15 December 2016
EMA/873329/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cinryze

International non-proprietary name: C1-esterase inhibitor, human

Procedure No. EMEA/H/C/001207/II/0045

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE: adverse event

ADR: adverse drug reaction(s)

AUC0-4: area under the serum concentration-time curve from time zero to 4 hours

C1 INH: C1 inhibitor

CHMP: Committee for Medicinal Products for Human Use

CL: clearance

Cmax: maximum observed plasma concentration

CSR: clinical study report

dL: deciliter

EMA: European Medicines Agency

EU: European Union

ePAR: European Assessment Reports

FDA: Food and Drug Administration

H: hour(s)

HAE: hereditary angioedema

ID: identification

ITT: intent-to-treat

ITT-S: intent-to-treat Safety (Dataset)

IV: intravenous

Kg: kilogram

MAA: marketing authorization application

MOA: mechanism of action

Mg: milligram

mL: milliliter

N, n: number

NA: not assessed

ND: not done

PD: pharmacodynamics

PDCO: Paediatric Committee

PIP: pediatric investigational plan

PK: pharmacokinetics

SAE: serious adverse event

SD: standard deviation

SOC: system organ class

SmPC: summary of product characteristics

TEAE: treatment-emergent adverse event

Tmax: time of maximum observed plasma concentration

U: unit(s)

US: United States

V: central volume of distribution

Y: year(s)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shire Services BVBA submitted to the European Medicines Agency on 2 June 2016 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, IIIB and A

Extension of Indication in children with hereditary angioedema (HAE) to include the treatment and pre-procedure prevention of angioedema attacks from 2 years and the routine prevention of angioedema attacks from 6 years; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The key messages of educational materials in the Annex II, the Package Leaflet and the Labelling are updated in accordance. In addition, an update of regional information in module 3.2.R due to the proposed dose recommendation for children is submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0299/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0299/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0299/2015.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application refers to the critical report addressing the possible similarity with authorised orphan medicinal products as submitted in the initial application.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 June 2016
Start of procedure:	18 June 2016
CHMP Rapporteur Assessment Report	16 August 2016
PRAC Rapporteur Assessment Report	18 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 September 2016
Request for supplementary information (RSI)	15 September 2016
PRAC Rapporteur Assessment Report	21 November 2016
PRAC members comments	
Updated PRAC Rapporteur Assessment Report	24 November 2016
CHMP Rapporteur Assessment Report	1 December 2016
PRAC Outcome	1 December 2016
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	8 December 2016
Updated PRAC Rapporteur Assessment Report	13 December 2016
Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

Cinryze (C1 esterase inhibitor [human] or C1 INH) has marketing authorization in 36 countries. The intravenous (IV) administration of 1000 U of Cinryze every 3 or 4 days was approved in the US for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE) in October 2008. In June 2011, IV administration of Cinryze was approved by the European Medicines Agency (EMA) for the treatment, routine prevention, and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE.

Mechanism of action

The primary function of C1 INH is to regulate activation of the coagulation, contact (bradykinin-forming), and complement pathways through the formation of pathway-specific complexes that result in inactivation of a target protease and consumption of C1 INH. With respect to the coagulation and contact pathways, C1 INH inhibits factor XIIa, kallikrein, and plasmin, which are factors primarily involved in formation of blood clots (factor XIIa), clot dissolution (plasmin), and regulation of bradykinin (kallikrein). Bradykinin primarily regulates vasodilation and fluid release, and unregulated activation of bradykinin, which may occur in the absence of C1 INH, can lead to uncontrolled swelling or angioedema. C1 INH inhibits the complement system by binding C1r and C1s (2 of the active enzyme subunits of the first component of the complement system [C1]) in the classical pathway and mannose-binding lectin-associated serine proteases in the lectin pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels.

Because these pathways are part of enzyme amplification cascades, without C1 INH, spontaneous or trigger-induced activation of these pathways can lead to unopposed activation and swelling.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

In accordance with Article 8(3) and (g) of Directive 2001/83/EC, as amended, and the Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), an Environmental Risk Assessment is not applicable to this Application as Cinryze (C1 esterase inhibitor [human]) is a protein.

2.3. Clinical aspects

2.3.1. Introduction

The HAE Development Program for IV Cinryze supporting marketing approval included 8 clinical studies that allowed paediatric subjects to participate. Data was provided in the marketing authorization application (MAA) from 46 unique paediatric subjects (2 to <18 years of age) who participated in the Phase 3 studies:

- Study LEVP 2005-1/A was a double-blind, placebo-controlled study evaluating Cinryze for the treatment of acute angioedema attacks in HAE subjects ≥6 years of age. Fifteen (15) paediatric subjects (6-17 years) participated in the study, with 12 subjects having exposure to Cinryze.

- Study LEVP 2006-1 was an open-label study evaluating repeat exposure Cinryze in the treatment of acute angioedema attacks in HAE subjects ≥1 year of age. Twenty-four (24) paediatric subjects (2-17 years) participated in the study.

- Study LEVP 2005-1/B was a double-blind, placebo-controlled study evaluating Cinryze for the prevention of angioedema attacks in HAE subjects ≥6 years of age. Four (4) paediatric subjects (9-17 years) participated in the study.

- Study LEVP 2006-4 was an open-label study evaluating Cinryze for the prophylactic treatment to prevent angioedema attacks and as treatment for acute angioedema attacks in subjects ≥1 year of age. Twenty-three (23) paediatric subjects (3-17 years) participated in the study.

In accordance with Regulation (EC) no. 1901/2006, the sponsor and the EMA agreed on a paediatric investigation plan (PIP) for Cinryze for the treatment and prevention of angioedema attacks in adolescents and children with C1 inhibitor deficiency. The PIP agreement was comprised of 4 clinical studies, 2 of which (LEVP 2006-1 and LEVP 2006-4) were completed and submitted with the original MAA and 2 new post-approval studies:

- Study 0624-203 was an open-label, single-dose study of IV Cinryze in paediatric subjects that was conducted in the US. The study evaluated the response and pharmacokinetics/pharmacodynamics of different doses of Cinryze for the treatment of acute angioedema attacks in children ≥2 to <12 years of age with HAE. Nine subjects were enrolled and completed the study.

- Study 0624-301 is an ongoing, randomized, single-blind, dose-ranging, crossover study of IV Cinryze conducted in the US and Europe. The study evaluates the response of 2 different doses of Cinryze (500 U and 1000 U) and 2 consecutive treatment periods (12 weeks) for the routine prevention of angioedema attacks in 12 children 6-11 years of age with HAE. In order to fulfill the PIP requirements it was agreed that the first 6 completed subjects would be included in an Interim Report.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1. Overview of Clinical Studies Providing Data on the Efficacy of Cinryze in the Management of HAE in the Paediatric Population

Study ID M5 Location	Short Description	Phase	Study Design	Pediatric Subjects Dosed	Dosage Regimen	Duration of Dosage/# Infusions in All Subjects
Treatment Studies						
0624-203 5.3.4.2	Treatment of acute HAE attacks in children <12 years	2	MC, OL, SD	9 6-11 years	10-25 kg: 1: 500 U IV (inclusive) 2: 1000 U IV[a] >25 kg: 3: 1000 U IV 4: 1500 U IV	Single dose 9
LEVP 2005-1/A 5.3.5.1	Treatment of acute HAE attacks in subjects ≥6 years	3	MC, R, DB, PC	12[b] 6-17 years	Treatment: 1000 U IV or placebo; if no response at 60 minutes, second dose Pre-procedure: 1000 U IV	Single dose 30
LEVP 2006-1 5.3.5.2	Treatment of acute HAE attacks with repeat exposure in subjects ≥1 year	3	MC, OL	24 2-17 years	Treatment: 1000 U IV if no response at 60 minutes, second dose Pre-procedure: 1000 U IV	Multiple doses 193
Prevention Studies						
0624-301[c] 5.3.5.2	Prevention of HAE attacks in children 6-11 years	3	MC, R, SB, DR	6 7-11 years	Twice/week for 12 weeks in 2 treatment periods. Randomized to: 500 U/1000U IV or 1000 U/500 U IV	24 weeks 285
LEVP 2005-1/B 5.3.5.1	Prevention of HAE attacks in subjects ≥6 years	3	MC, R, DB, PC	4 9-17 years	Twice/week for 12 weeks in 2 treatment periods. Randomized to: placebo/1000U IV or 1000 U IV/placebo	24 weeks 219
LEVP 2006-4 5.3.5.2	Prevention and treatment of HAE attacks in subjects ≥1 year	3	MC, OL	23 3-17 years	Prevention: Every 3-7 days 1000 U IV Treatment: 1000 U IV if no response at 60 minutes, second dose	Multiple doses 1795

DB=double-blind; DR=dose-ranging; HAE=hereditary angioedema; IV=intravenous; MC=multicenter; OL=open-label; PC=placebo-controlled; R=randomized; SB=single-blind; SD=single-dose

[a] Although planned per protocol, the study was unable to enroll subjects at the 1000 U dose in the lower weight category.
[b] Fifteen pediatric subjects participated in the study, with 12 subjects having exposure to CINRYZE.
[c] Interim analysis for the first 6 subjects completing the study. Study 0624-301 is ongoing.

2.3.2. Pharmacokinetics

Study 0624-203

Nine paediatric subjects aged 6-11 years were enrolled in this study. Subjects who could initiate treatment within 8 hours after onset of symptoms received Cinryze for treatment of a single acute attack. The IV doses

of Cinryze evaluated were 500 U and 1000 U in children ≥10 kg to ≤ 25 kg and 1000 U and 1500 U in children >25 kg.

Despite substantial recruitment efforts, subjects were not enrolled 1000 U dose group in the lower weight category. Therefore 9 subjects were enrolled and treated: 3 subjects (10-25 kg inclusive) received 500 U, 3 subjects (>25 kg) received 1000 U and 3 subjects (>25 kg) received 1500 U IV Cinryze. All 9 subjects received a single dose of Cinryze and completed the study. It should be mentioned that the study covered 8 female subjects, aged 6 to 11 years, all of them White.

All subjects demonstrated an increase in C4 plasma concentrations above baseline at 24 hours post-infusion indicating that administration of exogenous functional C1 INH was affecting the downstream complement cascade in all subjects.

Blood samples for PK evaluation were taken prior to Cinryze infusion, 1 hour and 24 hours post infusion. No subject agreed to the additional but optional blood sampling necessary to obtain a PK profile for antigenic and functional C1 INH levels (additional blood samples collected through 8 hours post-infusion on Day 1, and on Days 3, 5, and 8). As a result, no PK parameters were calculated for this study.

Individual plasma concentrations of C1 INH antigen, functional C1 INH activity, and C4 for all subjects were measured (see Table, below). Following the administration of 500, 1000, or 1500 U of Cinryze, all subjects, with the noted exception of one subject, achieved increases in C1 INH plasma antigen and functional activity above baseline values at 1 hour and 24 hours post-Cinryze infusion. The 1 hour and 24 hours post-dose concentrations for this subject are less than the baseline pre-dose concentration. Although no deviation was reported by the site and this cannot be corroborated, it appears that this subject's pre-dose and 1 hour post-dose samples were inadvertently switched or mislabeled.

Six of 9 subjects (67%) achieved functional C1 INH concentrations ≥0.7 U/mL at 1 hour post-injection. It is also noteworthy that all subjects demonstrated an increase in C4 plasma concentrations above baseline at 24 hours post-infusion, indicating that administration of exogenous functional C1 INH was affecting the downstream complement cascade in all subjects.

Table 2. Individual Plasma C1 INH Antigen, Functional Activity, and C4 Plasma Concentrations in Subjects with HAE Following 500, 1000, and 1500 U IV Cinryze Administration – ITT-S Population (Study 0624-203)

CINRYZE Dose (U/kg)	Study Day: Time point	C1 INH Antigen [g/L]	C1 INH Functional Activity [U/mL]	Complement C4 [mg/L]
		Value, Change from Baseline (denoted in parentheses)		
500 U IV CINRYZE; 10-25 kg (n=3)				
22.0	Day 1: pre-dose	**0.038**	**<0.050**	**49.00**
	1 hr post-dose	0.166 (0.128)	0.450 (NC)	41.00 (-8.00)
	Day 2: 24 hrs post-dose	0.124 (0.086)	0.340 (NC)	102.00 (53.00)
28.3	Day 1: pre-dose	**0.038**	**0.160**	**43.00**
	1 hr post-dose	0.174 (0.136)	0.760 (0.600)	34.00 (-9.00)
	Day 2: 24 hrs post-dose	0.114 (0.076)	0.440 (0.280)	78.00 (35.00)
20.8	Day 1: pre-dose	**<0.029**	**<0.050**	**19.00**
	1 hr post-dose	0.121 (NC)	0.340 (NC)	20.00 (1.00)
	Day 2: 24 hrs post-dose	0.116 (NC)	0.200 (NC)	83.00 (64.00)
1000 U IV CINRYZE; >25 kg (n=3)				
26.0	Day 1: pre-dose	**0.038**	**0.100**	**<61**
	1 hr post-dose	0.210 (0.172)	0.870 (0.770)	<61 (NC)
	Day 2: 24 hrs post-dose	0.125 (0.087)	0.450 (0.350)	138.00 (NC)
26.5 [a]	Day 1: pre-dose	**0.200**	**0.650**	**<61**
	1 hr post-dose	0.037 (-0.163)	0.060 (-0.590)	<61 (NC)
	Day 2: 24 hrs post-dose	0.136 (-0.064)	0.500 (-0.150)	96.00 (NC)
29.0	Day 1: pre-dose	**0.047**	**0.180**	**42.00**
	1 hr post-dose	0.210 (0.163)	0.930 (0.750)	39.00 (-3.00)
	Day 2: 24 hrs post-dose	0.136 (0.089)	0.580 (0.400)	103.00 (61.00)
1500 U IV CINRYZE; >25 kg (n=3)				
28.5	Day 1: pre-dose	**0.062**	**0.250**	**74.00**
	1 hr post-dose	0.240 (0.178)	1.030 (0.780)	69.00 (-5.00)
	Day 2: 24 hrs post-dose	0.160 (0.098)	0.680 (0.430)	160.00 (86.00)
51.9	Day 1: pre-dose	**0.040**	**0.210**	**61.00**
	1 hr post-dose	0.340 (0.300)	1.330 (1.120)	47.00 (-14.00)
	Day 2: 24 hrs post-dose	0.198 (0.158)	0.820 (0.610)	81.00 (20.00)
31.6	Day 1: pre-dose	**0.034**	**0.170**	**21.00**
	1 hr post-dose	0.187 (0.153)	0.760 (0.590)	23.00 (2.00)
	Day 2: 24 hrs post-dose	0.128 (0.094)	0.550 (0.380)	63.00 (42.00)

Source: Section 11, Table 11.4.1

U=units; kg=kilograms; g=grams; L=liters; mL=milliliters; mg=milligrams; y=years; F=female; M=male; hr(s)=hour(s); NC=not calculable

NOTE: Baseline (Day 1, pre-dose) values are **bolded**.

Study 0624-301

Blood samples were collected for the assessment of antigenic and functional C1 INH (PK), and C4 levels (PD), in addition. Samples were taken pre-infusion and 1 hour post- infusion for Dose 1 (week 1), 12 (week 6), and 24 (week 12) of each treatment period. Changes from baseline/ pre-dose level to 1 h post-dose were summarized for C1 INH antigen and C1 INH functional activity. The effect of Cinryze on complement C4 concentrations was explored, in addition.

Data Sets Analyzed

Six paediatric subjects aged 7-11 years were enrolled in this study. Subjects were randomized to 1 of 2 treatment sequences (A/B or B/A; A=500 U and B=1000 U), with each sequence consisting of two 12-week treatment periods. Subjects had to qualify for randomization by experiencing at least 1.0 angioedema attack (moderate or severe or required acute treatment) per month during the study's 12-week baseline observation period.

Two subjects were randomized to 500 U/1000 U Cinryze and 4 subjects were randomized to 1000 U/500 U Cinryze. All 6 subjects completed treatment (received 500 and 1000 U of Cinryze for 12 weeks each) and completed the study.

The Pharmacokinetic Set included all subjects in the Safety Set who had evaluable pharmacokinetic profiles; that is, subjects who had plasma samples drawn and tested for C1 INH in which pharmacokinetic parameters could be derived. All 6 subjects were included in the pharmacokinetic and pharmacodynamic analyses.

It should be mentioned that the study covered 6 female subjects, aged 7 to 11 years, 5 white, one Hispanic ethnicity, 23-47 kg bodyweight, normal BMI.

C1 INH Functional Activity Concentrations

Unadjusted individual C1 INH functional activity 1 h after Cinryze administration by dose number is presented, below. A composite statistical value was calculated by averaging the 1 h post dose C1 INH functional activity level at Dose 12 and 24 (baseline adjusted by the corresponding pre-dose levels) to illustrate the dose response in each subject following Cinryze 500 U and 1000 U IV administration (see below). When the Cinryze dose increased from 500 U to 1000 U, the average values of Dose 12 and Dose 24 functional C1 INH activity increased in the range of 41.5% to 157%.

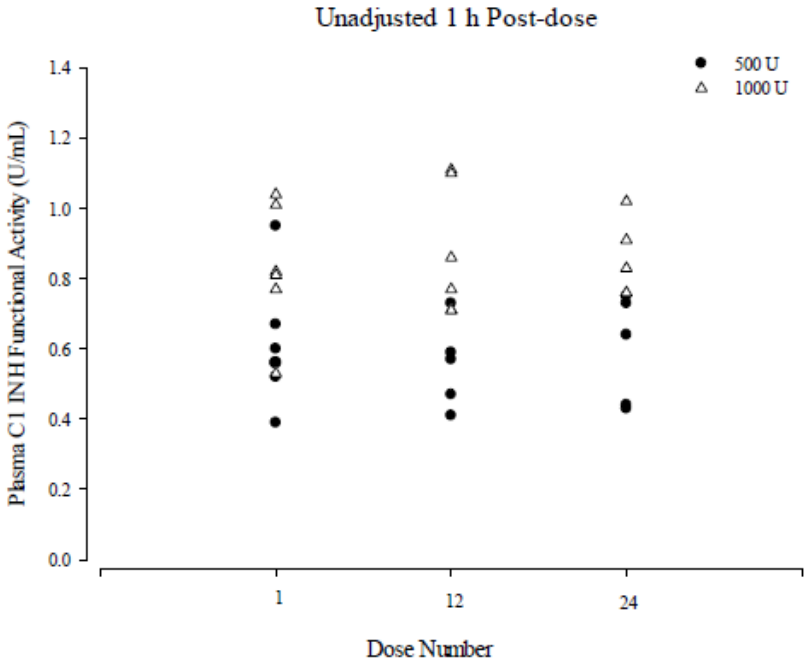


Figure 1. Unadjusted individual plasma C1 INH Functional Activity 1h post-dose at dose 1,12, and 24 following administration of 500 U and 100 U Cinryze

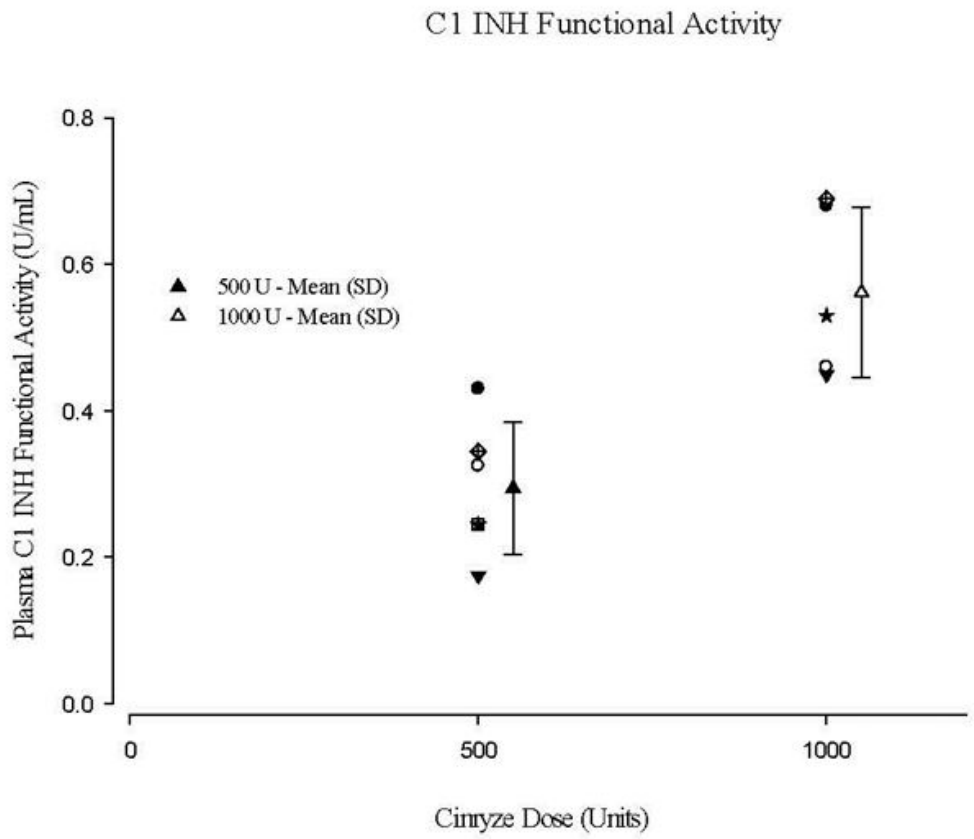


Figure 2. Individual of Average and Mean (SD) Plasma C1 INH Functional Activity (adjusted by pre-dose levels corresponding to the same dose) 1 h Post-dose at Dose 12 and Dose 24 versus Cinryze treatment

At steady-state, mean increases in C1 INH functional activity from baseline (before the first dose of investigational product in treatment period 1) at pre-dose ranged from 0.145±0.152 U/mL (Dose 12) to 0.108±0.081 U/mL (Dose 24), and from 0.210±0.098 U/mL (Dose 12) to 0.264±0.162 U/mL (Dose 24) for the 500 U and 1000 U doses, respectively. In addition, mean increases in C1 INH functional activity (adjusted by pre-dose levels corresponding to the same dose) at 1 h post-dose ranged from 0.262±0.082 U/mL (Dose 12) to 0.298±0.087 U/mL (Dose 24), and from 0.552±0.111 U/mL (Dose 12) to 0.545±0.129 U/mL (Dose 24), for the 500 U and 1000 U doses, respectively. Exposure to Cinryze as evaluated by C1 INH functional activity was demonstrated in every subject.

Table 3. Individual and Mean (SD) Pre-dose C1 INH Functional Activity at Dose 12 and 24 for 500 U and 1000 U of Cinryze

Individual Subject Data	Baseline-adjusted Pre-dose C1 INH Functional Activity (U/mL)			
	500 U		1000 U	
	Dose 12	Dose 24	Dose 12	Dose 24
	0.240	0.210	0.320	Missing
	0.110	0.140	0.050	0.450
	0.400	0.150	0.220	0.230
	0.000	0.010	0.210	0.410
	0.110	0.130	0.300	0.160
	0.010	0.010	0.160	0.070
Mean ± SD	**0.145 ± 0.152**	**0.108 ± 0.081**	**0.210 ± 0.098**	**0.264 ± 0.162**

C1 INH=C1 inhibitor; SD=standard deviation; U=units

Note: Pre-dose levels are baseline-corrected (ie, adjusted for level obtained prior to first dose of investigational product in treatment period 1).

Table 4. Individual and Mean (SD) 1 h Post-dose C1 INH Functional Activity at Dose 12 and 24 for 500 U and 1000 U of Cinryze

Individual Subject Data	Pre-dose adjusted 1 h Post-dose C1 INH Functional Activity (U/mL)			
	500 U		1000 U	
	Dose 12	Dose 24	Dose 12	Dose 24
	Missing	0.430	0.680	Missing
	0.260	0.230	Missing	Missing
	0.130	0.220	0.430	0.470
	0.340	0.310	0.490	0.430
	0.320	0.370	0.660	0.720
	0.260	0.230	0.500	0.560
Mean ± SD	**0.262 ± 0.082**	**0.298 ± 0.087**	**0.552 ± 0.111**	**0.545 ± 0.129**

C1 INH=C1 inhibitor; SD=standard deviation; U=units

Note: 1 h post-dose concentrations are adjusted for pre-dose levels corresponding to the same dose.

C1 INH Antigen Concentrations

Unadjusted individual C1 INH antigen concentration 1 h after Cinryze administration by dose number is presented, below. A composite statistical value was calculated by averaging the 1 h post dose C1 INH functional activity level at Dose 12 and 24 (baseline adjusted by the corresponding pre-dose levels) to illustrate the dose response in each subject following Cinryze 500 U and 1000 U IV administration (see below). When the Cinryze dose increased from 500 U to 1000 U, the average values of Dose 12 and Dose 24 functional C1 INH activity increased in the range of 41.5% to 157%.

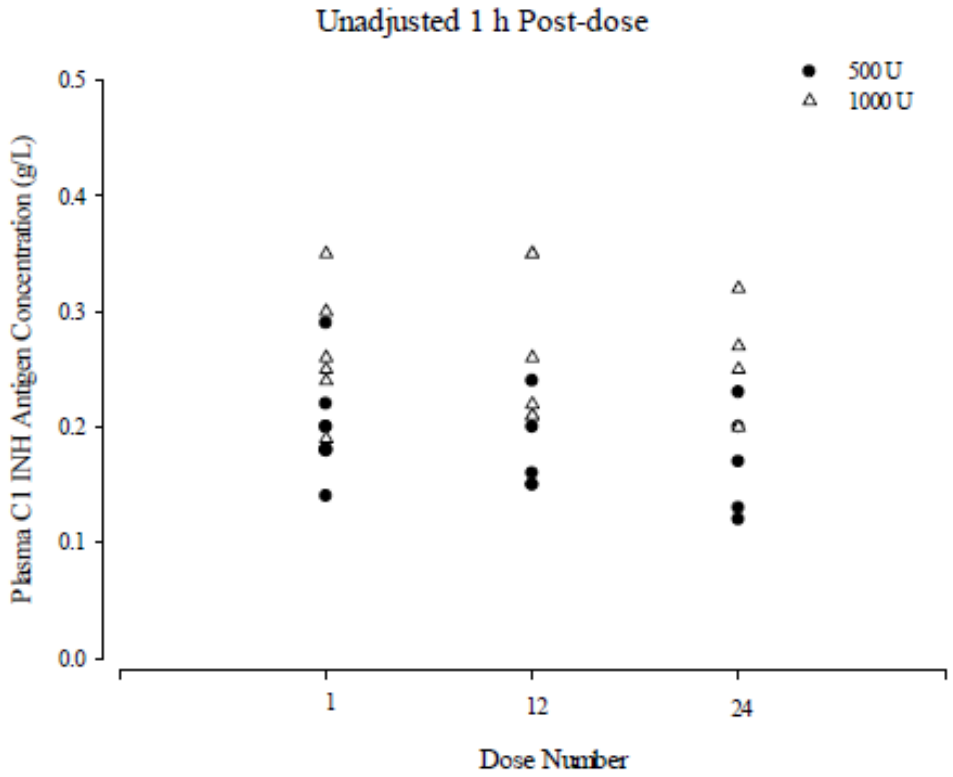


Figure 3. Unadjusted individual plasma C1 INH Antigen Concentration 1h post-dose at dose 1,12, and 24 following administration of 500 U and 100 U Cinryze

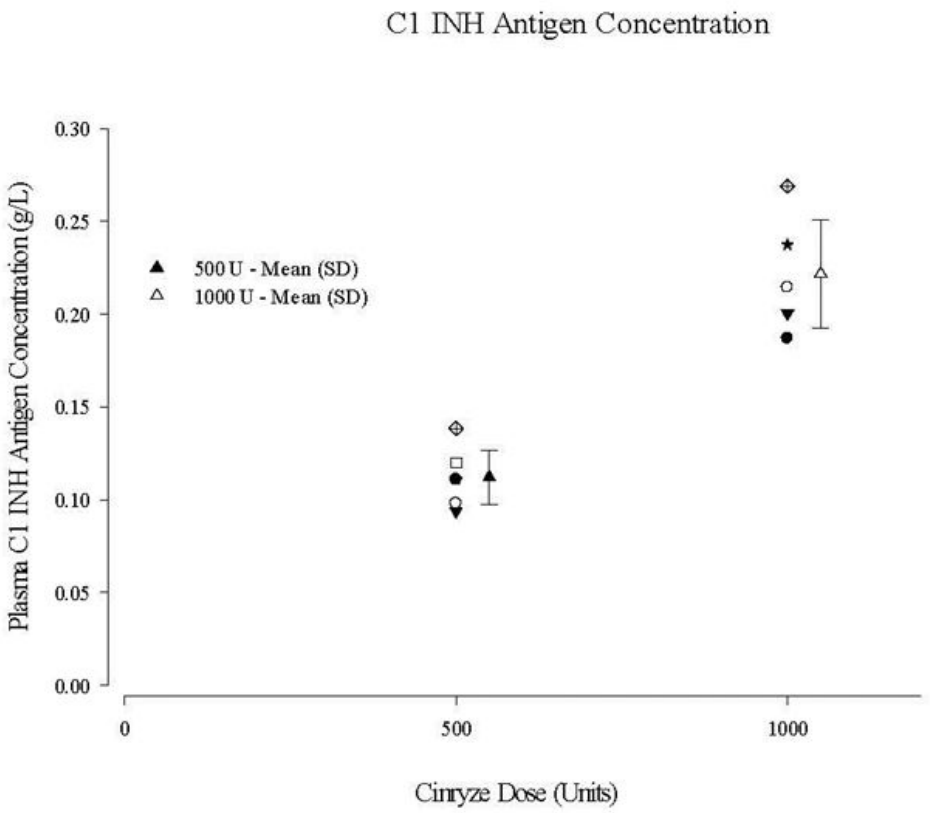


Figure 4. Individual of Average and Mean (SD) Plasma C1 INH Antigen Concentration (adjusted by pre-dose levels corresponding to the same dose) 1 h Post-dose at Dose 12 and Dose 24 versus Cinryze treatment

At steady-state, mean increases in C1 INH antigen levels from baseline (before the first dose of investigational product in treatment period 1) at pre-dose ranged from 0.145±0.152 U/mL (Dose 12) to 0.108±0.081 U/mL (Dose 24), and from 0.210±0.098 U/mL (Dose 12) to 0.264±0.162 U/mL (Dose 24) for the 500 U and 1000 U doses, respectively. In addition, mean increases in C1 INH functional activity (adjusted by pre-dose levels corresponding to the same dose) at 1 h post-dose ranged from 0.262±0.082 U/mL (Dose 12) to 0.298±0.087 U/mL (Dose 24), and from 0.552±0.111 U/mL (Dose 12) to 0.545±0.129 U/mL (Dose 24), for the 500 U and 1000 U doses, respectively. Exposure to Cinryze as evaluated by C1 INH functional activity was demonstrated in every subject.

Table 5. Individual and Mean (SD) 1 h Post-dose C1 INH Antigen Concentration at Dose 12 and 24 for 500 U and 1000 U of Cinryze

Individual Subject Data	Baseline-adjusted Pre-dose C1 INH Antigen (g/L)			
	500 U		1000 U	
	Dose 12	Dose 24	Dose 12	Dose 24
	0.049	0.008	0.082	Missing
	0.043	0.039	0.001	0.095
	0.053	0.008	0.037	0.028
	0.069	0.000	0.016	0.021
	0.016	0.015	0.088	0.132
	0.006	0.000	0.042	0.016
Mean ± SD	**0.039 ± 0.024**	**0.012 ± 0.013**	**0.044 ± 0.032**	**0.058 ± 0.047**

C1 INH=C1 inhibitor; SD=standard deviation; U=units

Note: Pre-dose levels are baseline-corrected (ie, adjusted for level obtained prior to first dose of investigational product in treatment period 1).

Table 6. Individual and Mean (SD) 1 h Post-dose C1 INH Antigen Concentration at Dose 12 and 24 for 500 U and 1000 U of Cinryze

Individual Subject Data	Pre-dose adjusted 1 h Post-dose C1 INH Antigen (g/L)			
	500 U		1000 U	
	Dose 12	Dose 24	Dose 12	Dose 24
	Missing	0.111	0.187	Missing
	0.082	0.076	Missing	Missing
	0.059	0.070	0.134	0.133
	0.055	0.086	0.128	0.173
	0.088	0.101	0.204	0.130
	0.076	0.070	0.153	0.169
Mean ± SD	**0.072 ± 0.014**	**0.086 ± 0.017**	**0.161 ± 0.033**	**0.151 ± 0.023**

C1 INH=C1 inhibitor; SD=standard deviation; U=units
Note: 1 h post-dose concentrations are adjusted for pre-dose levels corresponding to the same dose.

Effect of Cinryze Treatment on Complement C4 Concentrations

The effect of Cinryze treatment on the complement C4 levels was evaluated by the difference in complement C4 levels between baseline (prior to the first dose of Cinryze in Treatment Period 1) and pre-dose for Dose 12 and Dose 24 as steady-state (see Table, below). The levels of C4 were fluctuating over the treatment periods, suggesting no appreciable effect of Cinryze treatment on the C4 levels.

Table 7. Change from Baseline (Percent Increase) in Complement C4 Concentrations at Dose 12 and Dose 24 for 500 U and 1000 U of Cinryze

Individual Subject Data		Pre-dose Complement C4 Concentrations (mg/L)			
		500 U		1000 U	
	Baseline[a]	Dose 12	Dose 24	Dose 12	Dose 24
	75	95 (127%)	45 (60%)	125 (167%)	Missing
	120	30 (25%)	-10 (NC)	10 (8%)	90 (75%)
	50	60 (120%)	10 (20%)	41 (82%)	38 (76%)
	76	24 (32%)	-5 (NC)	24 (32%)	44 (58%)
	73	-11 (NC)	-12 (NC)	26 (36%)	22 (30%)
	42	19 (45%)	22 (52%)	68 (162%)	53 (126%)
Mean ± SD		**36.2±36.7**	**8.3±22.0**	**49.0±42.1**	**49.4±25.4**

NC=not calculated; SD=standard deviation; U=units
[a] Baseline concentrations obtained prior to first dose of investigational product in treatment period 1.

Effect of Body Weight on C1 INH Functional Activity and C1 INH Antigen Concentrations

C1 INH functional activity and plasma C1 INH antigen concentrations were assessed for the influence of subject's weight on these levels following Dose 12 and Dose 24 for both 500 U and 1000 U Cinryze. There appeared to be a slight trend towards lower systemic C1 INH functional activity and C1 INH antigen concentration exposure as body weight increased.

2.3.3. PK/PD modelling

Overview of Studies providing data for Population PK

The hereditary angioedema (HAE) Development Program for intravenous (IV) Cinryze supporting marketing approval included 8 clinical studies for treatment of angioedema attacks and routine prevention (prophylaxis) of angioedema attacks in adults (≥ 18 years of age), adolescents (12-17 years of age), and children (2-11 years of age). In 2 new studies, 0624-301 and 0624-203 out of these eight studies, the

pharmacokinetic/pharmacodynamic (PK/PD) properties of C1 INH in HAE paediatric populations for the treatment and prevention indications have been investigated.

The specific objectives of this project were to perform population PK and exposure-response analyses to support dosing of IV Cinryze in paediatric patients for the prevention and treatment of HAE attacks.

Data from table 8 were to be included in the population PK analysis. Table 9 gives an overview of clinical studies providing data on the pharmacology of cinryze in the management of HAE in the paediatric population. Descriptive statistics of categorical demographic data and continuous baseline characteristics are summarized in Table 10.

Table 8. Clinical Studies Serving as Data Base for Population PK Analysis

Phase	Study ID	Route/Dose Regimen	Indication	Population (disease/age)	# Patients	PK/PD Samples	
Studies for the Prevention of HAE (n=4)							
3	2005-1/B	IV/1000 U; BIW	Prevention	Patients with HAE/from Study 2005-1/A with > 2 attacks	25	Pre and post-dose approxi- mately every 28 days	
3b	2006-4	IV/1000 U; BIW	Prevention	Patients with HAE/ > 1 years	146	Predose, 1 h post first dose; then every 12 weeks	
4	0624-400	IV/1500, 2000, 2500 U; BIW	Prevention	Patients with inadequately controlled HAE/ ≥6 years	20	Predose at day 1 and week 12 for each step	
3b	**0624-301**	IV/500, 1000 U; BIW for 12 weeks randomized to 500-1000 (2) or 1000-500 (4 subjects)	Prevention **Paediatrics**	Patients with HAE/ 6 to 11 years	**6**/12 completed	Predose, 1 h post dose at Week 1, Week 6 and Week 12	
Studies for the Treatment of Acute HAE Attacks (n=3)							
3	2005-1/A	IV/1000 U	Acute Treatment	Patients with HAE/ > 6 years	36 Placebo: 35	Predose, and 1, 4, and 12 to 24 h postdose	
3b	2006-1	IV/1000 U, repeat 1h apart	Acute Treatment	Patients with HAE/ 2-80 years	113	Predose, 1 h postdose at each acute treatment	
3b	**0624-203**	IV/500, 1000, 1500 U	**Paediatrics** Acute	Patients with HAE/ < 12 years (> 25	**9**	Predose, 1 and 24 h postdose	

			Treatment	kg and <10- 25 kg)			
Additional Study (PK/HAE)							
1	2006-5	IV/1000U, repeat 1h apart	PK/HAE	Patients with HAE/adults	27	Predose, 5 min, 1, 3 and 6 h and 1, 2, 4, 7 days	

Table 9. Overview of Clinical Studies Providing Data on the Pharmacology of Cinryze in the Management of HAE in the Paediatric Population

Study ID M5 location	Short Description	Phase	Study Design	Pediatric Subjects Dosed	Dosage Regimen	Duration of Dosage/ # Infusions
Treatment Studies						
0624-203 5.3.4.2	Treatment of acute HAE attacks in children <12 years	2	MC, OL, SD	9 6-11 years	10-25 kg: 1: 500 U IV (inclusive) 2: 1000 U IV[a] >25 kg: 3: 1000 U IV 4: 1500 U IV	Single-dose 9
LEVP 2005-1/A 5.3.5.1	Treatment of acute HAE attacks in subjects ≥6 years	3	MC, R, DB, PC	12[b] 6-17 years	Treatment: 1000 U IV or placebo; if no response at 60 minutes, second dose Pre-procedure: 1000 U IV	Single-dose 30
LEVP 2006-1 5.3.5.2	Treatment of acute HAE attacks with repeat exposure in subjects ≥1 year	3	MC, OL	24 2-17 years	Treatment: 1000 U IV if no response at 60 minutes, second dose Pre-procedure: 1000 U IV	Multiple doses 193
Prevention Studies						
0624-301[c] 5.3.5.2	Prevention of HAE attacks in children 6-11 years	3	MC, R, SB, DR	6 7-11 years	Twice/week for 12 weeks in 2 treatment periods. Randomized to: 500 U/1000 U IV or 1000 U/500 U IV	24 weeks 285
LEVP 2005-1/B 5.3.5.1	Prevention of HAE attacks in subjects ≥6 years	3	MC, R, DB, PC	4 9-17 years	Twice/week for 12 weeks in 2 treatment periods. Randomized to: placebo/1000 U IV or 1000 U/placebo	24 weeks 219
LEVP 2006-4 5.3.5.2	Prevention and treatment of HAE attacks in subjects ≥1 year	3	MC, OL	23 3-17 years	Prevention: Every 3-7 days 1000 U IV Treatment: 1000 U IV if no response at 60 minutes, second dose	Multiple doses 1795

DB=double-blind; DR=dose-ranging; HAE=hereditary angioedema; MC=multicenter; OL=open-label; PC=placebo-controlled; R=randomized; SB=single-blind; SD=single-dose.

[a] Although planned per protocol, the study was unable to enroll subjects at the 1000 U dose in the lower weight category.

[b] Fifteen pediatric subjects participated in the study, with 12 subjects having exposure to CINRYZE.

[c] Interim analysis for the first 6 subjects completing the study. Study 0624-301 is ongoing.

Table 10. Summary of Baseline Characteristics – Categorical and Continuous Data

Indication/Sub-Groups		Number of HAE Patients Participated in Individual Studies (N=414) (%)								Overall by Indication (N=354)
		LEVP 2005-1A	LEVP 2005-1B	LEVP 2006-1	LEVP 2006-4	LEVP 2006-5	0624-400	0624-203	0624-301	
Indication	PK/HAE	-	-	-	-	27 (100%)	-	-	-	27 (7.6%)
	HAE Treat.	79 (100%)	-	108 (100%)	-	-	-	9 (100%)	-	165 (46.6%)
	HAE Prevent.	-	25 (100%)	-	141 (100%)	-	19 (100%)	-	6 (100%)	162 (45.8%)
										Overall by Unique Subject ID (N=278)
Age Group	2-5 years	-	-	1 (0.9%)	2 (1.4%)	-	-	-	-	3 (1.1%)
	6-11 years	6 (7.6%)	1 (4%)	10 (9.3%)	10 (7.1%)	-	-	9 (100%)	6 (100%)	32 (11.5%)
	12-17 years	8 (10.1%)	3 (12%)	13 (12%)	12 (8.5%)	1 (3.7%)	2 (10.5%)	-	-	26 (9.4%)
	18-64 years	62 (78.5%)	20 (80%)	78 (72.2%)	111 (78.7%)	26 (96.3%)	16 (84.2%)	-	-	207 (74.5%)
	65+ years	3 (3.8%)	1 (4.0%)	6 (5.6%)	6 (4.3%)	-	1 (5.3%)	-	-	10 (3.6%)
Sex	Male	19 (24.1%)	3 (12%)	35 (32.4%)	32 (22.7%)	10 (37.0%)	6 (31.6%)	1 (11.1%)	-	79 (28.4%)
	Female	60 (75.9%)	22 (88.0%)	73 (67.6%)	109 (77.3%)	17 (63.0%)	13 (68.4%)	8 (88.9%)	6 (100%)	199 (71.6%)
Race	White	72 (91.1%)	23(92%)	88 (81.5%)	118 (83.7%)	24 (88.9%)	17 (89.5%)	9 (100%)	5 (83.3%)	236 (84.9%)
	Black	3 (3.8%)	1 (4.0%)	9 (8.3%)	8 (5.7%)	2 (7.4%)	1 (5.3%)	-	-	17 (6.1%)
	Latino	4 (5.1%)	1 (4.0%)	4 (3.7%)	13 (9.2%)	-	1 (5.3%)	-	-	16 (5.8%)
	Asian	-	-	2 (1.9%)	-	1 (3.7%)	-	-	-	2 (0.7%)
	Amer.Indian	-	-	5 (4.6%)	1 (0.7%)	-	-	-	-	5 (1.8%)
	Other	-	-	-	1 (0.7%)	-	-	-	1 (16.7%)	2 (0.7%)

N = 278 corresponds to unique subject ID
N = 354 corresponds to total number based on subject's participation in the PK/HAE, HAE Treatment and HAE Prevention studies (i.e., 27, 165 and 162, respectively). Note: subjects were not counted more than once per indication.
N = 414 corresponds to total number based on subject's participation in different studies,
For example, Subjects ID participated in 5 studies (i.e., counted five times for the n=414 population), and in 2 indications (counted twice for the n=354 population)

Study	UNIQUE SUBJECT ID	Indication
2005-1/A		TREATMENT
2005-1/B		PREVENTION
2006-4		PREVENTION
2006-1		TREATMENT
0624-400		PREVENTION

Covariate	Statistics	Descriptive Statistics								
		LEVP 2005-1A	LEVP 2005-1B	LEVP 2006-1	LEVP 2006-4	LEVP 2006-5	0624-400	0624-203	0624-301	Overall
Age (years) at Baseline	n	79	25	108	141	27	19	9	6	278
	Arithmetic Mean	37.0	38.9	33.7	36.3	36	40.3	8.9	9.9	34.4
	SD	16.1	16.2	17.4	16.6	10.8	15.9	1.6	1.7	17.1
	Arithmetic CV%	43.7	41.6	51.6	45.6	30	39.4	18.1	17.4	49.7
	Median	36.9	40.1	34.9	35.9	35.5	40.7	9.1	10.8	35.1
	Min	6.3	9.2	2.5	3.2	17.3	14.7	6.4	7.3	2.5
	Max	74.8	73.4	80.9	82.7	57.4	73.4	11.0	11.2	82.7
Weight (kg) at Baseline	N	79	25	108	141	27	19	9	6	278
	Arithmetic Mean	77.7	79.1	73.7	74.9	79.2	84.8	33.8	34.5	73.8
	SD	24.5	24.1	23.7	20.5	22.6	21.5	11.6	9.5	24.0
	Arithmetic CV%	31.5	30.5	32.2	27.4	28.5	25.3	34.5	27.7	32.5
	Median	71.6	72.0	69.6	69.6	72.4	82.6	34.5	32	69.6
	Min	24.5	34.4	18.2	18.2	53.5	53.9	17.7	23.2	17.7
	Max	149.6	149.6	149.2	149.6	133.8	132.5	52.7	47.1	149.6

* For subjects with missing body weight at baseline, the median value in each age group by sex was used for imputation.
Median values for male subjects in the 2-5, 6-11, 12-17, 18-64 and >65 years group were 18.2, 33.6, 75.5, 97.5, and 99.8 kg, respectively.
No body weight values in female subjects were available in the 2-5 years group. Median values for female subjects in the 6-11, 12-17, 18-64 and >65 years group were 34.0, 60.7, 69.6, and 68.3 kg, respectively.

A total of 278 (out of 354) subjects (unique subject ID) treated with Cinryze were included in the population PK dataset. Of the 354 subjects, a total of 165 and 162 subjects were enrolled in studies designed for the treatment and prevention of HAE attacks, respectively, and a total of 27 HAE subjects were enrolled in the PK study (LEVP 2006- 5).

Of the 278 subjects included in the population PK analysis, 71.6% were female patients and 84.9% were of white origin. The combination of all studies provided a total of 61 paediatric patients (unique subject ID) with a total of 3, 32, and 26 subjects in the 2-5, 6-11 and the 12-17 years of age cohorts, respectively. Median (range) age and body weight were 35.1 years (2.5-82.7) and 69.6 kg (17.7 - 149.6), respectively. It is important to note that some subjects rolled-over in other studies. Baseline characteristics in these subjects were presented in the original study that they participated.

Considering the importance of assessing the effect of body weight and age in paediatric patients, the effect of missing body weight at baseline was explored. The number of patients with missing body weight at baseline is presented in Table 13.

From 278 subjects (unique subject ID) 3712 samples were assayed for C1INH, resulting in a total of 3617 measurable concentrations of C1INH included in the analysis. A total of 95 (2.6%) values were set to missing since concentrations were BLQ of the assay.

A comparison of pharmacokinetic and pharmacodynamic data in paediatric subjects (<18 years) across the treatment and prevention trials are provided in the two tables below (Table 11).

Table 11. Range of Observed C1INH functional Activity, C1INH Antigen and C4 Concentrations in Paediatric Subjects (<18 Years) in Studies LEV206-001 and 0624-203 (Treatment, left) and LEV206-4 and 0624-301 (Prevention, right)

Study	Treatment of HAE Attacks			
	LEVP 2006-1	0624-203		
CINRYZE Dose	1000 U	500 U	1000 U	1500 U
Body Weight	Not recorded	(10-25 kg)	(>25 kg)	
C1 INH functional activity (% or U/mL)[a]				
Pre-dose	0-54	<0.05-0.16	0.18-0.65	0.17-0.25
1 hour post-dose	53-94[b]	0.34-0.76	0.06-0.93	0.76-1.33
C1 INH antigen (mg/dL)				
Pre-dose	3.0-12.7	<2.9-3.8	3.8-20.0	3.4-6.2
1 hour post-dose	9.0-26.0[c]	12.1-17.4	3.7-21.0	18.7-34.0
Complement C4 (mg/L)				
Pre-dose	10-60	19-49	42-<61	21-74
1 hour post-dose	10-150	20-41	39-<61	23-69
24 hours post-dose	ND	78-102	96-138	63-160

Source: Module 5.3.5.2, LEVP 2006-1 CSR, Section 10, Table 10.3.5.4.2; Module 5.3.4.2, 0624-203 CSR, Section 11, Table 11.4.1

Note: The pre- and 1 hour post-dose range (minimum-maximum) of concentrations are provided for subjects who had both pre- and post-dose data. In Study LEVP 2006-1 mean concentration was summarized by attack number (1 through 32); therefore data shown is the range of mean concentrations across all attacks.

C1 INH=C1 inhibitor; dL=deciliter; L=liters; mg=milligrams; ND=not done; U=Units

[a] Units for C1 INH functional activity are U/mL for Study 0624-203 and % for Study LEVP 2006-1.

[b] Post-dose levels correspond to 20 to 88% mean increase from baseline.

[c] Post-dose levels correspond to mean change from baseline of 6.0 to 20.0 mg/dL.

Study	Prevention of HAE Attacks		
	LEVP 2006-4	0624-301	
CINRYZE Dose	1000 U	500 U	1000 U
C1 INH functional activity (% or U/mL)[a]			
Pre-dose	30.8-70.0	0.07-0.50	0.06-0.81
1 hour post-dose	60.2-92.0[b]	0.39-0.95	0.53-1.11
C1 INH antigen (mg/dL)			
Pre-dose	6.5-19.7	4.7-17.1	3.9-19.0
1 hour post-dose	16.5-34.0[c]	11.7-29.0	18.5-35.0
Complement C4 (mg/L)			
Pre-dose	65-360	60-190	42-210
1 hour post-dose	56-360	52-190	39-190

Source: Module 5.3.5.2, LEVP 2006-4 CSR, Section 10, Table 10.3.5.4.2; Module 5.3.5.2, 0624-301 Interim CSR, Appendix 16, Listing 5.3 and Listing 5.5

Note: The pre- and 1 hour post-dose range (minimum-maximum) of concentrations are provided for subjects who had both pre- and post-dose data. In Study LEVP 2006-4 mean concentration was summarized at set time points throughout the study (Day 1 through Week 108); therefore data shown is the range of summarized mean concentrations.

C1 INH=C1 inhibitor; dL=deciliter; L=liters; mg=milligrams; ND=not done; U=Units

[a] Units for C1 INH functional activity are % for Study LEVP 2006-4 and U/mL for Study 0624-301.

[b] Post-dose levels correspond to 22 to 46% mean increase from baseline.

[c] Post-dose levels correspond to mean change from baseline of 6.7 to 15.0 mg/dL.

Exploratory analyses were first performed to visually assess concentration-time profiles of C1INH. All studies had sparse sampling, with the exception of study LEVP 2006-5 which was a dedicated PK study in HAE patients with rich concentration-time profiles.

Individual concentration-time profiles of C1INH following single and two consecutive doses of Cinryze are presented in Figure 5.

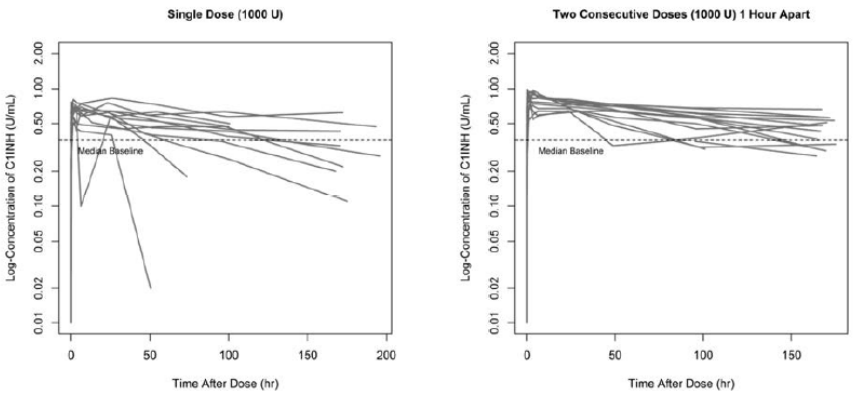


Figure 5. Observed Concentration-Time Profile of Functional C1INH (Study LEVP 2006-5, PK Study)

Population PK Modeling of Functional C1INH and Model Evaluation

Pop PK Approach

A population PK analysis of C1INH was performed based on data collected paediatric patients for the prevention (Protocol 0624-301; N=6) and treatment (Protocol 0624-203; N=9) of HAE attacks.

Due to the limited sample size of subject enrolled in younger age cohorts of Protocol 0624-301 and 0624-203, the dataset was enriched by including PK data collected in paediatric and adult patients with HAE enrolled in other clinical studies.

A one-compartment model, with baseline C1INH levels was used to assess the concentration-time profiles of functional C1INH following IV dosing of Cinryze. The population PK models included theoretical allometric functions on clearance (CL) and volume of distribution (V) of functional C1INH:

$$CL_i = CL \times \left(\frac{WT_i}{70}\right)^{0.75} \text{ and } Vc_i = Vc \times \left(\frac{WT_i}{70}\right)^{1.0}$$

The above allometric function with fixed body weight (WT) effect on CL and V was used to scale PK parameters in paediatric subjects.

The base and final model parameters after inclusion of covariates are presented in Table 12.

Table 12. Base and Final Model Including Covariates

Parameter	Units	Estimate	SE	RSE	CI95%	Shrinkage	Equation
OFV		-9403.0465					
CL	L/hr	0.0807	0.00599	7.4%	0.0690-0.0924		CL=tvCL·(Weight/70)$^{0.75}$
V	L	3.60	0.122	3.4%	3.36-3.84		V=tvV·(Weight/70)
BL	U/mL	0.331	0.0121	3.6%	0.307-0.355		BL=tvBL
BSV_CL		0.234(51.3%)	0.0775	33.2%	0.0817-0.385	56.4%	CL=CL·exp(ηCL)
BSV_V		0.131(37.5%)	0.0277	21.0%	0.0773-0.186	29.4%	V=V·exp(ηV)
BSV_BL		0.207(47.9%)	0.0256	12.4%	0.157-0.257	11.2%	BL=BL·exp(ηBL)
ResErr	U/mL	0.143				5.9%	C=Cpred+ResErr

BL = baseline C1INH; BSV: between-subjects variability; CL: clearance of functional C1INH; OFV: objective function value, ResErr = residual error model; RSE: relative standard error; V: central volume of distribution of functional C1INH.
NOTE: ω^2% were calculated as sqrt(exp(ω^2)-1)

Parameter	Units	Estimate	SE	RSE	CI95%	Shrinkage	Equation
OFV		-10727.8648					
CL	L/hr	0.105	0.00806	7.7%	0.0893-0.121		CL=tvCL·(Weight/70)$^{0.75}$
V	L	3.13	0.0877	2.8%	2.96-3.30		V=tvV·(Weight/70)
BL	U/mL	0.346	0.00852	2.5%	0.329-0.363		BL=tvBL
ASS_CL		-0.450	0.120	26.7%	-0.686--0.214		CL=CL·exp(ASS_CL) if new assay
COH_CL		-0.823	0.141	17.1%	-1.10--0.547		CL=CL·exp(COH_CL) if Study 2006-5
SEX_BL		-0.0687	0.0270	39.4%	-0.122--0.0157		BL=BL·exp(SEX_BL) if Female
AGEGRP1_V		0.319	0.106	33.2%	0.112-0.526		V=V·exp(AGEGRP1_V) if 2-6 yrs
AGEGRP2_V		0.196	0.0611	31.2%	0.0759-0.315		V=V·exp(AGEGRP2_V) if 6-12 yrs
RACE_V		-0.160	0.0534	33.3%	-0.265--0.0557		V=V·exp(RACE_V) if not white
BSL_BL		2.40	0.0980	4.1%	2.20-2.59		BL=BL·(1+BSL_BL·(BSL-0.32))
BSL_V		1.18	0.0795	6.8%	1.02-1.33		V=V·(1+BSL_V·(BSL-0.32))
TDOSEWT_V		0.346	0.0482	13.9%	0.252-0.441		V=V·(TDOSEWT/14.3)$^{TDOSEWT\_V}$ if dose>0
BSV_CL		0.134(37.9%)	0.0368	27.5%	0.0619-0.206	58.5%	CL=CL·exp(ηCL)
BSV_V		0.0512(22.9%)	0.0170	33.2%	0.0179-0.0845	33.2%	V=V·exp(ηV)
BSV_BL		0.0119(10.9%)	0.00456	38.3%	0.00295-0.0208	41.8%	BL=BL·exp(ηBL)
ResErr	U/mL	0.129				3.7%	C=Cpred+ResErr

ASS: functional assay; AGEGRP1: 2- 5 years; AGEGRP2: 6- 11 years; BSL: baseline C1INH; BSV: between-subjects variability; CL: clearance of functional C1INH; COH: cohort (PK population, study 2006-5 only); OFV: objective function value; ResErr = residual error model; RSE: relative standard error; TDOSEWT: total dose, weight adjusted (centered for 14.3 U/kg, i.e., 1000U/70kg), V: central volume of distribution of functional C1INH.
NOTE: ω^2% were calculated as sqrt(exp(ω^2)-1)

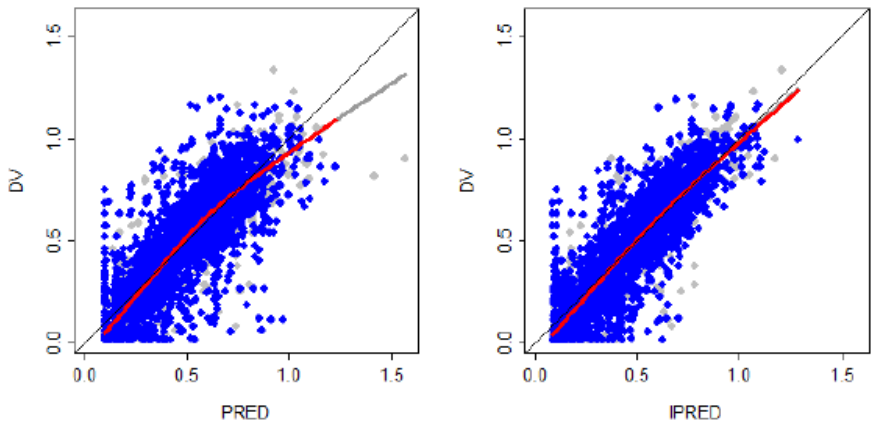
Evaluation of the base and final 1-compartment pop PK model

Model evaluation and selection were based on standard model diagnostics and goodness-of-fit criteria and by looking at pertinent graphical representations of goodness-of-fit (e.g. fitted and observed concentrations versus time) as depicted in Figure 6.

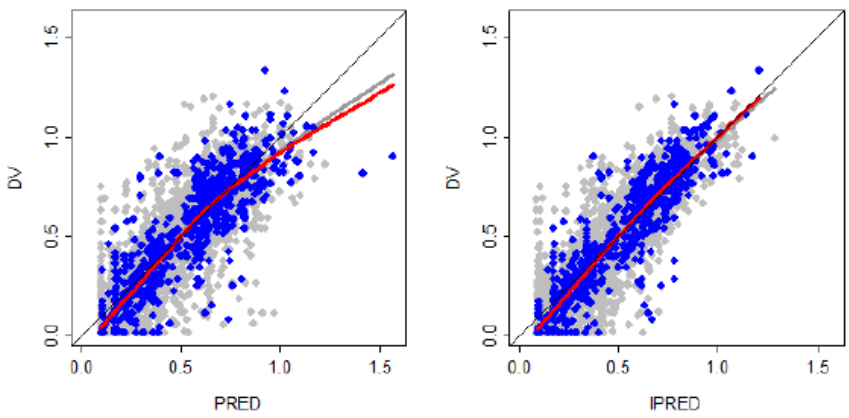
The quality-of-fit of the *base* model was evaluated using standard graphical representations of goodness-of-fit (e.g. fitted and observed concentrations versus time, conditional weighted residuals). The following diagnostic plots were derived:

- Observed data (DV) versus population predicted data (PRED) and individual predicted data (IPRED) with a line of unity and a trend line.
- DV versus time after first administration (Time) and DV versus time after previous dose (TAD) with trend lines for IPRED and PRED.
- Conditional weighted residuals (CWRES) versus PRED, versus TAD and versus Time.
- Quantiles-quantiles plot of CWRES (QQ plot).

The *final* population PK models was additionally qualified using a visual predictive check (VPC) to determine whether the model can appropriately simulate concentrations of C1INH within the range of those observed in the studies.



adults



paediatrics

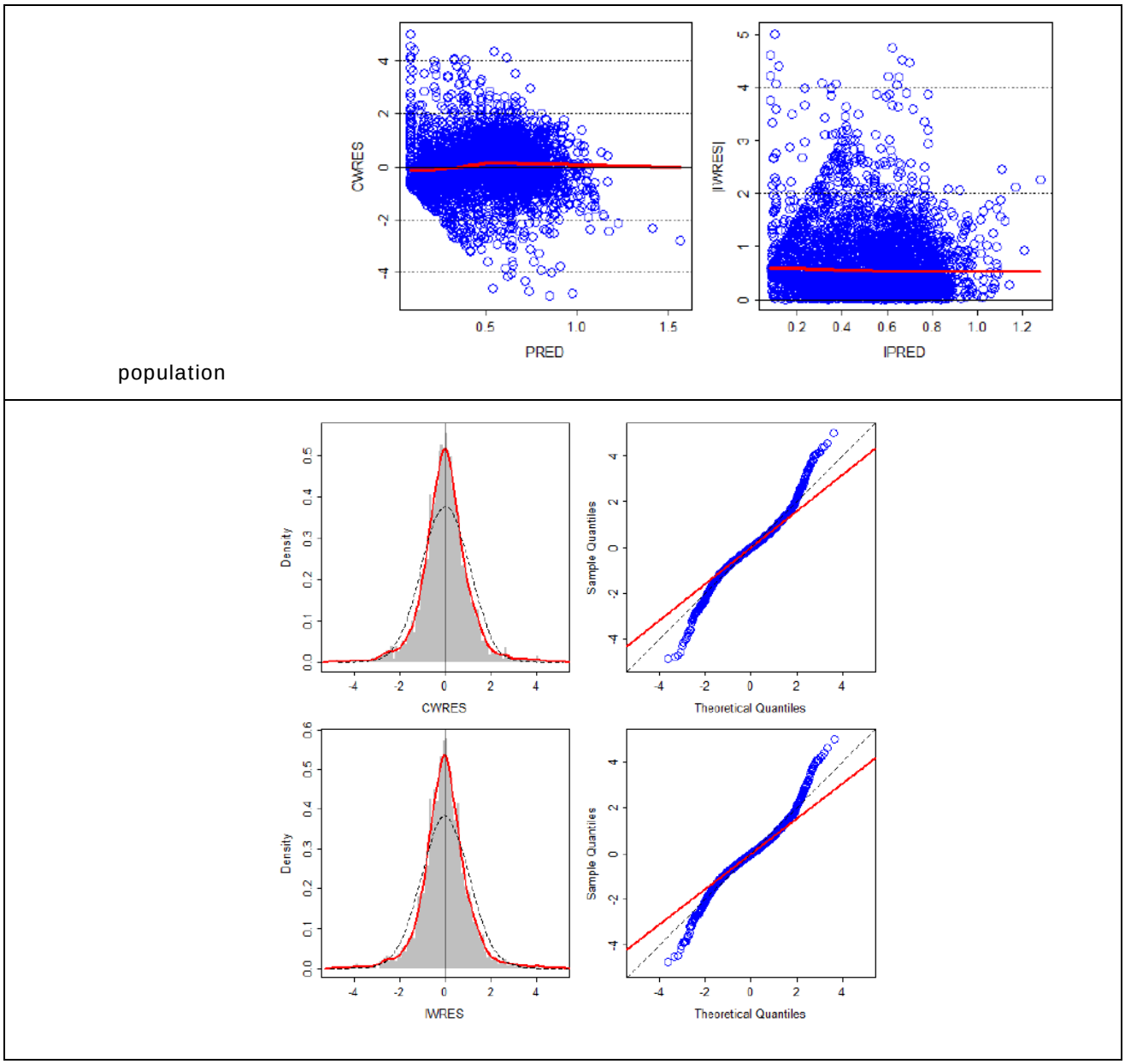


Figure 6. Diagnostic Plots

Covariate Analyses – Special populations

A covariate analysis was performed to assess sources of variability in the overall patient population. The following covariates were explored:

- Intrinsic Factors: Body Weight (as per allometric model), Age continuous, after taking into account body weight, Age categorical (2-5, 6-11 vs. 12-17 vs. adult), after taking into account body weight, Sex, Race, Baseline level of C1INH (as a single measure or average of pre-dose when available), Studies Designed for 1. Prevention of HAE 2. Treatment of HAE acute attacks 3. PK/HAE, HAE Attacks (Yes, No)
- Extrinsic Factors: Dose, LEVP Study (% activity converted to U) vs. non-LEVP study (U).

The population PK model was used to derive exposure parameters of C1INH in various paediatric age cohorts and sub-populations of interests (race and sex) and ultimately compare exposure to adult patients with HAE.

The relationships between covariates and PK parameters were firstly explored graphically to obtain information of covariates likely to affect the PK of functional C1INH. Scatter matrix plots presenting the relationships between the individual random effect of CL, V and endogenous C1INH and the continuous variables included locally weighted scatter plot smoothing (LOESS), Pearson correlation coefficients, and the corresponding p-value for each relationship. Box plots were used to describe the relationship for categorical covariates.

In a second step, covariates were included in the full model based on scientific or clinical interest, mechanistic plausibility, a priori knowledge about covariate effects and greatest correlation with post hoc PK parameters. Continuous covariates (i.e., observed baseline C1INH, and age) were included in the structural model with the following power function:

$$\theta_{in} = \theta_{TVn} \cdot \exp(\eta_{in})$$

$$\theta_i = \theta_{Typical} \cdot \left(\frac{Cov_i}{Cov_{\text{reference value}}} \right)^{\theta_{eff}}$$

where θi is the population value for subjects with covariate equal to Covi, θTypical is the typical value of the PK parameter for subjects having the covariate equal to the reference value (Covreference) and θeff is the effect values of the covariate on parameter θ. Categorical covariates were introduced into the model using an "if statement".

Body weight

Considering the importance of assessing the effect of body weight and age in paediatric patients, the effect of missing body weight at baseline was explored. The number of patients with missing body weight at baseline is presented in Table 13.

Overall, a total of 20 paediatrics unique subject ID had missing body weight information at baseline. For subjects with missing body weight at baseline, a model-independent approach was used to enrich the datasets by imputing median body values in each group. Median values for male subjects in the 2-5, 6-11, 12-17, 18-64 and >65 years group were 18.2, 33.6, 75.5, 97.5, and 99.8 kg, respectively.
No body weight values in female subjects were available in the 2-5 years group. Median values for female subjects in the 6-11, 12-17, 18-64 and >65 years group were 34.0, 60.7, 69.6, and 68.3 kg, respectively.

Table 13. Number of Subjects with Missing Body Weight at Baseline in Each Study

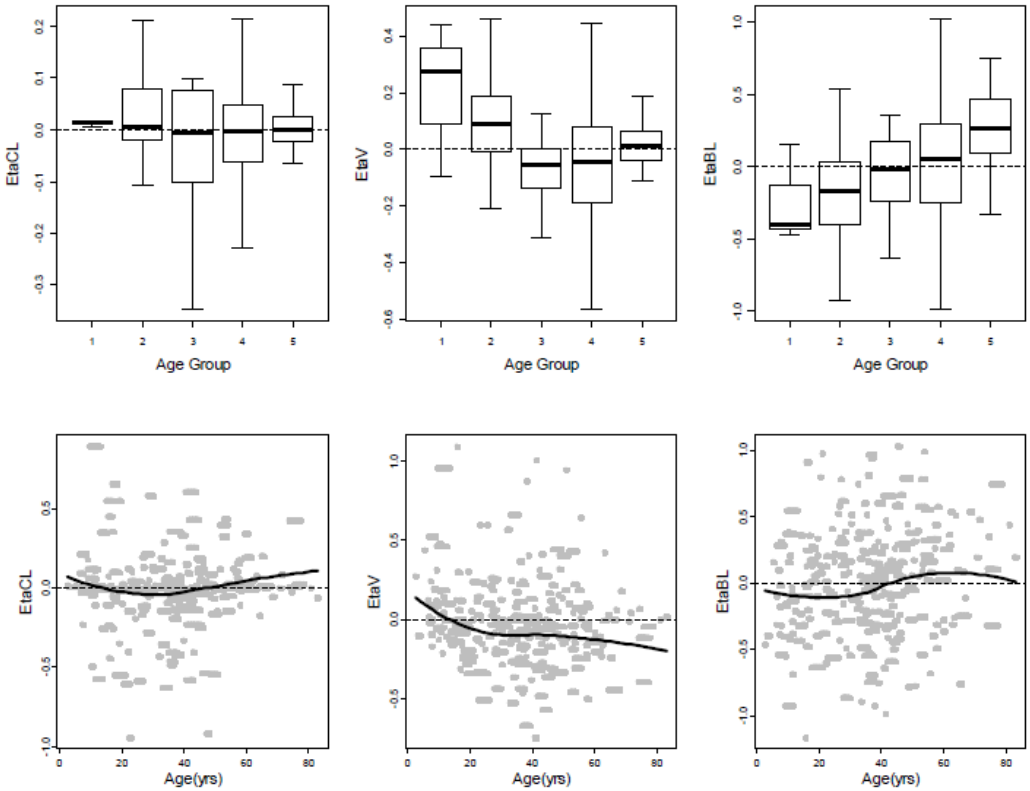
Age Group (years)	Weight Recorded (Y/N)	Number of Subjects with Missing Body Weight by Study							
		2005-1A	2005-1B	2006-1	2006-4	2006-5	0624-400	0624-203	0624-301
2-5	Y	-	-	-	-	-	-	-	-
	N	-	-	**1**	**2**	-	-	-	-
6-11	Y	9	1	6	6	-	-	9	6
	N	-	-	**4**	**4**	-	-	-	-
12-17	Y	16	3	9	7	1	2	-	-
	N	-	-	**4**	**5**	-	-	-	-
18+	Y	134	21	65	56	26	17	-	-
	N	**2**	-	**19**	**61**	-	-	-	-

A sensitivity analysis was performed by excluding patients with body weight imputation. The typical CL and V of C1INH were 0.096 L/h and 3.16 L based on the dataset without body weight imputation, respectively. Overall, these results suggest that body weight imputation did not affect the population estimates since typical population estimates were <10% of those observed without body weight imputation.

Age groups

Residual effects of age and body weight (after taking into account weight in the model) on the CL, V and baseline (BL) of C1INH are presented in the figure below.

For the BL and V of C1INH, a potential effect of age was observed in younger paediatrics (2-5 and 6-11 years) patients with HAE. The effect of age as a continuous parameter on V in younger patients was stronger than that observed for BL. The effects of age (categorical) on V were formally tested as part of the full model.

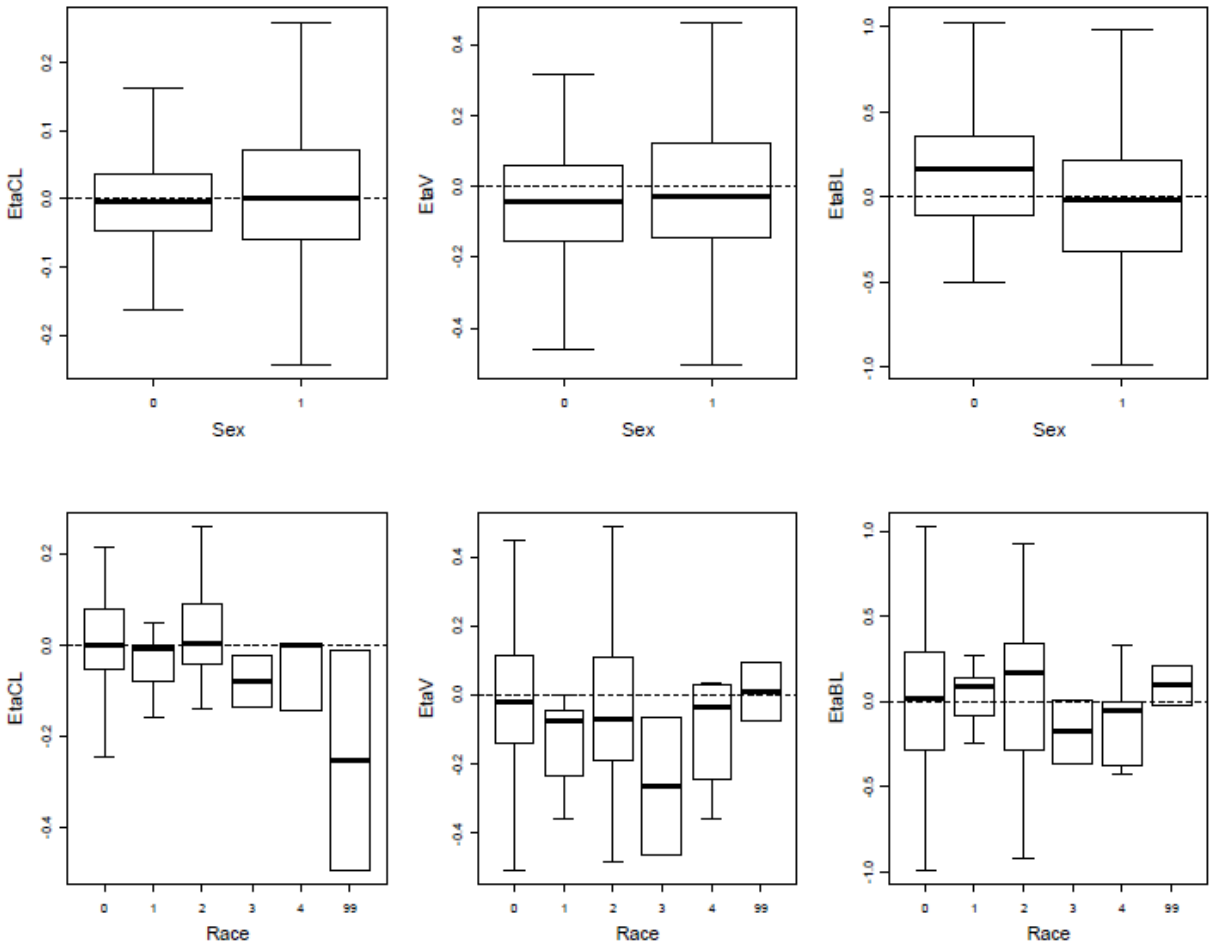


Legend: 1 = 2-5 years, 2 = 6-11 years, 3 = 12-17 years, 4 = 18-64 years, and 5= 65 + years

Figure 7. Effect of Age on PK Parameters of C1INH

Gender and Race

Residual effects of sex and race on the CL, V and baseline (BL) C1INH are presented in the Figure below. Results suggest a potential effect of sex on BL. Furthermore, race did not affect the V of C1INH, with the exception of Black (group 1) and Amer.Indian/Native (group 4). Results in Asian and other race should be interpreted with caution considering the very small sample size (i.e., 0.7% and 0.7% respectively). The effects of sex and race were formally tested as part of the full model.



Legend Top: 0 = Male, 1 = Females
Legend Bottom: 0 = White, 1 = Black, 2 = Latino, 3 = Asian, 4 =Amer.Indian/Native, 99 = Multiple/Other

Figure 8. Residual effects of sex and race on the CL, V and baseline (BL) C1INH

Dose and Baseline C1INH

Residual effects of dose (U/kg) and predose C1INH on the CL, V and baseline C1INH are presented in the Figure below. A positive relationship was observed between the Cinryze doses (U/kg) and V of C1INH. Positive trends were observed between baseline C1INH levels and V of C1INH. The significance of the above covariates on V was formally tested in the full model.

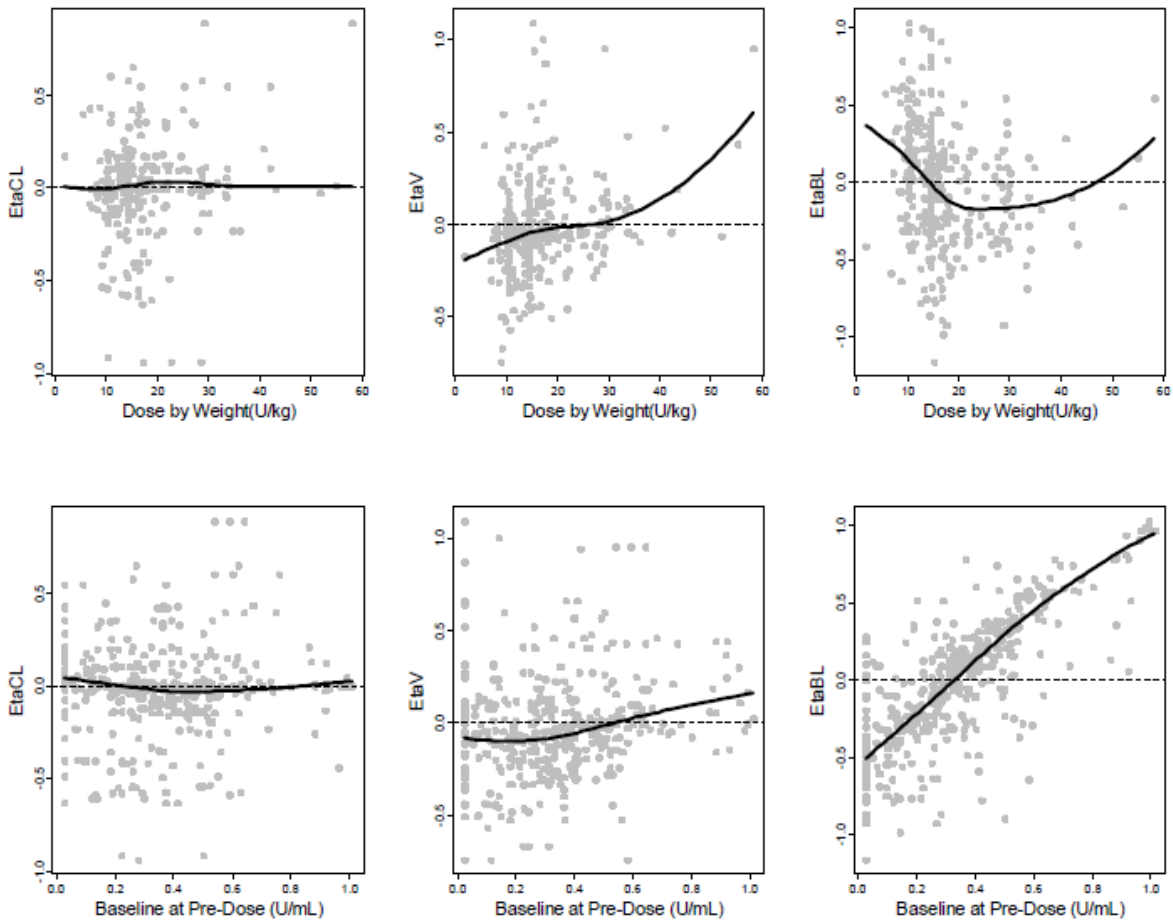


Figure 9. Residual effects of dose (U/kg) and predose C1INH on the CL, V and baseline C1INH

PK and PD Marker

Blood samples were collected for the assessment of antigenic and functional C1 INH (U/mL, PK) and Complement C4 levels (PD) in Study 0624-203 and Study 0624-301 (Table 11). Measurements were taken pre-infusion and 1 hour, and 24 hours after the start of the study drug infusion. The pharmacodynamics (PD) effects of Cinryze were evaluated in paediatric subjects with HAE, who lack a sufficient quantity or quality of C1 INH. This deficiency can lead to a reduction in the inhibition of activated complement component C1, in turn causing a decrease in complement C4 levels. Therefore, an increase in C4 levels may be a good measure of the PD effect of Cinryze.

In Study 0624-203, prior to the Cinryze dosing baseline levels of C1 INH functional activity ranged from <0.050-0.250 U/mL and C1 INH antigen ranged from <0.029-0.062 g/L. Following IV administration of 500, 1000, or 1500 U Cinryze, all subjects achieved increases in C1 INH plasma antigen and C1 INH functional activity above baseline values at 1 hour and 24 hours post-dose.

Complement C4 levels fluctuated over the treatment periods, suggesting no appreciable effect of Cinryze treatment.

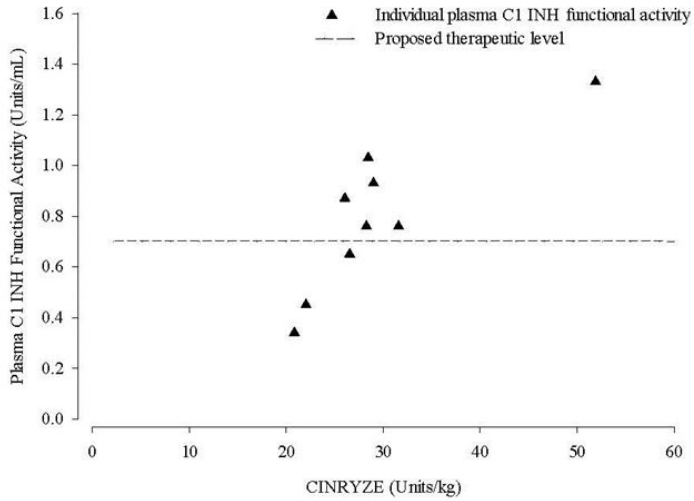
Dose proportionality and time dependencies

Study 0624-203 - Treatment

Prior to the Cinryze dosing baseline levels of C1 INH functional activity ranged from <0.050-0.250 U/mL and C1 INH antigen ranged from <0.029-0.062 g/L. Following IV administration of 500, 1000, or 1500 U Cinryze, all subjects achieved increases in C1 INH plasma antigen and C1 INH functional activity above baseline values at 1 hour and 24 hours post-dose (Table 11).

All subjects demonstrated an increase in C4 plasma concentrations above baseline at 24 hours post-infusion, indicating that administration of exogenous functional C1 INH was affecting the downstream complement cascade in all subjects.

An association between increasing dose (in U/kg) of Cinryze and increasing functional C1 INH activity was observed (see Figure 10).



Source: Section 11, Table 11.4.1

Figure 10. Individual Unadjusted C1 INH Functional Activity at 1 Hour Post-infusion Versus Cinryze Dose (U/kg) – ITT-S Population (Study 0624-203)

Study 0624-301 - Prevention

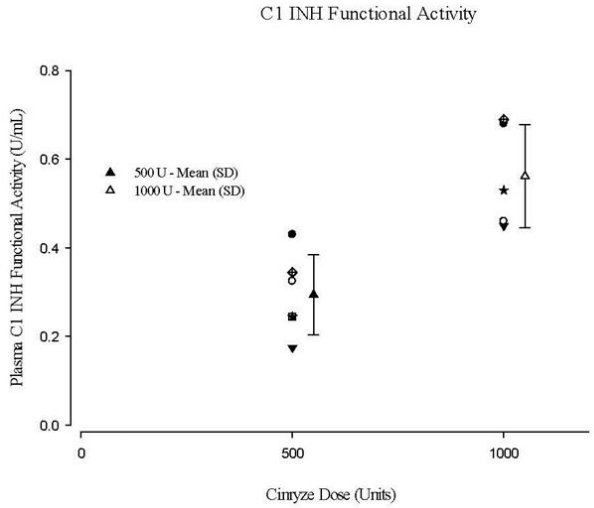


Figure 11. Individual of Average and Mean (SD) Plasma C1INH Functional Activity 1 Hour Post-dose For 500 and 1000 U IV Cinryze – ITT-S Population (Study 0624-301)

To illustrate the dose response in each subject following administration of 500 U and 1000 U IV Cinryze in Study 0624-301, a composite value was calculated by averaging the 1 h post-dose level at Dose 12 and Dose 24 (baseline adjusted by the corresponding pre-dose levels). When the dose increased from 500 U to 1000 U, the average values of Dose 12 and Dose 24 for functional C1 INH activity increased in the range of 41.5% to 157% (Figure 11).

At steady state, mean increases in C1 INH functional activity (adjusted by pre-dose levels corresponding to the same dose) at 1 h post-dose ranged from 0.262±0.082 U/mL (Dose 12) to 0.298±0.087 U/mL (Dose 24), and from 0.552±0.111 U/mL (Dose 12) to 0.545±0.129 U/mL (Dose 24), for the 500 U and 1000 U doses, respectively.

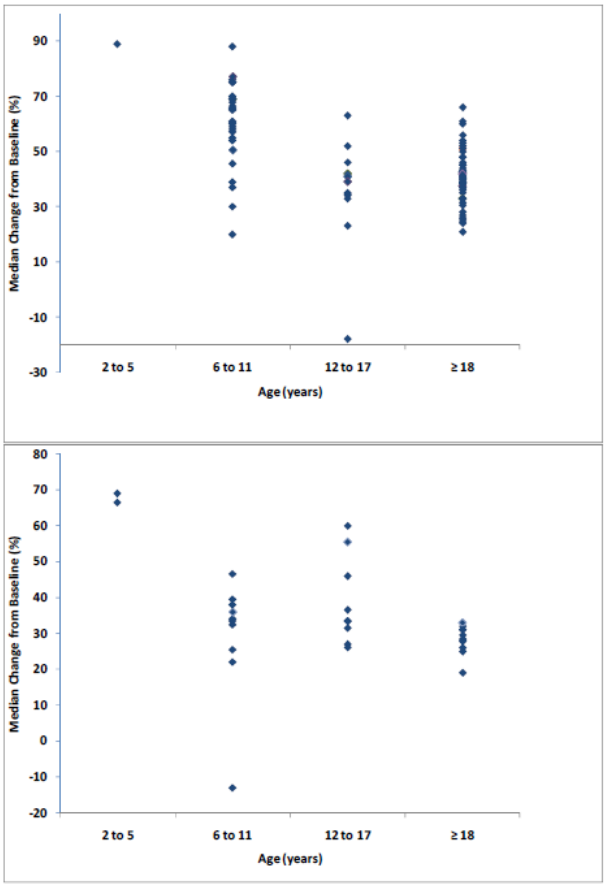
For C1 INH antigen, when the Cinryze dose increased from 500 U to 1000 U, the average values of Dose 12 and Dose 24 increased in the range of 68.5% to 119%. At steady state, mean increases in C1 INH antigen concentration (adjusted by pre-dose levels corresponding to the same dose) at 1 h post-injection ranged from 0.072±0.014 g/L (Dose 12) to 0.086±0.017 g/L (Dose 24), and from 0.161±0.033 g/L (Dose 12) to 0.151±0.023 g/L (Dose 24) for the 500 U and 1000 U doses, respectively.

Complement C4 levels fluctuated over the treatment periods, suggesting no appreciable effect of Cinryze treatment. However, no definitive conclusions could be drawn given that C4 levels historically show an increase >24 h after Cinryze administration and there was no comparative assessment of C4 levels during the baseline observation period.

Studies LEVP 2005-1/A, LEVP 2006-1, LEVP 2005-1/B and LEVP 2006-4

The incremental mean increase from baseline in functional C1 INH activity measured 1 hour post-dose in children 2 to <18 years of age ranged from 20% to 88% in Study LEVP 2006-1 (treatment) and from 22% to 46% in Study LEVP 2006-4 (prevention), compared with 21% to 66% and 25% to 32% in adults, respectively. The following figure illustrates the range of median change from baseline (pre- to post-infusion) in functional C1 INH in the three paediatric subgroups (ie, 2 to 5 years, 6 to 11 years, and 12 to 17 years, respectively) compared with adults (≥18 years) in Study LEVP 2006-1 (top) and Study LEVP

2006-4 (bottom). Comparison across subgroups should be interpreted with caution given the small number of paediatric subjects investigated and the heterogeneity within each subgroup.



Source: Adapted from Module 2.7.2 (MAA), Figure 6 and Figure 9.

Top: Symbols used to illustrate trending between various age groups in this figure represent median values for each acute attack number and not individual subject values.

Bottom: Within a given age range, each symbol represents the median change (for all subjects in that age range) in functional C1 INH values at specific time points during the study. Because subjects were followed for different periods of time, data are available from different numbers of time points in each age range.

Figure 12. Median change in functional C1 INH activity from pre to post infusion by age in studies LEVP 2006-1 (top) and LEVP 2006-4 (bottom)

Mean changes in levels of C1 INH antigen at 1 hour post-infusion in subjects <18 years of age ranged from 6.0 to 20.0 mg/dL in Study LEVP 2006-1 (treatment) and from 6.7 to 15.0 mg/dL in Study LEVP 2006-4 (prevention). The corresponding ranges in adult subjects were -11.0 to 16.0 mg/dL in Study LEVP 2006-1 (treatment) and 5.6 to 8.4 mg/dL in Study LEVP 2006-4 (prevention).

In addition, the increases in antigenic and functional C1 INH activity from pre- to post-infusion were generally similar for varying numbers of acute attacks in Study LEVP 2006-1, and were independent of duration of study participation in Study LEVP 2006-4, indicating consistent pharmacokinetics over repeated Cinryze administrations.

Complement C4 levels at 1 hour post-infusion were similar to values observed at pre-infusion in Studies LEVP 2006-1 and 2006-4, and did not appear to differ between age groups. This was not unexpected as previous studies (LEVP 2005-1/A and LEVP 2006-5) showed that C4 levels in HAE subjects do not increase appreciably until at least 12 hours and likely peak at around 48 hours post-infusion of exogenous C1 INH; therefore, 60 minute post-infusion C4 levels did not differ from baseline.

Exposure-Response Analyses

Objectives and Methodology

Exploratory exposure-response analyses for the prevention of HAE and treatment of HAE was to be performed based on studies listed in Table 8 with the exception of studies 2005-1/A and 2005-1/B due to the unblinded nature of the protocol.

For the prevention of HAE attacks, exposure-response analyses were performed for the following endpoint:

1) The probability of response (≤1 HAE attack/month). This response criterion was derived by averaging the number of HAE attacks over the study duration. If a subject rolled-over from one study to the next (for the prevention of HAE), the total duration was taken into account.

2) The time to the first HAE attack. If a subject rolled-over from one study to the next, time to the first HAE attack was available for each study. For these cases time to first averaged across studies for exposure-response analyses.

The above exploratory analyses were performed by plotting the probability of response as a function of exposure metrics of C1INH. The following exposure metrics under steady state were evaluated for the prevention program: area under the concentration-time curve from time 0 to 4 h under steady state conditions (AUC0-4,ss), minimum concentration under steady state conditions (Cmin,ss (predose)), maximum concentration under steady state conditions (Cmax,ss), and terminal elimination half-life (t1/2). The most predictive parameter was used for the final analysis.

Based on the above exploratory analysis, a logistic regression model was used to link the appropriate exposure metric to the probability of response. The following criteria were used to define responder status for the prevention of HAE program:

- Responders (subject deemed a "success"): ≤1.0 HAE attack/month
- Non-responders (subject deemed a "failure"): >1.0 HAE attack/month

The relationship between the exposure to C1INH and the probability of response (binary response: 0= non-responder and 1= responder) was modeled using a logistic regression model with the following form:

$$[\mathrm{P(Responder=1)}] = \left(\frac{\exp(F)}{1+\exp(F)} \right)$$

where F is called the logit and is a measure of the total contribution of all independent variables (exposure to C1INH) used in the model. The general functional form of the logit (F) used is:

$$\mathrm{F=Logit\{P(Responder=1)\}} = \gamma + Effect_{Exposure} \times Exposure + \varepsilon$$

Where:

γ = Intercept (i.e., the value of F without C1INH)

$Effect_{Exposure}$ = C1INH effect

$Exposure$= Exposure to C1INH

ε = Normally distributed error term

In addition, Kaplan-Meier plots were derived for the time to the first HAE attack by quartiles of PK for the prevention of HAE attacks.

For treatment of acute HAE attacks, exposure-response analyses were performed for the probability of relief of the defining symptom within 4 hours following initial treatment with Cinryze. The probability of response as a function of exposure metrics of C1INH was evaluated. The following exposure metrics after single dose were evaluated for the treatment of HAE attack program: area under the concentration-time curve from time 0 to 4 h (AUC0-4), maximum concentration (Cmax), time to maximum concentration (tmax) and t1/2 and the most predictive parameter was used for the final analysis.

- The following criteria were used to define responder status for the treatment of HAE program: Responders (subject deemed a “success”): relief of the defining symptom within 4 hours of Cinryze dosing
- Non-responders (subject deemed a “failure”): No relief of the defining symptom within 4 hours of Cinryze dosing

The relationship between the exposure to C1INH and the probability of response (binary response: 0= non-responder and 1= responder) was modeled using a similar logistic regression model. In addition, Kaplan-Meier plots were derived for the time relief of the defining symptom by quartiles of PK for the prevention of HAE attacks.

Exposure Predictions for Treatment of HAE Attacks

Using the final population PK model, actual dosing records and plasma concentrations of C1 INH (total functional activity, [ie, endogenous levels plus dosing effects of Cinryze]) for individual subjects, predicted single dose exposure to C1 INH for each subject following IV dosing with Cinryze as a function of age and dose for the prevention of HAE attacks (exposure-response population) was assessed and the results are presented in Table 14. For acute treatment of HAE attacks, some subjects (n=58) received a second dose of Cinryze at 1 hour after the first dose and exposure to these doses are summarized additionally.

Table 14. Predicted Exposure to C1INH Following Dosing of Cinryze as a Function of Age and Dose for Exposure-Response Analysis – Treatment of Acute HAE Attacks (Studies 2006-1 and 0624-203)

Age (years)	Dose	Number of Doses	Total Dose	Arithmetic Mean (Arithmetic CV%)						
				Baseline (U/mL)	CL (L/h)	V (L)	AUC_{0-4} (U·h/mL)	C_{max} (U/mL)	T_{max} (h)	$t_{1/2}$ (h)
2-5	500 U	2	1000 U (N=1)	0.101 (NA)	0.038 (NA)	0.991 (NA)	3.67 (NA)	1.09 (NA)	1.083 (NA)	18.0 (NA)
6-11	500 U	1	500 U (N=3)	0.129 (46.8)	0.028 (11.8)	0.964 (2.8)	2.46 (8.83)	0.647 (7.74)	0.083 (0.0)	24.5 (14.7)
	1000 U	1	1000 U (N=11)	0.188 (46.9)	0.056 (24.7)	1.881 (29.3)	2.85 (9.80)	0.757 (11.5)	0.167 (0.0)	23.9 (27.4)
		2	2000 U (N=5)	0.211 (43.7)	0.069 (23.5)	2.671 (36.1)	3.54 (15.1)	1.025 (17.8)	1.167 (0.0)	26.2 (16.7)
	1500 U	1	1500 U (N=3)	0.244 (16.8)	0.046 (22.4)	2.757 (21.8)	3.09 (14.0)	0.805 (14.3)	0.25 (0.0)	41.5 (5.74)
12-17	1000 U	1	1000 U (N=9)	0.315 (19.7)	0.094 (11.2)	2.661 (8.2)	2.64 (7.63)	0.692 (6.91)	0.167 (0.0)	19.8 (12.4)
		2	2000 U (N=8)	0.385 (47.2)	0.105 (32.7)	4.091 (35.4)	3.29 (13.9)	0.913 (12.5)	1.167 (0.0)	27.3 (26.7)
≥ 18 (Adults)		1	1000 U (N=63)	0.282 (51.7)	0.116 (18.0)	3.146 (35.2)	2.40 (14.6)	0.633 (13.1)	0.167 (0.0)	18.6 (23.7)
		2	2000 U (N=44)	0.305 (51.2)	0.115 (15.7)	4.041 (30.9)	2.97 (11.9)	0.836 (11.0)	1.167 (0.0)	24.2 (25.0)

AUC_{0-4}: area under the concentration-time curve from time 0 to 4 h, CL: clearance of functional C1INH, C_{max}: maximum concentration, NA: not applicable; T_{max}: time to maximum concentrations, $t_{1/2}$: terminal elimination half-life, V: central volume of distribution of functional C1INH.

Note: Cinryze was administered at a rate of approximately 1 mL (100 U/mL) per minute, i.e., 0.083-h for 500 U dose, 0.167-h for 1000 U dose, and 0.250-h for 1500 U dose.

In addition, using all data from both prevention (first dose) and acute treatment trials, the exposure to C1 INH following a single IV dose of Cinryze as a function of age, dose and body weight for the treatment of HAE (PK population) were simulated and are presented in Table 15.

Table 15. Predicted Exposure to C1INH Following Single Dose of Cinryze as a Function of Age Weight and Dose (Combined Indication).

Age / Weight		Mean Weight (kg) (CV%)	Dose	Arithmetic Mean (SD) (CV%)						
				Baseline (U/mL)	CL (L/h)	V (L)	AUC_{0-4} (U·h/mL)	C_{max} (U/mL)	T_{max} (h)	$t_{1/2}$ (h)
2-5 years		9.7 (72.0%)	500 U (n=3)	0.229 (0.222) (97.1%)	0.023 (0.012) (54.1%)	1.581 (1.514) (95.7%)	2.904 (0.375) (12.9%)	0.752 (0.111) (14.8%)	0.083 (0) (0)	41.7 (18.05) (43.3%)
			1000 U (n=3)	0.229 (0.222) (97.1%)	0.023 (0.012) (54.1%)	2.029 (1.943) (95.7%)	4.010 (1.047) (26.1%)	1.044 (0.290) (27.8%)	0.167 (0) (0)	53.5 (23.16) (43.3%)
6-11 years	10 to 25 kg	22.7 (9.2%)	500 U (n=7)	0.216 (0.100) (46.4%)	0.035 (0.009) (26.6%)	1.091 (0.172) (15.8%)	2.605 (0.194) (7.4%)	0.683 (0.048) (7.0%)	0.083 (0) (0)	22.1 (3.54) (16.0%)
			1000 U (n=7)	0.216 (0.100) (46.4%)	0.035 (0.009) (26.6%)	1.400 (0.221) (15.8%)	3.587 (0.190) (5.3%)	0.944 (0.050) (5.3%)	0.167 (0) (0)	28.4 (4.55) (16.0%)
	> 25 kg	43.0 (30.9%)	1000 U (n=35)	0.299 (0.156) (52.2%)	0.064 (0.021) (33.3%)	2.412 (0.898) (37.2%)	2.930 (0.336) (11.5%)	0.766 (0.088) (11.5%)	0.167 (0) (0)	27.0 (6.70) (24.8%)
			1500 U (n=35)	0.299 (0.156) (52.2%)	0.064 (0.021) (33.3%)	2.792 (1.039) (37.2%)	3.438 (0.397) (11.5%)	0.904 (0.112) (12.4%)	0.250 (0) (0)	31.2 (7.76) (24.8%)
12-17 years		68.7 (33.9%)	1000 U (n=38)	0.336 (0.154) (45.8%)	0.099 (0.025) (25.5%)	2.986 (0.845) (28.3%)	2.658 (0.394) (14.8%)	0.694 (0.093) (13.4%)	0.167 (0) (0)	21.2 (4.88) (23.0%)
			1500 U (n=38)	0.336 (0.154) (45.8%)	0.099 (0.025) (25.5%)	3.455 (0.978) (28.3%)	3.046 (0.359) (11.8%)	0.800 (0.086) (10.8%)	0.250 (0) (0)	24.5 (5.65) (23.0%)
≥18 (Adults)		81.1 (23.2%)	1000 U (n=304)	0.351 (0.181) (51.6%)	0.112 (0.021) (18.6%)	3.441 (1.074) (31.2%)	2.570 (0.484) (18.8%)	0.670 (0.114) (17.0%)	0.167 (0) (0)	21.4 (5.51) (25.8%)
			1500 U (n=304)	0.351 (0.181) (51.6%)	0.112 (0.021) (18.6%)	3.982 (1.243) (31.2%)	2.914 (0.437) (15.0%)	0.764 (0.104) (13.6%)	0.25 (0) (0)	24.7 (6.38) (25.8%)

Source: Module 5.3.5.3, Population PK and Exposure-Response Report, Appendix 3, Table 12.5:1

Note: A subject may be counted more than once if different dose levels were administered.

AUC_{0-4}=area under the concentration-time curve from time 0 to 4 h; CL=clearance of functional C1 INH; C_{max}=maximum concentration; CV=coefficient of variation; T_{max}=time to maximum concentrations; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; U=units; V=central volume of distribution of functional C1 INH

It is noted that PK data were available for 3 subjects with HAE between 2-5 years, but only 1 of 3 subjects was treated for an acute attack, and a second dose of Cinryze for this subject was administered at 1 hour after the first dose. The dose-exposure to C1 INH from these 3 subjects was included for the exposure assessment to enrich the PK dataset in this age group.

Exposure measurements (Table 14) were merged with the probability of response (relief of the defining symptom within 4 h of Cinryze dosing) as a function of Cinryze dose in studies 2006-1 (n=98 unique subjects ID with available response data) and 0624-203 (n=9 unique subjects ID with available response data) was explored in a first step. Response data from study 2005-1/A was removed from the exposure-response analysis due to the unblinded nature of the study, and the use of placebo. For patients with multiple attacks over time in study 2006-1, median time to relief was derived in each patient to determine the responder status. The probability of response by total dose is presented in Table 16.

Table 16. Probability of Response (Relief of the Defining Symptom within 4 h of Cinryze Dosing) by Age, Weight Cohort and Dose Level – Treatment of Acute HAE Attacks (Studies 2006-1 and 0624-203)

Age Group	Total Dose (U) [a,b]		Response (%)	Time to Relief (h)[c]		
				Responder	Median	Range
2-5 years	1000 (500 + 500 1 h after) (n=1)		100.0% (1/1)	Yes	3.58	NA
				No	-	-
6-11 years	10-25 kg	500 (n=3)	100.0% (3/3)	Yes	2.17	1.32 - 2.60
				No	-	-
		1000 (n=1)	100.0% (1/1)	Yes	0.75	NA
				No	-	-
	>25 kg	1000 (n=10)	90.0% (9/10)	Yes	1.18	0.75 - 2.17
				No	22.33	NA
		2000 (1000 + 1000 1 h after) (n=5)	60.0% (3/5)	Yes	2.00	1.50 - 3.50
				No	8.31	6.33 - 10.29
		1500 (n=3)	66.7% (2/3)	Yes	1.20	1.07 - 1.33
				No	102.33	NA
12-17 years	1000 (n=9)		100% (9/9)	Yes	1.00	0.50 - 1.25
				No	-	-
	2000 (1000 + 1000 1 h after) (n=8)		100% (8/8)	Yes	2.19	0.42 - 3.63
				No	-	-
18+ years (Adults)	1000 (n=63)		95.1% (60/63)	Yes	1.00	0.75 - 2.25
				No	12.79	10.83 - 48.00
	2000 (1000 + 1000 1 h after) (n=44)		84.1% (37/44)	Yes	2.09	1.17 - 4.00
				No	20.17	11.13 - 37.94

[a] As per Protocol 2006-1, if the attack did not abate by 1 h, a second dose of 500 or 1000 U open label Cinryze may have been administered
[b] A subject may be counted more than once if different dose levels were administered on several occasions of HAE attacks.
[c] Time to relief derived relative to 1 dose of Cinryze.
NA: not applicable

Relief of the defining symptom within 4 h of Cinryze dosing was observed in 100% (3/3) of patients treated with a single 500 U dose with a median time to relief of 2.17 h. The only subject who did not show improvement within 1 h following an initial 500 U dose (n=1), responded to treatment after receiving an additional 500 U dose 1 h after the initial dose, with a time to relief of 3.58 h.

Relief of the defining symptom within 4 h of Cinryze dosing was observed in 95.2% (79/83) of patients treated with a 1000 U dose. For subject who did not show improvement within 1 h following an initial 1000 U dose (n=57), an additional 1000 U dose of Cinryze resulted in a relief of the defining symptom within 4 h of Cinryze dosing in 84.2% of patients (48/57).

Relief of the defining symptom within 4 h of Cinryze dosing was observed in 66.7% (2/3) of patients treated with a single 1500 U dose.

Exploratory-exposure responses analyses were performed on the responder status (relief of the defining symptom within 4 h of Cinryze dosing) and time to relief. Due to the very low rate of failure, no exposure-response relationships were observed.

Exposure Predictions (Prevention)

Using the final population PK model, actual dosing records and plasma concentrations of C1 INH (total functional activity [ie, endogenous levels plus dosing effects of Cinryze]) of individual subjects, predicted steady-state exposure to C1 INH for each subject following IV dosing of Cinryze twice weekly as a function of age and dose for the prevention of HAE attacks (exposure-response population) was assessed and the results are presented in the following Table.

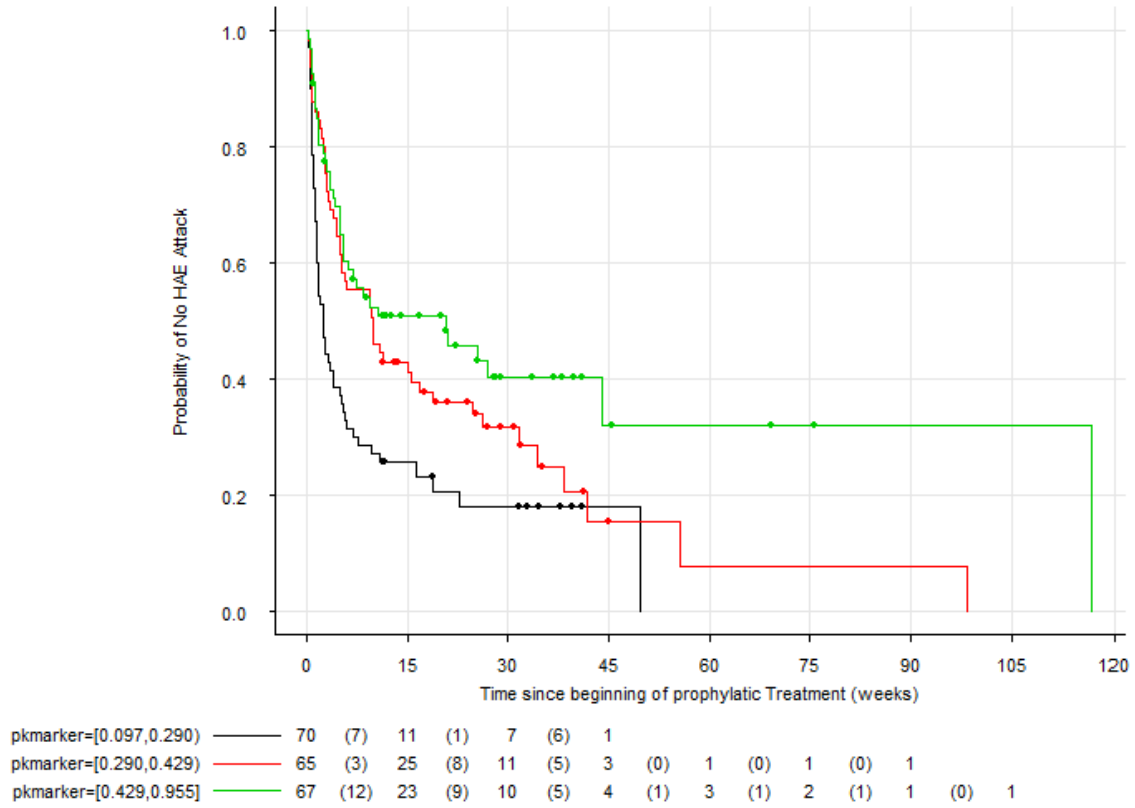
Table 17. Steady State Exposure to C1INH following Dosing of Cinryze as a function of Age Groups and Dose – Prevention of HAE (Exposure-Response Population)

Age (years)	Dose (BIW)	Arithmetic Mean (Arithmetic CV%)							
		Baseline (U/mL)	CL (L/h)	V (L)	$AUC_{0-4,ss}$ (U·h/mL)	$C_{max,ss}$ (U/mL)	$C_{min,ss}$ (Predose) (U/mL)	T_{max} (h)	$t_{1/2}$ (h)
2-5	500 U (n=1)	0.101 (NA)	0.038 (NA)	0.780 (NA)	2.75 (NA)	0.752 (NA)	0.112 (NA)	0.083 (NA)	14.1 (NA)
	1000 U (n=1)	0.486 (NA)	0.038 (NA)	2.226 (NA)	4.18 (NA)	1.073 (NA)	0.625 (NA)	0.167 (NA)	40.4 (NA)
6-11	500 U (n=6)	0.196 (44.1)	0.039 (20.8)	1.465 (22.4)	2.28 (13.2)	0.593 (12.7)	0.239 (37.5)	0.083 (0.0)	26.0 (10.2)
	1000 U (n=15)	0.304 (41.0)	0.059 (38.6)	2.358 (32.9)	3.22 (14.2)	0.839 (14.2)	0.378 (29.3)	0.167 (0.0)	28.8 (18.4)
12-17	1000 U (n=12)	0.360 (49.9)	0.099 (17.1)	3.135 (30.0)	2.79 (18.6)	0.727 (17.0)	0.384 (49.4)	0.167 (0.0)	21.8 (25.7)
	1500 U (n=2)	0.166 (61.2)	0.065 (12.5)	2.658 (29.0)	3.15 (5.42)	0.834 (7.21)	0.247 (44.7)	0.250 (0.0)	28.0 (16.8)
	2000 U (n=1)	0.094 (NA)	0.059 (NA)	2.334 (NA)	3.95 (NA)	1.062 (NA)	0.210 (NA)	0.333 (NA)	27.3 (NA)
	2500 U (n=1)	0.094 (NA)	0.059 (NA)	2.521 (NA)	4.59 (NA)	1.240 (NA)	0.254 (NA)	0.417 (NA)	29.4 (NA)
≥ 18 (Adults)	1000 U (n=114)	0.408 (44.1)	0.115 (15.8)	3.725 (29.1)	2.78 (19.1)	0.721 (17.5)	0.429 (43.9)	0.167 (0.0)	22.4 (24.7)
	1500 U (n=17)	0.171 (50.7)	0.078 (18.8)	3.099 (25.0)	2.83 (13.1)	0.750 (13.2)	0.239 (40.8)	0.250 (0.0)	27.4 (16.3)
	2000 U (n=12)	0.196 (46.0)	0.084 (15.6)	3.761 (20.5)	3.19 (12.9)	0.846 (12.7)	0.294 (37.8)	0.333 (0.0)	31.2 (17.6)
	2500 U (n=11)	0.184 (45.6)	0.083 (15.8)	3.987 (20.8)	3.63 (13.6)	0.969 (13.5)	0.320 (36.5)	0.417 (0.0)	33.5 (18.5)

$AUC_{0-4,ss}$: area under the concentration-time curve from time 0 to 4 h under steady state conditions, BIW: twice weekly; CL: clearance of functional C1INH, $C_{min,ss}$ (predose): minimum concentration under steady state conditions, $C_{max,ss}$: maximum concentration under steady state conditions, NA: not applicable; T_{max}: time to maximum concentrations, $t_{1/2}$: terminal elimination half-life, V: central volume of distribution of functional C1INH.
Note: Cinryze was administered at a rate of approximately 1 mL (100 U/mL) per minute, i.e., 0.083-h for 500 U dose, 0.167-h for 1000 U dose, and 0.250-h for 1500 U dose. BIW dosing interval set to 3.5 days.

Individual subject exposures to C1INH derived with the population PK model (AUC0-4,ss, Cmax,ss, and Cmin,ss (predose) and t1/2) were merged with the probability of response (≤1 HAE attack/month) in studies 2006-4 (n=141), 0624-400 (n=19) and 0624-301 (n=6) for an exploratory exposure-response analysis. Response data from study 2005-1/B was removed from the exposure-response analysis due to the unblinded nature of the study and the use of placebo. Logistic regressions on the probability of response (≤1 HAE attack/month) versus AUC0-4,ss, Cmax,ss, Cmin,ss (predose) and t1/2 were performed. No statistically significant relationships were observed for AUC0-4,ss, Cmax,ss and t1/2. On the other hand, a very strong and positive relationship was observed between Cmin,ss (p=0.0004) and the probability of response. When refractory subjects enrolled in study 0624-400 were removed from the analysis, the response across all Cmin,ss (predose) levels were very high.

The probability of No HAE attack over time was explored according to various PK parameters of C1INH (by tertiles). No exposure-response relationship was observed, with the exception of Cmin,ss (predose). The probability of No HAE attacks over time as a function of Cmin,ss (predose) tertiles is presented in Figure 13.



pkmarker = $C_{min,ss}$ (predose) in 1st (black), 2nd (red) and 3rd (green) tertiles.
Note: The lower part of the figure shows, for each tertile, the number of subjects still at risk for an HAE attack at the given time points and, in parentheses, the number of subjects censored between consecutive time points.

Figure 13. Probability of No HAE Attacks Over Time as a function of Cmin,ss (predose) Tertiles – Prevention of HAE Program (Studies 2006-4, 0624-400 and 0624-301)

Predose (Cmin,ss) values of C1INH in the 1st tertile (0.097 - 0.290 U/mL) were associated to the lowest probability of no HAE attack. Predose (Cmin,ss) values in the 3rd tertiles (0.429 – 0.955 U/mL) were associated to the highest probability of no HAE attack over time. Median time to a 50% probability of an HAE attack for the 1st, 2nd and 3rd tertiles of Cmin,ss (predose) were 2.43, 9.79, and 15.7 weeks, respectively. After removing study 0624-400, exposure-response relationships were observed for all exposure parameters.

2.3.4. Discussion on clinical pharmacology

The mechanism of action of C1 INH for relief of HAE attacks is not clear, yet, and based upon clinical effect in respective narrow patient-collective. Relevance of plasma-levels, trough- or peak-levels remains hypothetical.

Study 624-203

Blood samples for PK evaluation were taken prior to Cinryze injection, 1 hour and 24 hours post injection. No subject agreed to the additional but optional blood sampling necessary to obtain a PK profile for antigenic and functional C1 INH levels. As a result, no PK parameters were calculated for this study.

All 3 doses, 500, 1000 and 1500 IU, induced an increase of C1 INH activity and antigen after single-dose administration. One (1) of 3 subjects on 500 U and 5 of 6 subjects on 1500 and 1000 U achieved functional

C1 INH activities ≥0.7 U/ml at 1h p.i. which is assumed to represent an effective level. However, this target should be taken with caution as no dose-finding studies are available and the disease presents with inhomogeneous symptoms and responses.

Furthermore, an increase of Complement C4 has been achieved in all patients with a delay of more than 1 hour p.i. Such C4-increase might be interpreted as a PD effect of Cinryze.

Study 624-301

Samples were taken pre-infusion and 1 hour post- infusion for Dose 1 (week 1), 12 (week 6), and 24 (week 12) of each treatment period.

Both doses, 500 and 1000 IU, induced an increase of C1 INH activity and antigen. Data illustrate C1 INH elevation within a treatment regimen under study conditions but similar to a “prophylaxis regimen” under steady state conditions. Mean C1 INH activities 1h p.i. were 0.262-0.298 U/ml for 500 U and 0.5552-0.545 U/ml for 1000 U. Such numbers point to a dose-dependency, however; with large individual variability. Measurement of Complement C4 was chosen as a pharmacodynamics parameter. However, an effect was not demonstrated. This might be due to the short interval (24 hours p.i.), the test in place, or the restricted database, in general.

Results from 6 further subjects are awaited from this on-going study (see Section 2.6).

PK/PD modelling

Generally, paediatrics subjects are poorly reflected in the current analysis data set, especially children from age group 2-5 years of age as no subjects additional to the three already recruited patients were included since the initial MAA. For age group 6-11 years of age, 15 additional subjects were recruited; however, only sparse sampling data was collected. Full PK profiles are still only available for adult subjects. Nine (9) additional subjects have been recruited in study 0624-203 (treatment, receiving 500U, 1000U or 1500U IV) and 6 subjects in study 0624-301 (prevention, receiving 500U and/or 1000U BIW IV).

A population PK model was established to characterize the pharmacokinetics of Cinryze in paediatric age group, based on data collected in previous and new studies.

In total, 227 subjects were included in the analysis population; a total of 3, 32, and 26 subjects in the 2-5, 6-11, and 12-17 years of age cohorts, respectively. From these subjects, 3617 measurable concentrations of C1INH were included in the analysis. The final pop PK parameter suggest a typical 70 kg weighing subject to have CL, V and baseline C1INH values of 0.105 L/h, 3.13 L, and 0.346 U/mL, respectively. Model-based simulations for PK and exposure responses were conducted for indication treatment of HAE attacks and prevention separately.

PK exposure predictions are derived from the final pop PK model (one-compartment model with baseline C1INH levels) that seems to be miss-specified: Goodness-of-fit plots indicate that the inter-individual variability is only moderately captured and high percentage of shrinkage, that was detected for all estimates (> 20%, up to ~60%), suggest an over-parameterization. Body weight is structurally included (with fixed allometric exponents) and as covariate on volume. Measurement of bodyweight was missing for patients in the youngest age group (2-5 years) and partially lacking for all other age groups. Imputation of body weight seemed not to have a great impact on PK.

Comparison across subgroups should be interpreted with caution given the small number of paediatric subjects investigated and the heterogeneity within each subgroup.

Exploratory-exposure responses analyses were performed on the responder status (relief of the defining symptom within 4 h of Cinryze dosing) and time to relief. Due to the generally very low rate of failure, no

clear exposure-response relationships could be observed. A slight inverse relationship for exposure-response (decrease in percentage responders with increase in dose) could be detected. However, there are too few subjects investigated to draw quantitative conclusions.

Regarding prevention, the probability of No HAE attack over time was explored according to various PK parameters of C1INH (by tertiles). No exposure-response relationship was observed, with the exception of Cmin,ss (predose). After removing study 0624-400 (Phase 4 Study), exposure-response relationships were observed for all exposure parameters.

2.3.5. Conclusions on clinical pharmacology

Laboratory evaluation from both additionally submitted studies 624-203 and 624-301 demonstrate increase of C1 INH activity and C1 INH antigen with a dose-dependent effect. For study 624-203 a delayed increase of Complement C4 as a parameter for biologic activity has been demonstrated, in addition.

A population PK model was established and model-based simulations for PK and exposure responses were conducted for each indication treatment of HAE attacks and prevention, respectively.

Generally, paediatric subjects are poorly reflected in the analysis data set, especially children from age group 2-5 years. No new patients below the age of 6 years have been included since the data presented in the initial MAA. For age group 6-11 years, 15 additional subjects were sampled; however, only sparse sampling data was collected. Full PK profiles are only available for adult subjects. However, the CHMP acknowledges that the number of patients is extremely limited in the paediatric age-group due to the rarity of the condition, especially the 2-5 years, and, consequently, it will be difficult for the MAH to enrol further patients.

The conclusions on the dosing recommendations are discussed in Section 2.4.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study 624-203: Treatment

Open-label single-dose study to evaluate the response and pharmacokinetics/pharmacodynamics of different doses of CINRYZE [C1 inhibitor (human)] for treatment of acute angioedema attacks in children less than 12 years of age with hereditary angioedema (Protocol 0624-203)

Methods

This multicenter, open-label study was conducted at 6 sites in the US. Eligible subjects (2 to <12 years of age) who could initiate study drug treatment within 8 hours after onset of symptoms received treatment for a single acute HAE attack. Subjects may have been inpatient or outpatient. Qualified subjects received a single IV administration of CINRYZE; dosing was determined by subject weight category, as shown below. Individual doses could not exceed 100 U/kg.

Table 18. Study 624-203 – determination of dosing by subject weight category

Weight Category	CINRYZE Dose Group	Number of Subjects
10-25 kg (inclusive)	1: 500 U IV 2: 1000 U IV	3 3 [a]
>25 kg	3: 1000 U IV 4: 1500 U IV	3 3
a: No subjects in the lower weight category were enrolled into the 1000 U dose group.		

Within each of the two weight categories, the first 3 subjects treated were to receive the lower dose in that category, and the second 3 subjects treated were to receive the higher dose in that category. The study was open to enrolment within each of the two weight categories in parallel.

Beyond the single dose of CINRYZE administered in this study, additional treatment(s) for the HAE attack were permitted at the discretion of the investigator based on each subject's clinical response. However, for purposes of PK and efficacy assessments, use of additional medication specifically for treatment of HAE was ideally to be avoided through the 4-hour post-infusion assessment period.

The investigator determined the defining symptom (i.e., anatomical location) and overall severity of the HAE attack at baseline and rated the subject's overall response to treatment every 15 minutes after the start of the study drug infusion for a minimum of 1 hour. Assessments of response to treatment continued every 15 minutes until either the subject achieved relief sufficient to allow discharge from the study centre, or until 4 hours had elapsed post-infusion, whichever occurred earlier.

Pharmacokinetic/PD evaluations included assessment of antigenic and functional C1 esterase inhibitor (C1 INH) levels (PK) and C4 complement levels (PD). Safety was monitored through the recording of AEs and changes in physical examinations, vital signs (systolic and diastolic blood pressure and heart rate), and clinical laboratory testing. Investigators actively monitored subjects for possible venous thromboembolism (VTE), both deep venous thrombosis (DVT) and pulmonary embolism (PE), via medical history, physical examinations (including upper and lower extremity examinations), and laboratory testing.

Study participants

Eligible subjects (2 to <12 years of age) who could initiate treatment within 8 hours after onset of symptoms received Cinryze for treatment of a single acute attack. The IV doses of Cinryze evaluated were 500 U and 1000 U in children ≥10 kg to ≤25 kg and 1000 U and 1500 U in children >25 kg.

Treatments

CINRYZE was supplied as a lyophilized powder of 500 U (C1 INH)/vial for reconstitution with sterile water for injection. For all dose groups, subjects were to receive a single dose of CINRYZE, administered intravenously at a constant rate of approximately 1 mL (100 U)/minute, as tolerated.

Objectives

The objectives of the study were to evaluate (1) the dose response and (2) the pharmacokinetics (PK)/pharmacodynamics (PD) of intravenous (IV) administration of CINRYZE for the treatment of acute angioedema attacks in children above and below 25 kg and less than 12 years of age with hereditary angioedema (HAE); and (3) to determine the safety and tolerability following IV administration of CINRYZE in this study population.

Outcomes/endpoints

EFFICACY ASSESSMENTS: The investigator determined the defining symptom (i.e., anatomical location) and overall severity of the HAE attack at baseline, and rated the subject's overall response to treatment every 15 minutes after the start of the study drug infusion for a minimum of 1 hour. Assessments of response to treatment continued every 15 minutes until either the subject achieved relief sufficient to allow discharge from the study centre, or until 4 hours elapsed post-infusion, whichever occurred earlier. At each 15-minute interval, the investigator made an overall assessment of the symptoms/signs of the HAE attack relative to the previous assessment as: improved; unchanged; or worsened. The date and time of complete resolution of the HAE attack was recorded.

SAFETY ASSESSMENTS: Safety was monitored through the recording of AEs and changes in physical examinations, vital signs, and clinical safety laboratory testing. Investigators actively monitored subjects for possible VTE, both DVT and PE, via medical history, physical examinations (including upper and lower extremity examinations), and laboratory testing.

Statistical methods

Pharmacokinetics and Pharmacodynamics: Antigenic and functional C1 INH levels (PK) and C4 complement levels (PD) for individual subjects were evaluated using validated analytical methods. Results were summarized for each subject for change from pre- to post-infusion.

Efficacy: The primary efficacy endpoint was the presence of unequivocal beginning of relief of the defining symptom within 4 hours following initial treatment with CINRYZE. Secondary efficacy endpoints included time to unequivocal beginning of relief of the defining symptom and time to complete resolution of the HAE attack.

Summary statistics were provided for all efficacy endpoints by treatment dose groups and weight categories. No statistical test was performed for between treatment differences. Graphical presentations were provided, as appropriate. For all efficacy endpoints, the corresponding analyses were performed using the efficacy analysis population (ITT-E population).

Safety: Descriptive statistics (e.g., N, mean, SE, SD, median, range) were reported for baseline, post-baseline, and change from baseline values in clinical laboratory and vital signs parameters. Two summaries of treatment emergent adverse events (TEAEs) were provided: all TEAEs and all TEAEs related to study drug. Adverse events were coded using MedDRA (Medical Dictionary for Regulatory Activities) Version 16.0.

Results

Conduct of the study

Study 0624-203 was initiated in 2010 and conducted at 6 sites in the US. Last patient contact was in 2012.

Despite substantial recruitment efforts, subjects were not enrolled 1000 U dose group in the lower weight category. Therefore 9 subjects were enrolled and treated: 3 subjects (10-25 kg inclusive) received 500 U, 3 subjects (>25 kg) received 1000 U, and 3 subjects (>25 kg) received 1500 U IV Cinryze. All 9 subjects received a single dose of Cinryze and completed the study.

Nine paediatric subjects with HAE were enrolled and treated with a single IV dose of Cinryze in this study: 3 subjects (10-25 kg, inclusive) received 500 U Cinryze, 3 subjects (>25 kg) received 1000 U Cinryze, and 3 subjects (>25 kg) received 1500 U Cinryze. Subjects in the lower weight category were not enrolled in the 1000 U dose group. All 9 subjects completed treatment and the study.

Baseline data

All 9 subjects were white, and 8 of the 9 subjects were female. The median age was 9 years (range: 6-11 years).

All 9 subjects had a family history of HAE. During the year prior to study enrolment, these subjects reported a median of 0.3 attacks per month (range: 0-4 attacks); the majority of subjects (67%, 6/9) had <1 attack per month (2 subjects in each dose group). Overall, the most common historical attack locations were gastrointestinal/abdominal (78%, 7/9) and extremity (67%, 6/9); 2 of the 9 (22%) subjects (both 1500 U) reported laryngeal attacks within the prior year (did not require intubation). The mean number of hospital/emergency room visits necessary for angioedema attacks during the year prior to enrolment was

low across the 3 dose groups, ranging from a mean of 0.3-1.0. The majority of subjects (78%, 7/9) never had a laryngeal attack at any time prior to the study.

At baseline, the investigator determined the defining symptom (i.e., predominant anatomic location) and overall severity of the subject's HAE attack. For the majority (56%, 5/9) of subjects in the intent-to-treat efficacy (ITT-E) population, the defining symptom was gastrointestinal (GI)/abdominal: 2 (67%), 2 (67%), and 1 (33%) subjects in the 500 U, 1000 U, and 1500 U Cinryze groups, respectively. One (33%) subject in each of the 3 dose groups reported extremity symptoms; facial symptoms were reported by the remaining subject (1500 U Cinryze).

Outcomes and estimation

All 9 (100%) subjects met the primary endpoint of the study, achieving unequivocal beginning of relief of the defining symptom within 4 hours of initiation of treatment with Cinryze. As shown in the Table below, median time to unequivocal beginning of relief of the defining symptom was 0.5 hours (range: 0.25-2.5 hours): 1.25, 0.25, and 0.5 hours in the 500 U, 1000 U, and 1500 U Cinryze groups, respectively. The majority (67%) of the 9 subjects achieved unequivocal beginning of relief of the defining symptom within 0.5 hours (0.25 hours, n=4; 0.5 hours, n=2), including 1 (1000 U Cinryze) of 2 subjects whose defining symptom (GI/abdominal) was severe. The median time to complete resolution (from start of Cinryze infusion) of the HAE attack for the 9 subjects was 13.6 hours (range: 1.6-102.3 hours): 13.6, 10.0, and 29.1 hours in the 500 U, 1000 U, and 1500 U Cinryze groups, respectively (secondary efficacy endpoints).

Of note, for 1 subject (defining symptom: severe extremity attack) in the 1500 U dose group, the time to complete resolution of the HAE attack (102.3 hours) was significantly longer than that of other study subjects; this subject had an average of 2 HAE attacks per month during the year prior to enrolment as well as having a history of laryngeal attacks. It is not unusual for swelling associated within an extremity attack to require 4-5 days for complete resolution, especially for severe swelling.

Table 19. Efficacy Endpoints – Unequivocal Beginning of Relief of the Defining Symptom (Presence of [Primary] and Time to [Secondary]) and Time to Complete Resolution of the HAE Attack (Secondary) – ITT-E Population (Study 0624-203)

Endpoint	IV CINRYZE			
	500 U (10-25 kg)	1000 U (>25 kg)	1500 U (>25 kg)	All Subjects
ITT-E population, N	3	3	3	9
PRIMARY ENDPOINT:				
Unequivocal Beginning of Relief of the Defining Symptom Occurred Within 4 Hours Following Initiation of Treatment with CINRYZE [a] (N, %)				
Yes	3 (100%)	3 (100%)	3 (100%)	9 (100%)
SECONDARY ENDPOINTS:				
Time to Unequivocal Beginning of Relief of the Defining Symptom (hours) [b]				
Mean ± SD	1.08 ± 0.76	0.33 ± 0.14	1.08 ± 1.23	0.83 ± 0.82
Median	1.25	0.25	0.50	0.50
Range (min, max)	0.25, 1.75	0.25, 0.50	0.25, 2.50	0.25, 2.50
Time to Complete Resolution of the Attack (hours) [c]				
Mean ± SD	20.8 ± 14.37	11.3 ± 10.44	44.33 ± 52.08	25.48 ± 31.21
Median	13.58	10.00	29.07	13.58
Range (min, max)	11.48, 37.35	1.57, 22.33	1.58, 102.33	1.57, 102.33

Study 624-301: Prevention

"A Phase 3, Multicenter, Randomized, Single-blind, Dose-ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age With Hereditary Angioedema."

Methods

Subjects were randomized to 1 of 2 treatment sequences (A/B or B/A; A=500 U and B=1000 U), with each sequence consisting of two 12-week treatment periods of twice weekly infusions (2x24 doses, overall). Subjects had to qualify for randomization by experiencing at least 1.0 angioedema attack (moderate or severe or required acute treatment) per month during the study's 12-week baseline observation period.

Treatments

Subjects received Cinryze (500 U or 1000 U) IV injection twice weekly (every 3 or 4 days) for 12 weeks in two sequential crossover treatment periods. Subjects were to receive both treatments (A=500 U and B=1000 U), assigned in random order (A/B or B/A). No placebo or reference product was used in this study.

Objectives

The primary objective of this study is to assess the relative efficacy of two dose levels of CINRYZE (500 U and 1000 U) administered by IV injection every 3 or 4 days to prevent angioedema attacks in children 6-11 years of age. The secondary and other objectives of the study are to: (1) assess the safety and tolerability of the 2 dose levels; (2) characterize the pharmacokinetics/pharmacodynamics; (3) assess the immunogenicity; and (4) assess the impact of treatment on health status (quality of life) following intravenous (IV) administration of CINRYZE in children 6-11 years of age with hereditary angioedema (HAE).

Outcomes / endpoints

Primary efficacy endpoint was the number of angioedema attacks, normalized to a 12-week treatment period. No statistical comparisons of the Cinryze doses were made due to the small number of subjects.

Secondary efficacy endpoints were Cumulative Attack Severity, Cumulative Daily Severity, and the number of angioedema attacks requiring acute treatment during each treatment period.

Study participants

All 6 subjects had a confirmed diagnosis of Type I HAE (low levels of C1 INH protein). Five (83%) of the 6 subjects had a family history (first-degree relative) of HAE.

During the 3 months prior to screening, the median number of angioedema attacks for subjects was 4.0 (range: 3-6 attacks). Overall, subjects reported typical angioedema attack locations as gastrointestinal (GI)/abdominal (100%), extremity or peripheral (83%), facial (50%). One subject reported a history of genitourinary attacks and 1 subject had a history of upper airway attacks. The mean for the average overall duration of the angioedema attacks was approximately 2 days for all subjects (range: 1-3 days) and the average overall severity of the attacks was moderate for the majority of subjects (83%, 5/6); 1 (17%) subject reported attacks of severe intensity.

Table 20. Subject Demographic and Baseline Characteristics by Treatment Sequence

Characteristic[a]	Sequence A/B 500/1000 U CINRYZE (N=2)	Sequence B/A 1000/500 U CINRYZE (N=4)	All Subjects (N=6)
Age (years)[b]			
Mean (SD)	10.5 (0.71)	9.3 (2.06)	9.7 (1.75)
Median	10.5	9.5	10.5
Min, Max		7, 11	7, 11
Sex - n (%)			
Male	0	0	0
Female	2 (100)	4 (100)	6 (100)
Ethnicity - n (%)			
Hispanic or Latino	1 (50.0)	0	1 (16.7)
Not Hispanic or Latino	1 (50.0)	4 (100)	5 (83.3)
Race - n (%)			
White	1 (50.0)	4 (100)	5 (83.3)
Multiple: Black, Caucasian	1 (50.0)	0	1 (16.7)
Weight (kg)			
Mean (SD)	37.35 (10.394)	33.03 (10.374)	34.47 (9.549)
Median	37.35	30.90	32.00
Min, Max		23.2, 47.1	23.2, 47.1
Height (cm)			
Mean (SD)	148.90 (5.515)	140.08 (18.307)	143.02 (15.098)
Median	148.90	141.50	147.50
Min, Max		118, 159	118, 159
BMI (kg/m^2)[c]			
Mean (SD)	16.71 (3.448)	16.69 (3.136)	16.69 (2.877)
Median	16.71	16.84	16.84
Min, Max		13.1, 20.0	13.1, 20.0

Max=maximum; min=minimum; n=number of subjects; SD=standard deviation; U=Units.
Note: Percentages were based on the Safety Set.
Treatment A=Intravenous infusion of CINRYZE 500 U twice weekly (every 3 or 4 days) for 12 weeks.
Treatment B=Intravenous infusion of CINRYZE 1000 U twice weekly (every 3 or 4 days) for 12 weeks.
[a] The baseline value for a characteristic was the value from the visit time point as specified in the statistical analysis plan.
[b] Age was calculated as the difference between date of birth and date of informed consent, truncated to years.
[c] Body mass index was calculated as (weight[kg]/height[$m]^2$).

Sample size

As planned, a total of 12 subjects will be randomized in this study. Currently 6 subjects have completed the study and this interim CSR summarizes the results of the first 6 completers to fulfil the EU PIP commitment for CINRYZE. Two of the 6 subjects were randomized to treatment sequence A/B (500/1000 U IV CINRYZE) and 4 subjects were randomized to sequence B/A (1000/500 U IV CINRYZE). All 6 subjects were included in the Safety Set, Full Analysis Set, and the Pharmacokinetic and Pharmacodynamic Set for data analyses purposes.

Statistical methods

A sample size of 12 randomized subjects was considered to be a reasonable target for meeting the study objectives, given the limited pool of eligible paediatric HAE subjects who fall within the age range.

No formal statistical analyses of the data have been performed; rather statistical comparisons of the CINRYZE doses will be made when all subjects have completed the study.

All pharmacokinetic and pharmacodynamic analyses were performed using the respective Pharmacokinetic or Pharmacodynamic Set. Individual subject concentrations of C1 INH antigen, C1 INH functional activity, and complement C4 were summarized by treatment using descriptive statistics for each collection time point.

In addition, the change from baseline (prior to the first dose in treatment period 1) to pre-dose levels and the change from each corresponding pre-dose level to 1 h post-dose for Dose 12 and Dose 24 in each treatment period were summarized for C1 INH antigen and C1 INH functional activity. Individual and summary (ie, mean, and SD) figures of plasma concentration-time profiles concentrations were provided.

All efficacy analyses were based on the Full Analysis Set. Summary statistics were provided for the primary endpoint (normalized number of angioedema attacks) and secondary endpoints (cumulative attack-severity, cumulative daily-severity, and number of angioedema attacks requiring acute treatment). For analyses related to the number of angioedema attacks during treatment (primary endpoint) as well as secondary efficacy endpoints, the number of attacks was normalized for the number of days subjects participated in a given period and expressed as a monthly frequency. All subjects' available individual data for the number of angioedema attacks during each treatment period were listed using the Safety Set. Graphic presentation was applied to view the pattern of angioedema attacks in this crossover study design using the Full Analysis Set.

All safety analyses were based on the Safety Set. The number and percentage of subjects reporting treatment-emergent adverse events (TEAEs) were tabulated in the following ways:

- By system organ class (SOC), preferred term, and treatment (including absolute count of events)
- By SOC, preferred term, and maximum severity
- By SOC and preferred term for any serious TEAEs
- By SOC and preferred term for TEAEs that in the opinion of the investigator were related to the investigational product.

Treatment-emergent AEs were summarized by dose group and by the time of onset (eg, during administration of investigational product or within 24 hours of a completed injection). Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA Version 17.0).

Clinical laboratory test and vital sign measurements were summarized using descriptive statistics. The number and percentage of subjects with potentially clinically important values, as determined by pre-defined criteria, were tabulated. The results of all immunogenicity testing (ie, antibodies to C1 INH) were listed.

Results

Conduct of the study

Study 0624-301 was initiated in 2014 and is currently ongoing, with study sites in the US, EU, and other regions. The results for the first 6 subject completing the study are available for this submission.

Baseline data

The design of this study allowed an evaluation of a subject's baseline HAE profile. During the study's baseline observation period (12 weeks), subjects were allowed to remain on prophylactic HAE therapy and/or receive on-demand HAE therapy for acute attacks. Subjects had to qualify for randomization during this period based on the number of attacks experienced (≥1.0 angioedema attacks per month [average] that were moderate or severe or required acute treatment). For the 6 subjects who qualified, a total of 41 attacks were recorded. The number of attacks for each subject was normalized and resulted in a mean baseline of 2.26 (±1.62) attacks per month. Other data associated with the attacks (severity, duration, acute treatments) were also recorded and the results from the baseline observation period were used to assess the efficacy of the 500 U and 1000 U Cinryze doses (ie, by comparing a subject's response with Cinryze prophylaxis relative to their baseline).

Outcomes and estimation

Both Cinryze doses showed clinical benefit relative to the baseline observation period (OP) as assessed by the primary and all secondary efficacy endpoints. During 12 weeks of treatment with each dose, both 500 U and 1000 U of Cinryze (administered twice weekly) reduced the burden of disease by lowering the number of angioedema attacks, lessening the severity and duration of attacks, and the requirement for acute treatment compared with baseline.

Table 21. Primary and Secondary Efficacy Endpoints (Scale Score Normalized per month) (Full Analysis Set)

Endpoints	Observation Period	Treatment A 500 U CINRYZE	Difference: OP-A	Treatment B 1000 U CINRYZE	Difference: OP-B
Number of subjects full analysis set	6	6	6	6	6
Number of angioedema attacks					
Mean (SD)	2.262 (1.622)	0.372 (0.470)	-1.890 (1.310)	0.372 (0.573)	-1.890 (1.106)
(Min, Max)	(1.00, 5.44)	(0.00, 1.11)	(-4.33, -0.65)	(0.00, 1.48)	(-3.96, -1.00)
Cumulative attack-severity					
Mean (SD)	4.090 (2.241)	0.622 (0.907)	-3.468 (2.040)	0.495 (0.727)	-3.595 (1.604)
(Min, Max)	(2.01, 8.32)	(0.00, 2.25)	(-7.21, -1.59)	(0.00, 1.85)	(-6.47, -2.01)
Cumulative daily-severity					
Mean (SD)	7.510 (4.763)	1.997 (4.026)	-5.513 (2.570)	0.928 (1.190)	-6.582 (3.715)
(Min, Max)	(2.01, 15.03)	(0.00, 10.13)	(-9.72, -2.01)	(0.00, 2.60)	(-12.81, -2.01)
Number of attacks requiring acute treatment					
Mean (SD)	0.697 (0.783)	0.062 (0.151)	-0.635 (0.649)	0.000 (0.000)	-0.697 (0.783)
(Min, Max)	(0.00, 2.15)	(0.00, 0.37)	(-1.78, 0.00)	(0.00, 0.00)	(-2.15, 0.00)

Max=maximum; min=minimum; OP=observation period; SD=standard deviation; U=Units.
A-OP: The difference between Treatment A and the Observation Period.
B-OP: The difference between Treatment B and the Observation Period.
Treatment A=Intravenous infusion of CINRYZE 500 U twice weekly (every 3 or 4 days) for 12 weeks.
Treatment B=Intravenous infusion of CINRYZE 1000 U twice weekly (every 3 or 4 days) for 12 weeks.

Fourty-one (41) angioedema attacks were reported during the baseline observation period. With Cinryze twice weekly treatment, 6 attacks were reported with the 500 U dose and 6 attacks were reported with 1000 U dose. Note, two subjects had no angioedema attacks with either the 500 U or 1000 U dose of Cinryze. One subject had no attack with 500 U of Cinryze and one subject had no attack during dosing with 1000 U of Cinryze. Therefore, 4 of the 6 subjects were attack-free during at least 1 of the two 3-month Cinryze treatment periods.

Table 22. Summary of Unadjusted Angiooedema Attack Data Prior to and During Study Participation by Subject

Period	Total Number of Attacks	Severity (Sev/Mod/Mild)	Location(s)	Requiring Acute Treatment
Subject (B/A)				
3 mo prior to screen	5	Moderate*	GI, FA, EX	unknown
Baseline observation	17	1/7/9	UA, GI, FA, EX	1[a]
#1 – 1000 U CINRYZE	4	0/1/3	GI, FA, EX	0
#2 – 500 U CINRYZE	3	0/0/3	GI, FA, EX	0
Subject (A/B)				
3 mo prior to screen	6	Moderate*	GI, FA, EX	unknown
Baseline observation	4	0/4/0	All GI	4[b]
#1 – 500 U CINRYZE	0	na	na	na
#2 – 1000 U CINRYZE	0	na	na	na
Subject (B/A)				
3 mo prior to screening	4	Moderate*	UA, GI	unknown
Baseline observation	6	1/4/1	All GI	6[c]
#1 – 1000 U CINRYZE	0	na	na	na
#2 – 500 U CINRYZE	1	0/0/1	UA	1[d]
Subject (A/B)				
3 mo prior to screening	3	Moderate*	GI, EX	unknown
Baseline observation	4	0/3/1	GI, EX	0
#1 – 500 U CINRYZE	0	na	na	na
#2 – 1000 U CINRYZE	0	na	na	na
Subject (B/A)				
3 mo prior to screening	3	Moderate*	GI, GE, FA, EX	unknown
Baseline observation	6	0/4/2	GI, FA, EX	1[e]
#1 – 1000 U CINRYZE	1	0/0/1	FA	0
#2 – 500 U CINRYZE	0	na	na	na
Subject (B/A)				
3 mo prior to screening	4	Severe*	GI, EX	unknown
Baseline observation	4	3/1/0	GI, EX	1[f]
#1 – 1000 U CINRYZE	1	0/1/0	GI	0
#2 – 500 U CINRYZE	2	2/0/0	GI, EX	0[g]

*=average severity; BID=twice daily; C1 INH=C1 esterase inhibitor; EX=extremity or peripheral; FA=facial; GE=genitourinary; GI=gastrointestinal/abdominal; IV=intravenous; mo=months; mod=moderate; na=not applicable; sev=severe; U=units; UA=upper airways

[a] Subject received 1 unit of fresh frozen plasma as acute treatment for a severe attack with GI and facial symptoms. The subject also received a single oral dose of prochlorperazine (anti-emetic) for an attack of moderate intensity including GI symptoms.

[b] Subject received a single administration of IV C1 INH (dose unknown) as acute treatment for each of the 4 GI attacks.

[c] Subject received a single administration of IV C1 INH (dose unknown) as acute treatment for each of the 6 GI attacks.

[d] Subject received a single dose of 1000 U IV C1 INH as acute treatment for the mild upper airways attack.

[e] Subject received a single dose of 500 U IV C1 INH as acute treatment for the mild facial attack.

[f] Subject had 2 severe GI attacks that were of 3-4 days duration. For both attacks the subject received an oral dose of drotaverine hydrochloride (once for 1 attack and BID for 2 days for the other attack). The subject also received acute treatment with tranexamic acid (BID for 2 days; dose unknown) for 1 of the attacks.

[g] Subject experienced a severe GI attack of 4 days duration. The subject received 3 symptom management medications for the attack; drotaverine hydrochloride (2 mL IV; dose unknown), baralgina (5 mL IV; dose unknown), and metoclopramide (2 mL IV; dose unknown).

Supportive studies

In the original marketing authorization application (MAA) 4 studies included information on the efficacy of Cinryze in paediatric subjects:

Study LEVP 2005-1/A

This study was a double-blind, placebo-controlled study evaluating Cinryze for the treatment of acute angioedema attacks in subjects ≥6 years of age with HAE. Fifteen paediatric subjects (6-17 years) participated in the study, with 12 subjects having exposure to Cinryze. Subjects were randomized to receive a single dose of study drug (placebo or 1000 U IV Cinryze); those who did not respond to the randomized treatment could receive a second infusion of the study drug (placebo or 1000 U IV Cinryze) at 60 minutes

following the initial treatment. In addition, subjects could be treated with open- label 1000 U IV Cinryze if they presented with laryngeal angioedema or if they required emergency or non-cosmetic surgical procedures.

Study LEVP 2006-1

This study was an open-label study evaluating repeat exposure Cinryze in the treatment of acute angioedema attacks in subjects ≥1 year of age with HAE. Twenty-four (24) paediatric subjects (2-17 years) participated in the study. Treatment for acute attacks was 1000 U of IV Cinryze with a second 1000 U dose 60 minutes later if needed. In addition, short-term pre-procedure prophylaxis with 1000 U IV Cinryze was permitted during the study.

Study LEVP 2005-1/B

This study was a double-blind, placebo-controlled study evaluating Cinryze for the prevention of angioedema attacks in subjects ≥6 years of age with HAE. Four (4) paediatric subjects (9-17 years) participated in the study. Subjects were randomized to treatment (placebo or 1000 U IV Cinryze) which was administered twice weekly during two 12-week crossover treatment periods (ie, duration of treatment was 24 weeks).

Study LEVP 2006-4

This study was an open-label study evaluating Cinryze for the prophylactic treatment to prevent angioedema attacks and as treatment for acute angioedema attacks in subjects ≥1 year of age with HAE. Twenty-three (23) paediatric subjects (3-17 years) participated in the study. Subjects received 1000 U of Cinryze every 3-7 days for the prevention of HAE attacks or as needed for the treatment of acute HAE attacks, for as long as the study was in effect. For treatment of acute attack, subjects received 1000 U of IV Cinryze which could be repeated after 60 minutes if there was no symptom relief.

Table 23. Number of Paediatric Subjects Exposed to Cinryze and Total Infusions by Age Group, Indication, and Study – ITT-S Population

Indication Study [a]	2-5 years Number of Subjects (number of infusions)	6-11 years Number of Subjects (number of infusions)	12-17 years Number of Subjects (number of infusions)
Treatment			
LEVP 2005-1/A	0	6 (19)	6 (11)
LEVP 2006-1	1 (2)	10 (116)	13 (75)
Prevention			
LEVP 2005-1/B	0	1 (93)	3 (126)
LEVP 2006-4	2 (47)	9 (828)	12 (920)
Total [b]	**3 (49)**	**26 (1,056)**	**34 (1,132)**

ITT-S=intent-to-treat safety

[a] Subjects may have been exposed to CINRYZE in one or more studies.

[b] A subject may be counted more than once in the total if the subject participated in more than one study; therefore, this number represents the total number of subject exposures within each age subset.

Since the data for efficacy and safety for children below 6 years of age are very scarce and have not been expanded compared to the time of marketing authorisation, the MAH provided at the CHMP's request new information on 6 patients 3 to 5 years of age from post-marketing data that were treated off-label with Cinryze for prevention or acute treatment of angioedema attacks.

Six (6) patients 3 to 5 years were identified from the post-marketing safety database for the reporting period 01 Jan 1990 through 25 Sep 2016. They received routine prophylactic treatments with IV Cinryze and the dose regimens varied from 500 U (1-2 times per week) to 1000 U (1-2 times per week). The safety profiles from these post-marketing experiences were consistent with that observed in the clinical development program. In most cases these patients were identified when brought to the ER or hospitalized due to breakthrough angioedema attacks, which were treated with either Cinryze or Berinert, depending on the availability. Five out of these 6 patients continue the use of prophylactic Cinryze treatments currently and the status for 1 patient is unknown.

Table 24. Treatment of 6 Children from 3-5 years

Dose Regimen Route	Dates of Treatment or Treatment Duration	Reason for Exposure	Preferred Term	Case Receipt Date
Unknown IV	2010 to Unknown	HAE prophylaxis	Drug administered to patient of inappropriate age	31 Aug 2016
1000 U every 3-4 days IV	2012 Ongoing	HAE prophylaxis	Drug administered to patient of inappropriate age	29 Jun 2015
1000 U every 4 days IV	2010 ongoing	HAE prophylaxis	Drug administered to patient of inappropriate age	06 Aug 2015
1000 U/weekly; frequency increased to 3 times weekly IV	2010	HAE prophylaxis	Drug administered to patient of inappropriate age Inappropriate schedule of drug administration	13 May 2016
1000 U twice weekly IV	2008 ongoing	HAE prophylaxis	Product use issue	15 Jan 2013
500 U weekly IV	2008 to unknown	HAE prophylaxis	Off label use	01 Sep 2009
1000 U weekly IV	Not reported	HAE prophylaxis	Off label use Inappropriate schedule of drug administration	20 Sep 2010 05 Nov 2010
1000 U IV	2010	Acute HAE treatment	Hereditary Angioedema	21 Dec 2010
1000 U twice weekly IV	2014 Ongoing	HAE prophylaxis	Product Use Issue Drug administered to patient of inappropriate age	16 Sep 2014 25 Aug 2014 27 Oct 2015 02 Jun 2016

2.4.2. Discussion on clinical efficacy

The hereditary angioedema (HAE) Development Program for intravenous (IV) Cinryze supporting marketing approval included 8 clinical studies for treatment of angioedema attacks and routine prevention (prophylaxis) of angioedema attacks in adults (≥18 years of age), adolescents (12-17 years of age), and children (2-11 years of age). Two new studies, 0624-301 and 0624-203 out of these eight studies, provided pharmacokinetic/pharmacodynamic (PK/PD) data of C1 INH in HAE paediatric populations for the treatment and prevention indications.

Study 624-203

Nine subjects (age range: 6 - 11) were enrolled and received a single dose of Cinryze: 3 subjects (10 - 25 kg) received 500 Units; 3 subjects (>25 kg) 1000 Units, and 3 subjects (>25 kg) 1500 Units. All 9 (100%) subjects achieved unequivocal beginning of relief of the defining symptom within 4 hours following initiation of treatment with Cinryze. Median interval was 0.5 hours (range: 0.25-2.5 hours): 1.25, 0.25, and 0.5 hours

in the 500 Units, 1000 Units, and 1500 Units Cinryze groups, respectively. Median interval to complete resolution of the HAE attack for the 9 subjects was 13.6 hours (range: 1.6-102.3 hours). The CHMP noted that predominantly female subjects were enrolled in the trial.

For all 3 doses, 500, 1000 and 1500, the primary efficacy endpoint was met by all subjects. For the secondary efficacy endpoints, a dose of 1000 U might be faster in its effect for beginning and complete resolution of the respective symptoms when compared with the 500 U or 1500 U results. However, patient numbers are very low (3 patients in each dosage group) and severity, location, and natural progress of the respective symptoms seem to vary considerably. Hence, these results should be taken with caution.

One (1) of 3 subjects on 500 U and 5 of 6 subjects on 1500 and 1000 U achieved functional C1 INH activities ≥0.7 U/ml at 1h p.i. which is assumed to represent an effective level.

Of note, for 1 subject (defining symptom: severe extremity attack) in the 1500 U dose group, the time to complete resolution of the HAE attack (102.3 hours) was significantly longer than that of other study subjects; this subject had an average of 2 HAE attacks per month during the year prior to enrolment as well as having a history of laryngeal attacks. It is not unusual for swelling associated within an extremity attack to require 4-5 days for complete resolution, especially for severe swelling.

Study 624-301

The aim of the study is to provide further knowledge on the safety and efficacy of Cinryze for the prevention of angioedema attacks in children from 6 to less than 12 years of age with HAE. In order to fulfil the PIP requirements it was agreed that at least 6 patients would need to be enrolled. The results for these first 6 subjects completing the study are available for this submission.

Six paediatric subjects (6 to 11 years of age) were enrolled and randomized to twice weekly dosing for 12 weeks in 2 treatment sequences (500/1000 Units or 1000/500 Units). Both doses resulted in similar reduction of attack-frequency and showed clinical benefit regarding severity, duration, and requirement for acute treatment of attacks.

Twice weekly administrations of 500 or 1000 U in the sense of a prophylaxis regimen have been demonstrated to be effective in 6 of 6 subjects from 7 to 11 years of age with recurrent HAE attacks of moderate or severe intensity. Clinically significant reduction in frequency and severity of the attacks compared to the observational period was compelling. Benefit of both regimens was similar.

However, the C4-increase has not been found in study 624-301.

Data was collected from three subjects in age group 2-5 years only from studies LEVP 2006-1 and LEVP 2006-4. Nine (9) subjects (treatment) and 6 subjects (prevention) of age group 6-11 years were included resulting from the 2 new studies 0624-301 and 0624-203. The combination of all studies provided a total of 61 paediatric patients (unique subject ID) with a total of 3, 32, and 26 subjects in the 2-5, 6-11 and the 12-17 years of age cohorts, respectively.

Since the data for efficacy and safety for children below 6 years of age are very scarce and have not been expanded since the time of marketing authorisation, the MAH provided at the CHMP's request new information on 6 additional patients (3-5 years) which have been extracted from the safety database. Dose-regimen and respective AE-narratives are available. Cinryze has been used for prophylaxis in all 6 patients. Only one exposure in one patient was due to an acute treatment. Dose-regimen reflects 1000 IU in individual frequency as the "usual" dose – even in the 3 year-old patient. Body weight is not available. The narratives mainly identified breakthrough angioedema attacks. No additional risk has been documented.

2.4.3. Conclusions on the clinical efficacy

The MAH submitted two additional studies to substantiate efficacy regarding acute HAE treatment and prophylaxis in the paediatric population, aged 6-11 years. Both studies are based upon a narrow database (9 and 6 paediatric subjects). However, clinically significant response on attack-relief, reduction in frequency and severity of the attacks compared to the observational period was compelling. In such rare indication, data add significant information on efficacy of Cinryze for treatment of paediatric patients. In addition, the CHMP acknowledges that the number of patients is extremely limited in the paediatric age-group due to the rarity of the condition, especially the 2-5 years, and, consequently, it will be difficult for the MAH to enrol further patients.

As a consequence, the CHMP endorsed the proposed extension of indication in the following indications:

- Treatment and pre-procedure prevention of angioedema attacks in children (2 years old and above) with hereditary angioedema (HAE).
- Routine prevention of angioedema attacks in children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

In addition, the proposed doses of 500 U (10-25 kg bodyweight) and 1000 U (>25 kg bodyweight) in children aged 2 to 11 years in were found acceptable by the CHMP in the treatment and pre-procedure prevention of angioedema attacks. However, considering the limited number of patients enrolled in the < 6 years age group, the following statement was included in Section 4.2 of the SmPC: “Data supporting dosing recommendations in children less than 6 years old are very limited”.

The proposed dose of 500 U of Cinryze every 3 or 4 days as the recommended starting dose for routine prevention against angioedema attacks in children aged 6 to 11 years was found acceptable by the CHMP in the routine prevention of angioedema attacks.

2.5. Clinical safety

Introduction

The safety of Cinryze for use in the treatment and prevention of angioedema attacks in paediatric subjects with HAE is supported by data from 2 PIP studies. These studies include one Phase 2, open-label, single-dosed (0624-203 [Treatment]) and 1 ongoing Phase 3, randomized, single-blind, dose-ranging, crossover study (Study 0624-301 [Prevention]. In addition, 4 supportive Phase 3 studies included in the original MAA for safety of Cinryze for use in the treatment and prevention of angioedema attacks in paediatric subjects with HAE are provided. These studies include two Phase 3, randomized, placebo-controlled studies (LEVP 2005-1/A [Treatment] and LEVP 2005-1/B [Prevention]) and 2 larger open-label extension studies (LEVP 2006-1 [Treatment] and LEVP 2006-4 [Prevention]).

Risks of particular interest for Cinryze and other C1 INH products in patients with HAE include hypersensitivity, thrombosis, the risk of transmission of infectious diseases, and the development of anti-C1 INH antibodies.

Patient exposure

Study 0624-203

Nine subjects were enrolled and treated with a single IV dose of Cinryze: 3 subjects received 500 U (10-25 kg, inclusive), 3 subjects received 1000 U (>25 kg), and 3 subjects received 1500 U (>25 kg). The median

number (range) of Cinryze units per kilogram of body weight was 22.0 (20.8-28.3), 26.5 (26.0-29.0), and 31.6 (28.5-51.9) U/kg in the 500 U, 1000 U, and 1500 U Cinryze groups, respectively.

Study 0624-301

The extent of subject exposure to Cinryze is summarized in Table 25.

Table 25. Summary of Investigational Product Exposure, Safety Set-(Study 0624-301)

	Treatment A 500 U Cinryze (N=6)	**Treatment B 1000 U Cinryze (N=6)**
Total number of injections		
Mean (SD)	23.8 (0.41)	23.7 (0.82)
Median	24.0	24.0
Min, max	23.0, 24.0	22.0, 24.0
Average daily dose (U/day)		
Mean (SD)	145.9 (3.73)	289.8 (10.69)
Median	147.2	292.7
Min, max	138.6, 148.1	268.3, 296.3
Total Dose (U)		
Mean (SD)	11916.7 (204.12)	23666.7 (816.50)
Median	12000	24000
Min, max	11500, 12000	22000, 24000
Length of exposure (weeks)		
Mean (SD)	11.7 (0.12)	11.7 (0.07)
Median	11.6	11.7
Min, max	11.6, 11.9	11.6, 11.7
Total exposure (person-years)	1.3	1.3
Compliance [a]		
<90%	0	0
≥90%-<100%	1 (16.7)	1 (16.7)
100%	5 (83.3)	5 (83.3)

Max=maximum; min=minimum; n=number of subjects; SD=standard deviation; U=Units. Note: Treatment A=Intravenous infusion of Cinryze 500 U twice weekly (every 3 or 4 days) for 12 weeks. Treatment B=Intravenous infusion of Cinryze 1000 U twice weekly (every 3 or 4 days) for 12 weeks.

[a]Compliance for a specified period (or treatment) is defined as the total number of doses actually taken by a subject during that period divided by the number of doses expected to be taken during the same period multiplied by 100.

Combined Exposure Data from all Treatment and Prevention Studies

In the 2 supportive Phase 3 studies for treatment of angioedema attacks (LEVP 2005-1/A and LEVP 2006-1), and the 2 supportive Phase 3 studies for prevention of angioedema attacks (LEVP 2005-1/B and LEVP 2006-4) there were 46 unique paediatric subjects (aged 2-17 years) who received a total of 2,237 infusions of IV Cinryze. Altogether, in these 4 studies, there were 26 unique 6-11-year-old subjects, who received a total of 1,056 infusions of Cinryze. The majority of infusions used Cinryze doses of 1000 U.

With the addition of studies 0624-203 (N=9) for treatment of angioedema attacks and 0624-301 (N=6) for prevention of angioedema attacks, there are 15 additional paediatric subjects aged 6-11 years old, who received a total of 294 infusions of Cinryze.

Thus, of the total 61 unique paediatric subjects aged 2-17 years who have received Cinryze, 32 subjects 6-11 years old received a total of 1,350 infusions and 3 subjects 2-5 years old received a total of 49

infusions. Overall across all studies, the 61 unique paediatric subjects (2-17 years of age) received a total of 2,531 infusions of Cinryze (see Table 26).

Table 26. Total Number of Cinryze Infusions Administered by Paediatric Age Group, Indication, and Study–ITT-S Population (Treatment and Prevention Studies)

Indication / Study	Total Number of Infusions			Total
	2-5 years	6-11 years	12-17 years	
Treatment				
0624-203[#]		9		9
LEVP 2005-1/A	0	19	11	30
LEVP 2006-1	2	116	75	193
Prevention				
0624-301		285		285
LEVP 2005-1/B	0	93	126	219
LEVP 2006-4	47	828	920	1,795
Total, N	**49**	**1,350**	**1,132**	**2,531**

Note: Subjects may have been exposed to CINRYZE in one or more LEV studies

Adverse events

Treatment Emergent Adverse Events across Paediatric Population

In all 6 studies, administration of Cinryze to paediatric subjects was generally well tolerated across the paediatric population. Most of the reported TEAEs were mild or moderate in intensity. No clinically meaningful trends in the overall incidence of subjects reporting a TEAE considered by the investigator to be related to Cinryze were observed within any of these 6 studies, when analyzed by age.

Table 27. Incidence of Treatment-Emergent Adverse Events Among Subjects Exposed to Cinryze by Age Group, Indication, and Study -ITT-S Population (Treatment and Prevention Studies)

Indication / Study [a], n/N (%)	2-5 y	6-11 y	12-17 y
Treatment			
0624-203	--	1/9 (11%)[b]	--
LEVP 2005-1/A	--	0/6	0/6
LEVP 2006-1	0/1	6/10 (60%)	3/13 (23%)
Prevention			
0624-301	--	5/6 (83.3%)[c]	--
LEVP 2005-1/B	--	1/1 (100%)	3/3 (100%)
LEVP 2006-4	1/2 (50%)	8/9 (89%)	8/12 (67%)
Total, n/N [d]	**1/3**	**21/41**	**14/34**

y=years; n/N=number of subjects with ≥1 TEAE/number of subjects in a given age group by study

a: Subjects may have been exposed to CINRYZE in one or more studies.

b:- Related TEAEs in 10-25Kg weight group exposed to 500U IV CINRYZE

c: Any related TEAE (n,%) in Treatment A (500 U CINRYZE):4/6 (66.7%), and Treatment B (1000 U CINRYZE): 5/6 (83.3%)

d: n/N=number of reports of ≥1 TEAE across the studies (a given subject may be counted in this total more than once if the subject participated and had a TEAE in more than one study) / number of subject exposures.

Overall, there were 8 paediatric subjects (six in the 6 to 11 years age group and two in the 12 to 17 years age group) with treatment-emergent AEs considered to be related to Cinryze.

Table 28. Incidence of Treatment-Emergent Adverse Events Related to Study Drug Among Subjects Exposed to Cinryze by Age Group, Indication, and Study- ITT-S Population (Treatment and Prevention Studies)

Indication Study [a], n/N (%)	2-5 y	6-11 y	12-17 y
Treatment			
0624-203	--	1/9[b]	--
LEVP 2005-1/A	--	0/6	0/6
LEVP 2006-1	0/1	0/10	0/13
Prevention			
0624-301	--	2/6 (33.3%)[c]	--
LEVP 2005-1/B	--	1/1 (100%)	0/3
LEVP 2006-4	0/2	2/9 (22%)	2/12 (17%)
Total, n/N [d]	**0/3**	**6/41**	**2/34**

y=years; n/N=number of subjects with ≥1 treatment-related TEAE/number of subjects in a given age group by study

a: Subjects may have been exposed to CINRYZE in one or more studies.

b: Related TEAEs in 10-25Kg weight group exposed to 500U IV CINRYZE

c: Any related TEAE (n, %) in Treatment A (500 U CINRYZE): 1/6 (16.7%), and Treatment B (1000 U CINRYZE): 1/6 (16.7%)

d: n/N=number of reports of ≥1 treatment-related TEAE across the studies (a given subject may be counted in this total more than once if the subject participated and had a treatment-related TEAE in more than one study)/number of subject exposures.

Study 0624-203 (Treatment)

Among the 9 paediatric subjects (6-11 years of age) exposed to Cinryze, only 1 paediatric subject (11%) who received 500 U Cinryze (28.3 U/kg) for a GI/abdominal angioedema attack, reported 2 treatment-emergent adverse events (TEAEs) including mild nausea on Day 1 and mild diarrhea on Day 2, both of which resolved without treatment within 1 day. The investigator considered both events to be possibly related to study drug and not related to the HAE attack.

Study 0624-301 (Prevention)

Among 6 paediatric subjects (7-11 years of age), 55 TEAEs were reported by 5 (83.3%) subjects. Twenty-five TEAEs were reported by 4 (66.7) subjects following treatment with 500 U Cinryze, and 30 TEAEs were reported by 5 (83.3) subjects following treatment with 1000 U Cinryze. The majority (53/55, 96%) of TEAEs experienced by subjects were of mild to moderate intensity; 45 (81.8%) TEAEs were mild, 8 (14.5%) TEAEs were moderate and 2 (3.7%) TEAEs were of severe intensity.

Overall, the most frequently reported TEAEs were angioedema attacks (4 [66.7%] subjects). A similar incidence in angioedema attacks were observed for the 500 U and 1000 U doses of Cinryze (3 subjects in each dose group reported a total of 6 attacks; that is, during the treatment periods of the study 12 angioedema attacks were reported as TEAEs). Besides being an endpoint assessment for the study, HAE attacks were also recorded as AEs per protocol.

Other TEAEs frequently reported (by 2 [33.3%] or more subjects overall) were within the SOCs of infections and infestations (nasopharyngitis, upper respiratory tract infection), general disorders and administrative site conditions (fatigue), and psychiatric disorders (irritability). In general, the TEAE profile was similar following treatment with 500 U or 1000 U of Cinryze.

Thirty-two TEAEs (occurring in 2 [33.3%] subjects at the same site) were considered by the investigator to be related to 500 U or 1000 U Cinryze. There were 18 reported TEAEs of fatigue (9 for each Cinryze dose) and 14 reported TEAEs of irritability (7 for each Cinryze dose); all TEAEs of fatigue and irritability were moderate in intensity that could be considered associated with the investigational product.

Serious adverse event/deaths/other significant events

There were no deaths, or SAEs reported in the paediatric population included in the clinical studies, 0624-203, 0624-301, and LEVP 2005-1/A with Cinryze.

Eleven non-fatal, treatment-emergent SAEs were reported in 4 paediatric subjects in Studies 2005-1/B and 2006-4. In addition, in Study 2006-1, one subject had 2 non-treatment-emergent SAEs. None of the SAEs were considered related to Cinryze.

No subject in the age range of 2-11 years in the Clinical Development Program experienced SAEs that were thromboembolic in nature or related to hypersensitivity, or acquired blood-transmissible infections or developed anti-C1 INH antibodies.

Laboratory findings

There were no clinically significant safety signals in clinical laboratory parameters or vital signs relative to Cinryze administration.

The immunogenicity of Cinryze was evaluated by an assessment of anti-C1 INH antibodies in the 5 completed marketing approval studies (LEVP 2005 1/A, LEVP 2005-1/B, LEVP 2006-5, LEVP 2006-1, and LEVP 2006-4). Collectively, the data from these single and multiple-dose studies suggested that there was no evidence of clinically relevant anti-C1 INH antibody development following administration of Cinryze in subjects aged 2 years and above.

Based on available data from completed marketing-approval clinical studies, there is no evidence of clinically relevant anti-C1 INH antibody development following administration of Cinryze in the age range of 2-11 years old subjects in the paediatric study population. In Study 0624-203, there was no assessment of anti-C1 INH antibody formation following Cinryze administration. The MAH clarified that they didn't assess it since Study 0624-203 was a single dose study. In Study 0624-301, all subjects tested negative for anti-C1 INH antibodies following 6 months of treatment (2.3 person-years of exposure) with Cinryze.

Safety related to drug-drug interactions and other interactions

No studies examining potential drug interactions for Cinryze have been conducted. There are no known drug interactions.

Discontinuation due to adverse events

No paediatric subject in any clinical studies, 0624-203, 0624-301, LEVP 2005-1/A, LEVP 2005-1/B, LEVP 2006-5, LEVP 2006-1, or LEVP 2006-4 discontinued study drug (Cinryze or placebo) due to an AE.

Post marketing experience

The safety profile from post-marketing experience is consistent with that seen in the clinical development program. No new safety issues have been identified in the post-marketing environment for paediatric subjects.

2.5.1. Discussion on clinical safety

Additional safety data were provided by two new studies: Study 0624-203 (treatment) and Study 0624-301 (prevention).

Assessment of the safety profile from study 0624-203 (treatment) indicates that IV administration of single doses of 500 U (in subjects weighing 10-25 kg, inclusive), and 1000 U and 1500 U (in subjects weighing >25 kg) of Cinryze was safe and generally well tolerated in children treated for a single acute HAE attack. Only one of 9 paediatric subjects reported 2 TEAEs including mild nausea and mild diarrhoea on, which were considered possibly related to study drug by the investigator. Of note, this patient was treated for a GI/abdominal angioedema attack. A shortcoming of this study is that anti-C1 INH antibody formation following Cinryze administration was not assessed.

Based on available data from completed marketing-approval clinical studies, there is no evidence of clinically relevant anti-C1 INH antibody development following administration of Cinryze in the age range of 2-11 years old subjects in the paediatric study population.

The safety profile from study 0624-301 correlates with the usual experience in prevention studies. TEAEs comprise angioedema attacks, infections of the upper respiratory tract, fatigue and psychiatric disorders like irritability. The last two disorders (32 events occurring in 2 patients) were considered to be related to investigational product by the investigator.

Overall, no deaths or other SAEs occurred during these studies, and no subjects had study drug interrupted or discontinued due to an adverse event. No new safety issues have been identified. In addition, no subjects experienced a TEAE that was thrombotic or thromboembolic in nature during the study.

There is no evidence for additional safety concerns in the age group 2-5 years based upon information from the safety database.

2.5.2. Conclusions on clinical safety

Administration of Cinryze to paediatric subjects was safe and generally well tolerated across the paediatric population including the two additional paediatric trials. Most of the reported TEAEs were mild or moderate in intensity. There were no apparent differences in the types of TEAEs among paediatric subjects (2-5, 6-11, and 12-17 years) compared to adults (≥18 years).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.2 with the following content:

Safety concerns

Important Identified Risks	Thrombosis with high doses
	Thrombosis in patients with thrombogenic risk factors
	Hypersensitivity reactions
	Development of C1INH antibodies
	Adverse events with self or home administration
Important Potential Risks	Transmission of infectious diseases
	Medication error
Missing Information	Use in children (less than 12 years of age)
	Limited information is available for use in pregnancy.
	Use in non-Caucasian patients

Pharmacovigilance plan

Study / Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
0624-301, Phase 3 study (Category 3)	A Phase 3, Multicenter, Randomized, Single-blind, Dose-ranging,Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age With Hereditary Angioedema	Assessment of safety, pharmacokinetics and clinical effect of CINRYZE in children	Ongoing	Final study report by Nov 2017
0624-401, Phase 4 PAOS study/ Icatibant Outcome Survey (IOS), Disease Registry for compliance with an Annex II.D condition (Registry) (Category 1)	A European multi-center, multi-country, post-authorisation, observational study (registry) of patients with HAE who are administered CINRYZE (C1 inhibitor [human]) for the treatment or prevention of HAE attacks	To characterise the safety and use of CINRYZE in routine clinical practice when administered for (1) routine prevention of angioedema attacks, (2) pre-procedure prevention of angioedema attacks, and/or (3) treatment of angioedema attacks. To monitor severe attacks and laryngeal attacks, as well as cases in which treatment with CINRYZE is initiated more than 4 hours after onset of an attack.	Ongoing	With submission of PSURs

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Thrombosis with high doses	SmPC Section 4.4 under *Thrombotic events*	None proposed
Thrombosis in patients with thrombogenic risk factors	SmPC Section 4.4 under *Thrombotic events*	None proposed
Hypersensitivity reactions	SmPC sections 4.3 and 4.4 under *Hypersensitivity*	None proposed
Development of C1 INH antibodies	None proposed at this time.	None proposed
Adverse events with self or home administration	SmPC section 4.4 under *Home treatment and self-administration* and 6.6	Educational material for Healthcare Professionals Educational materials for Non-Healthcare Professionals
Transmission of infectious diseases	SmPC Section 4.4 under *Transmissible agents*	None proposed
Medication error	SmPC sections 4.1, 4.2 and 4.4 under *Thrombotic events* and *Paediatric population*	None proposed
Use in children (less than 12 years of age)	SmPC sections 4.2 and 4.4 under *Paediatric population*	None proposed
Limited information is available for use in pregnancy.	SmPC section 4.6.	None proposed
Use in non-Caucasian patients	SmPC section 5.2.	None proposed

2.7. Update of the Product information

The indication of Cinryze is extended in order to include the treatment and pre-procedure prevention of angioedema attacks in children (2 years old and above) with hereditary angioedema (HAE) and the routine prevention of angioedema attacks in children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC have been updated. The key messages of educational materials in Annex II, the Labelling and the Package Leaflet are updated in accordance.

For all changes to the Product Information (PI) please refer to the full PI attached in a separate file containing all accepted changes together with critical comments and revisions.

The proposed dose recommendation for children implies changes to Annex A (presentations). A consequential update of regional information in eCTD Module 3.2.R has also been submitted. This is acceptable.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- Consultation with Target Patient Groups was performed on the English version of the PIL for Cinryze 500 Units powder and solvent for solution for injection in August and September 2009. The content of the current Patient Leaflet has been fully tested and assessed for readability. In 2010 a bridging report was submitted when the applicant introduced a Mix2Vial and diagrams to facilitate reconstitution.

- The proposed revisions to the Patient Leaflet are minor: mainly the proposed dose for paediatrics

- Many paediatric patients administering Cinryze are likely to be assisted by carers/parents and the Patient Leaflet has already been tested in this population.

2.8. Significance of paediatric studies

The CHMP is of the opinion that studies LEVP 2006-1, LEVP 2006-4, 0624-203, 0624-301, which are contained in the agreed Paediatric Investigation Plan P/0299/2015, which is completed, and have been completed after 26 January 2007, are considered as significant.

The assessment criteria of the significance of studies, as defined in Section 4.2 of the European Commission Communication " Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies" (2014/C 338/01) has been fulfilled, taking into account the study type of clinical studies LEVP 2006-1, LEVP 2006-4, 0624-203, 0624-301:

- Study LEVP 2006-1: Open-Label Safety/Efficacy Repeat Exposure Study of C1 Esterase Inhibitor (Human) in the treatment of acute Hereditary Angioedema (HAE) Attacks.
- Study LEVP 2006-4: Open-Label Use of C1 Esterase Inhibitor (Human) for the prophylactic treatment to prevent Hereditary Angioedema (HAE) Attacks and as treatment in acute HAE Attacks.
- Study 0624-203 was an open-label single-dose study to evaluate the response and pharmacokinetics/pharmacodynamics of different doses of CINRYZE [C1 inhibitor (human)] for treatment of acute Angioedema Attacks in children less than 12 years of age with hereditary angioedema.
- Study 0624-301 was a Phase 3, multicenter, randomized, single-blind, dose-ranging, Crossover Study to evaluate the Safety and Efficacy of intravenous administration of CINRYZE (C1 Esterase Inhibitor [Human]) for the prevention of Angioedema Attacks in children 6 to 11 years of age with Hereditary Angioedema.

Those studies make an important contribution to the treatment of children and they are carried out in a subset considered particularly difficult to study.

3. Benefit-Risk Balance

Cinryze is intended for treatment, pre-procedure prevention and the routine prevention of angioedema attacks in patients with hereditary angioedema (HAE). Efficacy has been established within the initial MAA evaluation and has been confirmed since then. Two additional studies (624-203 and 624-301) have been submitted for the current procedure, aiming at extension of the indication of Cinryze for the paediatric population in the treatment and pre-procedure prevention of angioedema attacks in children (2 years old and above) with hereditary angioedema (HAE) and the routine prevention of angioedema attacks in children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

Benefits

Beneficial effects

In line with the results observed as part of the initial MAA evaluation, treatment with Cinryze in study 624-203 resulted in increases in antigenic and functional C1 INH levels for all 3 doses (500, 100 and 1500 U) after single-dose administration. All subjects on the respective 3 doses met the primary efficacy endpoint (relief within 4 hours). An assumed target level of 0.7 U/ml was achieved for 6 of 9 subjects. C4-increase, which might represent a pharmacodynamics-marker for function of the C1-inhibitor, has been found.

In Study 0624-301, plasma C1 INH antigen and functional activity were measured from 6 patients pre-dose and 1h following IV administration of two dose levels of Cinryze (500 Units and 1000 Units) every 3 or 4 days for 12 weeks. Both Cinryze doses resulted in relevant plasma levels of C1 INH antigen and functional activity.

At the CHMP's request, the MAH submitted data from their safety data-base covering 6 subjects <6 years of age and mainly reflecting HAE breakthrough-events. Patients were on prophylaxis and received mainly 1000 U doses. The efficacy of Cinryze in the age-group 2-5 years of age was confirmed.

Uncertainty in the knowledge about the beneficial effects

The evaluation of efficacy is challenging as the respective disease covers inhomogeneous location, variable clinical consequences and differing severities in a narrow patient collective. This assessment is even more difficult in the paediatric age-group considering the rarity of the condition.

Since the initial MAA submission, the MAH has provided additional data for 15 subjects in the age-group of 6-12 years but the age-group below 6 years remains unchanged (3 subjects included in the inital MAA application).

The presented additional data for 6 patients <6 years at the CHMP's request derive from the safety-data-base. Cinryze has been used for prophylaxis in all 6 patients. Only one exposure in one patient was due to an acute treatment.

PK-sampling was reduced to one pre-dose and two post-dose samples (1 hour and 24 hours p.i.) for study 0624-203 as no subject agreed to the additional but optional blood sampling necessary to obtain a PK profile for antigenic and functional C1 INH levels (additional blood samples collected through 8 hours post-infusion on Day 1, and on Days 3, 5, and 8). As a result, no PK parameters were calculated for this study and no meaningful PK-evaluation is possible with such truncated data.

The C4-increase has not been found in study 624-301.

Risks

Unfavourable effects

No new safety issues have been identified in the two additional paediatric studies.

There is no evidence for additional safety concerns in the age group 2-5 years based upon information from the safety data-base submitted during the application.

The safety profile of Cinryze appears to be similar in the different age groups.

Based on available data from completed marketing-approval clinical studies, there is no evidence of clinically relevant anti-C1 INH antibody development following administration of Cinryze in the age range of 2-11 years old subjects in the paediatric study population.

Uncertainty in the knowledge about the unfavourable effects

In general, the clinical database is narrow for the paediatric population.

With regard to immunogenicity, anti-C1 INH antibody formation following Cinryze administration has not been addressed in Study 0624-203.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The benefits from the therapy with Cinryze have been demonstrated in treatment and prevention of HAE attacks. The efficacy of Cinryze in the paediatric population, including the younger age-group, is confirmed.

The identified unfavourable effects and risks are in general in line with those of other C1 INH products and therefore do not raise further concerns.

The clinical data-base is narrow for the paediatric population especially for children < 6 years of age.

Benefit-risk balance

The efficacy in the paediatric population, including the younger age-group, is evident. The safety profile of Cinryze appears to be similar in the different age groups.

Despite the narrow data-base, in such rare indication, the data add significant information on the efficacy of Cinryze for treatment of paediatric patients. In addition, the CHMP acknowledges that the number of patients is extremely limited in the paediatric age-group due to the rarity of the condition, especially the 2-5 years, and, consequently, it will be difficult for the MAH to enrol further patients.

Discussion on the Benefit-Risk Balance

Hereditary angioedema is a serious, debilitating, and potentially fatal disease caused by a rare autosomal dominant mutation on chromosome 11 that leads to a decrease in C1 INH activity. Attacks range in severity from mild to severe, with GI involvement causing nausea, vomiting, and diarrhoea, or may even mimic an acute surgical emergency. Laryngeal swelling can be life threatening and these attacks account for the mortality risk described for HAE. Hence, HAE attacks require prompt treatment, often in an emergency room. Optimal management of C1 INH deficiency should include treatment of acute attacks, short-term prophylaxis and long-term prophylaxis in order to minimise the frequency and severity of recurrent attacks.

The MAH submitted two additional studies to substantiate efficacy regarding acute HAE treatment and prophylaxis in the paediatric population, aged 6-11 years. Both studies are based upon a narrow database

(9 and 6 paediatric subjects). However, clinically significant response on attack-relief, reduction in frequency and severity of the attacks compared to the observational period was compelling. In such rare indication, data add significant information on efficacy of Cinryze for treatment of paediatric patients.

In conclusion, the CHMP is of the opinion that the benefit/risk of Cinryze in children with hereditary angioedema (HAE) in the treatment and pre-procedure prevention of angioedema attacks from 2 years and the routine prevention of angioedema attacks from 6 years is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA, IIIB and A

Extension of Indication in children with hereditary angioedema (HAE) to include the treatment and pre-procedure prevention of angioedema attacks from 2 years and the routine prevention of angioedema attacks from 6 years; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The key messages of educational materials in the Annex II, the Package Leaflet and the Labelling are updated in accordance. In addition, an update of regional information in module 3.2.R due to the proposed dose recommendation for children is submitted.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following amended condition:

Conditions and requirements of the marketing authorisation

- **Additional risk minimisation measures**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that all healthcare professionals who are expected to prescribe Cinryze are provided with an Educational pack.

The educational pack should contain the following:

Summary of Product Characteristics and Patient Information Leaflet for Cinryze

Educational material for healthcare professionals

Educational materials for non-healthcare professionals

The educational material for healthcare professionals should include information on the following key elements:

There are limited data on the use of this medicinal product in home or self-administration.

It is the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of Cinryze

It is the responsibility of the prescribing physician to provide appropriate training to the non-healthcare professional who will administer the treatment at home, such as the patient for self- administration or a family member. Regular review of the administration by the patient/carer needs to be performed to ensure maintenance of optimal practice.

The training to be provided should address the following elements

Precaution for storage

Doses and Indications of treatment

Preparation of one dose of Cinryze (500 Units) by reconstituting one vial

Preparation of one dose of Cinryze (1000 Units) by reconstituting two vials

Method of reconstitution of each vial

Technique of intravenous injection

Method and rate of administration of one dose of Cinryze (500 Units)

Method and rate of administration of one dose of Cinryze (1000 Units)

Instruction to seek emergency treatment by health care professionals in case of failure to gain venous access or in case of lack of efficacy

Instruction in handling possible adverse reactions

Information on the need to keep a diary to document each treatment received at home and to bring it at each visit. The information collected should include:

Date and time of treatment

Batch number and dose received

Indication for treatment (acute attack or prophylaxis)

Response to treatment

Any adverse reactions

It is the responsibility of the prescribing physician to verify that all the necessary skills have been acquired by the non-healthcare professional and that Cinryze may be safely and effectively administered at home.

The existence of a post marketing registry in which health care professionals are encouraged to enter patients

The educational material for non-healthcare professionals should include information on the following key elements:

There are limited data on the use of this medicinal product in home or self-administration.

For some patients the prescribing physician may decide that Cinryze may be administered at home by a non-healthcare professional such as a family member or by self-administration.

Necessary skills have to be acquired by non-healthcare professionals before Cinryze may be safely and effectively administered at home.

Their prescribing physician will provide training on the following elements:

Precaution for storage

Doses and indications of treatment

Preparation of one dose of Cinryze (500 Units) by reconstituting one vial

Preparation of one dose of Cinryze (1000 Units) by reconstituting two vials

Method of reconstitution of each vial

Technique of intravenous injection

Method and rate of administration of one dose of Cinryze (500 Units)

Method and rate of administration of one dose of Cinryze (1000 Units)

Instruction to seek emergency treatment by health care professionals in case of failure to gain venous access or in case of lack of efficacy

Instruction in handling possible adverse reactions

Information on the need to keep a diary to document each treatment received at home and to bring it at each visit. The information collected should include:

Date and time of treatment

Batch number and dose received

Indication for treatment (acute attack or prophylaxis)

Response to treatment

Any adverse reactions

A leaflet providing detailed information on the key elements of the training that should be kept at home for further reference.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0299/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0299/2015 have been completed after the entry into force of that Regulation.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cinryze is not similar to Firazyr within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1