseline C1-INH functional activity were assessed during model development. PK parameters were estimated using the first-order conditional estimation method with interaction. The following covariates were considered before the start of the analysis: bodyweight, gender, age, HAE type (I or II), subject population (healthy or HAE patient), baseline C1-INH functional activity and region where the study was conducted. Each covariate was evaluated individually based on the range of values in the dataset, scientific interest, mechanistic plausibility, exploratory graphics and previous reporting in other patient populations. After visual exploration, a backward elimination approach was employed to test covariates of interest (ie, that showed a trend in the visual exploration), including bodyweight and age on CL and V_d.

2.4.2 | Model evaluation (visual predictive check)

Model evaluation was conducted using the final model to simulate 1000 datasets based on bodyweight (the only covariate found to influence clearance), sampling times and the dosing histories contained in the dataset. The 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.

2.4.3 | Simulations

Based on the distribution of individual weights in a HAE population, the final model was used to simulate plasma profiles of C1-INH functional activity in 1000 patients with HAE from first dose up to steady state, following twice-weekly dosing of 40 IU/kg (SC), 60 IU/kg (SC), 1000 IU (IV) or 2500 IU (IV).

3 | RESULTS

3.1 | PK population

A total of 124 subjects (108 with HAE and 16 healthy volunteers) were included in the PK analysis dataset, which comprised of a total of 2103 C1-INH functional activity observations. Population demographics are summarized in Table 1.

3.2 | Population PK model

3.2.1 | Base model

C1-INH functional activity was best described by a linear one-compartment PK model with first-order absorption, when administered subcutaneously with structural parameters for CL and V_d, first-order K_a, and baseline C1-INH functional activity (Table S1), where the mean population F of C1-INH (SC) was fixed to the value previously described.[17] The observed C1-INH functional activity was modelled as the sum of the patient's endogenous C1-INH plus administered (exogenous) C1-INH.

As expected, the baseline C1-INH functional activity was unambiguously different between healthy subjects and those with HAE, therefore separate baseline parameters were estimated for each population.

3.2.2 | Full model

The relationships between the model parameters, and covariates of clinical interest (gender, age and bodyweight) were examined visually then added simultaneously to form a full model. The small number of non-Caucasian subjects included (<10% of the population) meant that race could not be included as a covariate for the analysis. A summary of the final PK parameter estimates is provided in Table 2. The only statistically significant covariate effect was that of bodyweight on CL, which was accounted for in the final model by including bodyweight as a covariate on CL (Table 2).

The final model can be described by the following equation:

$$\mathrm{CL} = 0.830 * \left(\frac{\mathrm{WT}}{80.5}\right)^{0.738}$$

In which CL is the individual value of clearance, and WT the bodyweight of the subject (median 80.5 kg). Overall, age and gender did not have an effect on the PK of C1-INH functional activity. Additionally, a comparison of age as a binary effect (categorized as >17 years [n = 117] vs ≤17 years [n = 7]) did not show a relevant difference in the PK of C1-INH functional activity in adults and adolescents.

TABLE 1 Summary of population demographics by study

Covariate	Statistic or category	Study 1	Study 2	Study 3	Overall
Total number					
Age (years) 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 I	NA	16	78	94
	Type II		2	12	14
Total number of samples		496	545	1062	2103

C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; Max, maximum; Min, minimum; N, total number of subjects; NA, not assessed.

TABLE 2 Final population pharmacokinetic parameter estimates

	NONMEM estimates			
Parameter (units)	**Point estimate**	**%RSE**	**%IIV**	**%RSE**
CL (IU/h•%)	0.830*	6.40	24.2	22.9
V_d (IU/%)	43.3†	9.60	39.2	32.2
K_a (h^{-1})	0.0146	16.1	82.2	14.5
BASE (%) (Healthy volunteers; h)	105	3.20	11.03	17.8
BASE (%) (HAE subjects; h)	23.2	3.68	29.5	9.76
F	0.427	FIX	49.1	12.6
Effect of bodyweight on CL	0.738	23.8		
Inter-individual or inter-occasion variability				
ω^2_{CL}	0.0587			
ω^2_{V}	0.153			
ω^2_{BASEHV}	0.0122			
$\omega^2_{BASEHAE}$	0.0868			
ω^2_{Ka}	0.675			
ω^2_{F}	0.241			
Residual variability		**CV%**		**%RSE**
σ^2_{prop}		23.4		5.10

%RSE, percent relative standard error of the estimate = SE/parameter estimate * 100; σ^2_{prop}, proportional component of the residual error model; 95% CI, 95% confidence interval on the parameter; CL, clearance; CV, coefficient of variation of proportional error (=$[\sigma^2_{prop}]^{0.5}$ * 100); *F*, bioavailability; h, hours; HAE, hereditary angioedema; HV, healthy volunteer; IIV, inter-individual variability; K_a, absorption rate constant; NA, not applicable; ω^2, variance of inter-individual variability parameter; V_d, volume of distribution.

*CL = 1.03 mL/h/kg

†V_d = 0.05 L/kg.

3.2.3 | Final model evaluation

The observed concentrations for healthy subjects and patients at the 10th and 90th percentiles and median were inspected for agreement with simulated concentrations at the 10th, 50th and 90th percentiles. This assessment did not indicate any substantive deficiency in the ability of the final reference model to characterize trends and variability in the observed PK data (Figure S1).

Visual evaluation of the individual *post-hoc* estimates revealed that CL was lower in patients enrolled in Study 2 (COMPACT II) compared to Study 3 (COMPACT III). This was quantified in the final model as a categorical covariate and the CL was estimated to be 40% lower in Study 2. The individual *post-hoc* CL and V_d estimates from the 2 models showed no difference. On further evaluation of the distribution of the individual estimates in each study, it became apparent that in order to gain an assessment of population PK parameters in subjects with HAE, the population CL estimate from the pooled model best reflected the overall HAE population, as Study 2 appears to be a small subset of the overall population in the analysis. A test of the effects of baseline C1-INH values, starting bodyweight and V_d failed to explain these differences.

3.2.4 | Simulations of C1-INH (SC) vs C1-INH (IV)

A summary of the model-predicted geometric mean maximum plasma C1-INH functional activity levels (C_{max}), minimum functional activity levels (C_{trough}), median time to peak concentration (T_{max}), half-life and area under the activity-time curve from pre-dose to the end of the dosing interval at steady state ($AUC_{0-\tau}$) are presented in Table 3. Based on the final model, mean C_{max} was 48.7% for 40 IU/kg and 60.7% for 60 IU/kg, and 56.3% and 104% for 1000 IU and 2500 IU C1-INH (IV). Mean C_{trough} was 40.2% for 40 IU/kg and 48.0% for 60 IU/kg; these values were higher than the 29.5% and 37.8% calculated with 1000 IU and 2500 IU C1-INH (IV) (Figure 1). The median T_{max} of ~59 hours is characteristic of SC administration of proteins.

The simulated C1-INH functional activity curves showed a lower peak-to-trough ratio with a more consistent elevation of the C1-INH functional activities for the 40 and 60 IU/kg SC doses (1.2 and 1.3, respectively) compared to those after 1000 and 2500 IU IV doses (1.9 and 2.8, respectively) (Figure 1).

4 | DISCUSSION

This analysis demonstrated that the PK of C1-INH (SC) was best described by a one-compartment model with first-order absorption and first-order elimination. Bodyweight was found as the only significant covariate describing CL (with the weight exponents on CL estimated to be 0.74 in the final model). To illustrate the magnitude of this effect, a subject with a baseline weight of 60 kg would have a CL of 0.67 IU/hour· %, whereas a subject with a baseline weight of 90 kg would have a CL of 0.90 IU/hour· %. The absorption rate was 0.0146 $hour^{-1}$. The C_{trough} of 60 IU/kg C1-INH (SC), twice-weekly was simulated to be 48.0%, compared to 30% of 1000 IU C1-INH (IV) twice-weekly. For C1-INH (SC), the population mean bioavailability (~43%), CL (1.03 mL/hour/kg) and V_d (0.05 L/kg) are consistent with previous estimates reported in the literature.[22-25] The model absorption rate of 0.0146 $hour^{-1}$ for SC dosing is reflective of the slow transport through the lymphatic system, which is thought to play a major role in the SC absorption of large molecules—such as C1-INH which has a molecular weight of approximately 105 kDa.[25,26]

The current analysis is a comprehensive pooled population PK analysis conducted using data from 3 clinical studies, and is thus a more comprehensive characterization of C1-INH population PK in the entire HAE population. The lower CL estimates in Study 2 compared to Study 3 are most likely due to the smaller sample size in Study 2, or due to the higher rate of HAE attacks prior to screening in Study 3, which may have an impact on the CL of C1-INH (SC). The consumption of C1-INH during a HAE attack has not previously been characterized and therefore the C1-INH kinetics cannot be quantified.

Until recently, C1-INH was only used as an IV formulation. The PK of C1-INH (IV) has been described by Martinez-Saguer et al[27] who demonstrated the median half-lives of functional C1-INH plasma levels to be 39.1 hours after on-demand therapy and 30.9 hours for patients on individual replacement therapy. The PK profile of C1-INH

TABLE 3 Summary of pharmacokinetic parameters of steady-state C1-INH (SC) from the simulation population stratified by dose

Dose	C_{max} (%)	T_{max}[a] (h)	C_{trough} (%)	$AUC_{0-\tau}$ (%·h)	Apparent half-life[a,b] (h)
40 IU/kg SC	48.7 (26.9-96.2)	58.7 (23-134)	40.2 (22.2-77.9)	1700 (558-5110)	68.7 (24.0-250)
60 IU/kg SC	60.7 (31.8-128)	58.7 (23-134)	48.0 (25.1-102)	2540 (837-7670)	68.7 (24.0-251)
1000 IU IV	56.3 (38.9-81.7)	-	29.5 (16.9-49.7)	98,400 (61,200-162,000)	-
2500 IU IV	104 (69.7-160)	-	37.8 (19.6-70.2)	246,000 (153,000-404,000)	-

$AUC_{0-\tau}$, area under the activity-time curve from predose to the end of the dosing interval at steady state; C_{avg}, average plasma C1-INH functional activity at steady state; C_{max}, maximum plasma C1-INH functional activity levels; C_{min}, minimum plasma C1-INH functional activity levels; C_{trough}, minimum plasma C1-INH functional activity levels; h, hours; IU, international unit; SC, subcutaneous; T_{max}, time to maximum activity.
Data presented as geometric mean (95% CI).
[a]Data presented as median (95% CI).
[b]Calculated using a non-compartmental analysis module in Phoenix©.

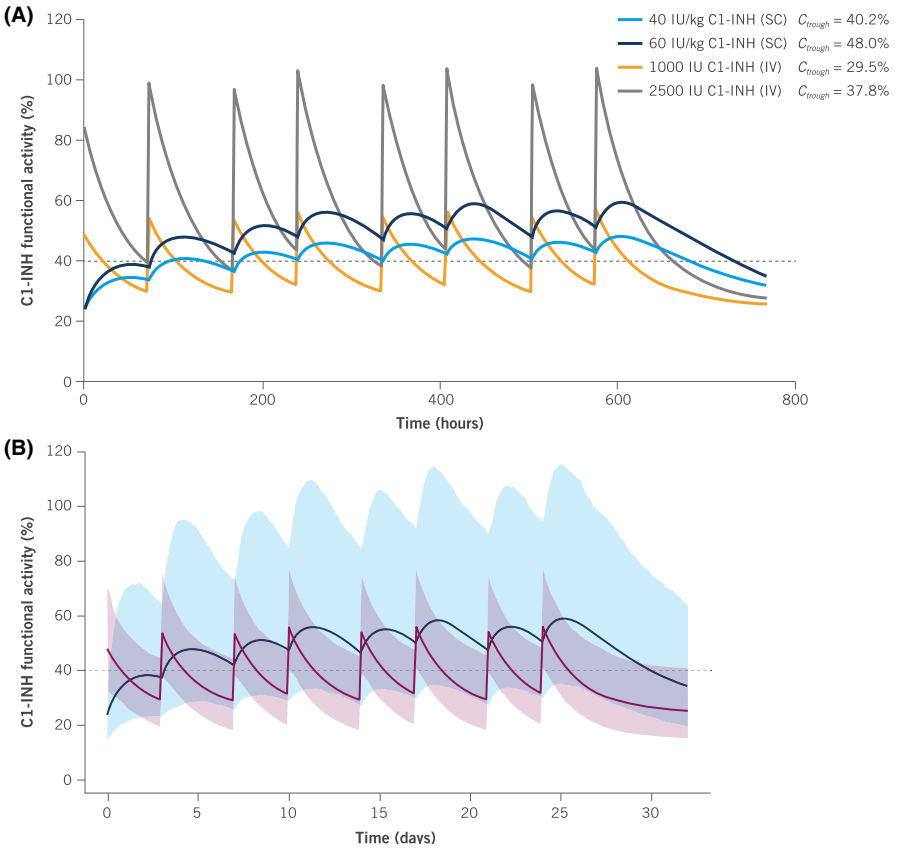

FIGURE 1 Simulated median steady-state C1-INH functional activity vs time after twice-weekly C1-INH (SC) 40 IU/kg, C1-INH (SC) 60 IU/kg, C1-INH (IV) 1000 IU, and C1-INH (IV) 2500 IU (A). Simulated median (90% CI) simulated C1-INH functional activity time profiles for twice-weekly 60 IU/kg C1-INH (SC) and 1000 IU (C1-INH (IV) (B)

(SC) is different from that of C1-INH (IV). Due to the longer absorption phase after SC administration and the proposed lymphatic transport of C1-INH (SC), the T_{max} is estimated to be ~59 hours and the apparent half-life ~69 hours, resulting in higher trough levels at the next dosing interval with twice-weekly dosing. Simulations of 40 and 60 IU/kg twice-weekly dosing of C1-INH (SC) have calculated a mean C_{trough} of 40.2% and 48.0% C1-INH functional activity, respectively, which were higher than the 29.5% C_{trough} values estimated after 1000 IU C1-INH (IV). Even with the highest dose of 2500 IU C1-INH (IV) twice-weekly, the C_{trough} values were estimated to be 39%, which is lower than that found for C1-INH (SC) at the 60 IU/kg dose. With the FDA-approved bodyweight dosing of 60 IU/kg, simulations suggest that the majority of patients will have C_{trough} values above the clinically meaningful 40% threshold, below which patients are more likely to experience attacks.[24]

The differences in calculated C_{trough} values suggest that patients with HAE who administer C1-INH (SC) prophylaxis may experience less time having lower C1-INH functional activity compared to those who administer IV prophylaxis. Results from an exposure-response analysis of the relationship between C1-INH functional activity and risk of HAE attacks confirmed that a greater reduction in the relative risk of a HAE attack correlates with increasing C1-INH functional activities.[28] Thus, maintenance of higher C_{trough} values after SC prophylaxis compared to IV prophylaxis offers greater protection to HAE patients from experiencing a HAE attack.

Performing a pooled population PK analysis enabled the inclusion of data from all studies, including sparse data, from the phase III study to characterize the PK of C1-INH (SC). A population PK analysis of the phase II study provided a good description of C1-INH functional activity and revealed a significant effect of bodyweight on CL.[17] The use of population modelling throughout the process assisted in designing studies with optimal samples for PK and to make comparisons of various dosing scenarios without conducting the clinical trials.

In conclusion, our analysis demonstrates that in patients with HAE, long-term prophylaxis with bodyweight-based SC dosing of C1-INH provides consistent and higher trough levels of C1-INH functional activity at the next dosing interval compared with IV route of administration at the currently recommended dosing (1000 IU and 2500 IU twice-weekly).

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CONFLICT OF INTERESTS

DP, MT, AF and JS are employees of CSL Behring. BZ has acted as a paid consultant to Adverum, Alnylam, BioCryst, CSL Behring, Novartis, Sanofi and Shire, and has received or may receive funding from Shire and Ionis, unrelated to this work. TC has received fees from CSL Behring for speaking and consulting. MC has received consulting and speaker fees, and for attending symposia from Shire, CSL Behring and Pharming. He has also received funds for research from Shire and Pharming, and consulting fees from BioCryst and Adverum. HL received funding to attend conferences and educational events, has acted as a medical advisor or speaker, has received departmental funding, has received financial and other assistance with patient care projects and has participated in clinical trials with the following companies: Adverum, BioCryst, CSL Behring, Kalvista, and Pharming and Shire (Dyax). HHL has acted as a paid consultant and speaker to CSL Behring and has received funding for research carried out in this work. WL reports consultant fees from Adverum, BioCryst, CSL Behring and Shire, as well as speakers' fees from CSL Behring and Shire. He also reports grants and research support from Hereditary Angioedema Association and BioCryst, CSL Behring, Circassia and Shire. IMS has no conflicts of interest to declare. JJ has acted as a paid consultant, speaker and researcher for Shire PLC and CSL Behring. He has also acted as a paid consultant and speaker for Pharming and a researcher for BioCryst. JB has received consultancy fees from Shire, CSL Behring and Biocryst; has received research support from Shire; has received lecture fees from Shire, Pharming and CSL Behring; and is a HAEA organization Medical Advisory Board member. MAR reports funding for research related to this work. Unrelated to this work he reports research funding from BioCryst, Pharming, Shire, as well as consultant fees from Adverum, Alnylam, BioCryst, CSL Behring, Kalvista, Pharming, Shire and speaker honorarium from CSL Behring, Pharming and Shire. CHK has received honoraria for presentations and for Advisory Board work. She has also received institutional funding for clinical trials. PKK has received fees for speaking and consulting, as well as research grants from CSL Behring and Shire.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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