



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ruconest

International non-proprietary name: conestat alfa

Procedure No. EMEA/H/C/001223/II/0031

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

Term	Explanation
C1INH	C1 inhibitor
CI	Confidence Interval
C _{max}	Maximum concentration
DLP	Data Lock Point
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
FAS	Full Analysis Set
HAE	Hereditary angioedema
INN	International Non-proprietary Name
IS	Investigator Scores
iv	Intravenous(ly)
MAH	Marketing Authorisation Holder
mITT	Modified Intention-to-Treat
mL	Millilitre
n/N	Number(s)
OLE	Open Label Extension
PD	Pharmacodynamics
pdC1INH	plasma-derived C1 inhibitor
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPK	Population PK
PSUR	Periodic Safety Update Report
RCT	Randomised Controlled Trial
rhC1INH	Recombinant human C1 inhibitor
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
U	Unit(s)
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pharming Group N.V submitted to the European Medicines Agency on 7 August 2015 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 and IIIB

Extension of Indication to include adolescents in the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. As a consequence sections 4.1, 4.2, and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0010/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/103/2011 was not yet completed as some measures were deferred.

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 included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Greg Markey Co-Rapporteur: N/A

Timetable	Dates
Submission date	7 August 2015
Start of procedure:	19 September 2015
CHMP Rapporteur Assessment Report	13 November 2015
CHMP members comments	7 December 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 December 2015
Request for supplementary information (RSI)	17 December 2015
CHMP Rapporteur Assessment Report	9 February 2016
CHMP members comments	16 February 2016
Updated CHMP Rapporteur Assessment Report	22 February 2016
Opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

Problem statement

Hereditary angioedema (HAE) has an estimated prevalence of (about) 1 out of 10,000. There is no known difference in prevalence across ethnic groups or gender. The European Register of Hereditary Angioedema reports a median age of symptom onset of 11 years and a median age of diagnosis at 26 years.

In its most common form, hereditary angioedema presents as marked swelling of the face, mouth and/or airway (leading to difficulty breathing) and intestinal oedema (causing abdominal pain). Swelling can occur in any part of the body. Episodes may occur spontaneously or in response to triggers such as trauma, medications, viral illness and stress. The frequency of acute angioedema attacks varies widely but on average is approximately 4-5 times per year. Patients have reported as few as 0 and as many as 50 attacks per year.

C1 esterase inhibitor is a protease inhibitor belonging to the serpin superfamily. Its main function is the inhibition of the complement system to prevent spontaneous activation. Deficiency of C1 esterase inhibitor is associated with hereditary angioedema. In the absence of C1 inhibitor, excessive amounts of bradykinin are generated. Bradykinin promotes inflammation by increasing the leakage of fluid through the walls of blood vessels into body tissues. C1-inhibitor concentration in blood is about 0.25 g/L. The blood concentration of C1-inhibitor is low in 85% of the cases of hereditary angioedema and in the remaining 15% the protein circulates in normal amounts but is dysfunctional.

Mutations in the SERPING1 gene cause hereditary angioedema type I and type II. The SERPING1 gene provides instructions for making C1 inhibitor protein which blocks the activity of certain proteins that promote inflammation. Mutations that cause hereditary angioedema type I lead to reduced levels of C1 inhibitor in the blood while mutations that cause type II result in the production of a C1 inhibitor that functions abnormally.

About the product

Ruconest (INN, conestat alfa) is the recombinant analogue of human C1 esterase inhibitor and is obtained from the milk of rabbits expressing the gene encoding for human C1 esterase inhibitor. The amino acid sequence of the recombinant form is identical to endogenous human C1 esterase inhibitor. Ruconest is presented as a powder for solution for injection and is intended for intravenous administration.

Ruconest has the following indication (taken from the current SmPC):

4.1 Therapeutic indications

Ruconest is indicated for treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

Ruconest has the following posology (taken from the current SPC):

4.2 Posology and method of administration

Ruconest should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema.

Ruconest should be administered by a healthcare professional.

Patients who have not previously received Ruconest should be tested for the presence of IgE antibodies against rabbit epithelium (dander) prior to initiation of Ruconest (see section 4.4).

Posology

- Adults up to 84 kg body weight

One intravenous injection of 50 U/kg body weight.

- Adults of 84 kg body weight or greater

One intravenous injection of 4200 U (two vials).

In the majority of cases a single dose of Ruconest is sufficient to treat an acute angioedema attack.

In case of an insufficient clinical response, an additional dose (50 U/kg body weight up to 4200 U) can be administered (see section 5.1).

Not more than two doses should be administered within 24 hours.

Dose calculation

Determine the patient's body weight.

- Adults up to 84 kg body weight

For patients up to 84 kg calculate the volume required to be administered according to the formula below:

$$\text{Volume to be administered (ml)} = \frac{\text{body weight (kg)} \times 50 \text{ (U/kg)}}{150 \text{ (U/ml)}} = \frac{\text{body weight (kg)}}{3}$$

- Adults of 84 kg body weight or greater

For patients of 84 kg or above the volume required to be administered is 28 ml, corresponding to 4200 U (2 vials).

Paediatric population

The safety and efficacy of Ruconest in children (age 0 to 12 years) has not yet been established. Currently available data on adolescents (age 13 to 17 years) are described in section 5.1, but no recommendation on a posology can be made.

Elderly (>65 years old)

Data in patients older than 65 years are limited.

There is no rationale for patients older than 65 years to respond differently to Ruconest.

Renal impairment

No dose adjustment is necessary in patients with renal impairment since conestat alfa does not undergo renal clearance.

Hepatic impairment

There is no clinical experience with Ruconest in patients with hepatic impairment. Hepatic impairment may prolong the plasma half-life of conestat alfa, but this is not thought to be a clinical concern. No recommendation on a dose adjustment can be made.

Method of Administration

For intravenous use.

For instructions on reconstitution of Ruconest before administration, see section 6.6.

The required volume of the reconstituted solution should be administered as a slow intravenous injection over approximately 5 minutes.

The European Commission granted a marketing authorisation valid throughout the European Union for Ruconest on 28 October 2010. The original marketing authorisation application for Ruconest was supported by main studies C1 1205 and C1 1304 conducted with adults as well as subjects aged 14 to <18 years. At the time of licence grant, the CHMP restricted the indication for adults only. On 16 July 2014, the US FDA approved Ruconest for adolescent and adult HAE patients, with the same dosing as in the European labelling.

The company now submits the complete, integrated study report of the adolescent subjects who took part in studies C1 1205 and C1 1304 in support of the current variation application together with post marketing data in adolescents to gain an indication for Ruconest in this population.

Other medicinal products available

Berinert 500 units Powder and solvent for solution for injection/infusion is an extract of human plasma that contains the active substance: human C1-esterase inhibitor. Berinert is indicated for management of Hereditary angioedema types I and II. Berinert was approved via mutual recognition procedure DE/H/481/001/MR in 2009 with DE as RMS and multiple EU countries as CMS. The Berinert SmPC bears warnings on transmission of infectious agents.

Icatibant (Firazyr) is a synthetic decapeptide with a structure similar to bradykinin and is a selective competitive antagonist at the bradykinin type 2 receptor. Firazyr was approved by a centralised procedure EU/1/08/461/01,02 in 2008 and has orphan status. Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema in adults (with C1-esterase-inhibitor deficiency). Firazyr is administered subcutaneously.

Ruconest will hence be the first medicinal product in Europe to bear the indication for management of hereditary angioedema in adolescents.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

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

The main clinical studies that contributed towards the original application for a market licence and represent the basis for the integrated summary submitted are summarised as follows:

Study C1 1304-01

Table 2: Summary of Studies Included in the Analysis

Study ID Type of study	Objective(s)	Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Treated Patients	Duration of Treatment
C1 1304-01 RCT [Module 5.3.5.1.2] Phase 3	Efficacy, Safety & Tolerability	Randomized, saline-controlled, double-blind	rhC1INH 100 U/kg Saline (vehicle) single dose iv infusion at a flow rate of 6 mL/min	32 (16 rhC1INH and 16 Saline administrations)	Single dose
C1 1304-01 OLE [Module 5.3.5.2.3] Phase 3	Efficacy, Safety, Tolerability & PK/PD	Open label extension	rhC1INH 2,100 units initial dose with the provision for a second dose of 2,100 units or 4,200 units	57 (194 administrations)	Single dose with the option of second dose

Study C1 1205-01

Study ID Type of study	Objective(s)	Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Treated Patients	Duration of Treatment
					for the same attack
C1 1205-01 RCT [Module 5.3.5.1.1] Phase 2	Safety, Tolerability, Efficacy & PK/PD	Randomized, saline-controlled, double-blind	rhC1INH 50 or 100 U/kg Saline (vehicle) single dose iv infusion at a flow rate of 6 mL/min	38 (25 rhC1INH and 13 Saline administrations)	Single dose
C1 1205-01 OLE [Module 5.3.5.2.2] Phase 2	Safety, Tolerability, Efficacy & PK/PD (subset of patients only)	Open label extension	rhC1INH 50 U/kg initial dose, upon clinical response a repeat dose of 50 U/kg could be given	38 (79 administrations)	Single dose with the option of second dose for the same attack

RCT=Randomized controlled trial, OLE=Open label extension, HAE=Hereditary Angioedema, PK=Pharmacokinetic, PD=Pharmacodynamic, iv=Intravenous

The current application is based on an integrated analysis of the Safety, Immunogenicity, Pharmacokinetic and Efficacy with Recombinant Human C1 Inhibitor for the treatment of Acute Hereditary Angioedema Attacks in Adolescent Patients Participating in Randomized and Open Label phases of these studies.

2.3.2. Pharmacokinetics

Pharmacological data was evaluated in above mentioned safety and efficacy trials and is therefore described and discussed in the chapters below.

2.3.3. Pharmacodynamics

Pharmacodynamic data was evaluated in above mentioned safety and efficacy trials and is therefore described and discussed in the chapters below.

2.3.4. PK/PD modelling

PK/PD modelling was evaluated based on the above mentioned safety and efficacy trials and is therefore described and discussed in the chapters below.

2.4. Clinical efficacy

2.4.1. Main studies

Study title: An Integrated Analysis of the Safety, Immunogenicity, Pharmacokinetic and Efficacy with Recombinant Human C1 Inhibitor for the Treatment of Acute Hereditary Angioedema Attacks in Adolescent Patients Participating in Randomized and Open Label Phases of Studies C1 1304-01 and C1 1205-01.

Study C1 1205; was a randomised, placebo-controlled, double-blind Phase II study on the safety and efficacy of rhC1INH at doses of 50 and 100U/kg in relieving eligible attacks of angioedema with involvement of sub-mucosal tissues in patients with HAE.

Study C1 1304; was a randomised, placebo-controlled, double-blind, multi-centre study performed in order to demonstrate the efficacy of rhC1INH at 100 U/kg in patients with HAE with attacks of angioedema.

Methods

Study participants

Study C1 1205

Patients were screened when asymptomatic and had to fulfil the following criteria to be included in the study (major criteria):

- Aged 12 years and above.
- Clinical and (central) laboratory diagnosis of HAE with Baseline plasma level of functional C1INH <50% of normal, without evidence for acquired angioedema (AAE) (by a low plasma level of C1q and/or presence of anti-C1INH antibodies).

For randomization into the study, which took place when the patient presented with an attack, the patient had to fulfil all of the following criteria:

1. Above Screening criteria were still met.
2. Evidence for exacerbation or development of an abdominal attack and/or of facial-oropharyngeal angioedema and/or laryngeal angioedema and/or of urogenital angioedema and/or peripheral angioedema.
3. Onset of eligible symptoms within 5 hours before medical evaluation of eligibility had occurred.
4. Patient VAS scores of overall severity of angioedema symptoms at least at 1 eligible location at the time of evaluation (Time -1 hour) of at least 50 mm, where 0 mm meant 'no symptoms at all' and 100 mm meant 'extremely disabling'.

Study C1 1304

Patients were screened when asymptomatic and had to fulfill the following criteria to be included in the study:

- Aged at least 16 years.
- Clinical and central laboratory diagnosis of HAE with HAE with baseline plasma level of functional C1INH <50% of normal.

For randomization into the study, the patient had to fulfil all of the following criteria in addition to the screening criteria:

1. Evidence for exacerbation or development of an abdominal attack and/or of facial-oropharyngeal angioedema and/or laryngeal angioedema and/or of urogenital angioedema and/or peripheral angioedema. Patients had to notify and discuss symptoms with the Investigator prior to travelling to the study centre.
2. Onset of eligible symptoms within 5 hours before medical evaluation of eligibility had occurred.
3. Patient VAS score of overall severity of angioedema symptoms of ≥ 50 mm at least 1 anatomical location at the time of evaluation (Time -1 hours).
4. No clear improvement (improvement defined as a decrease in VAS score of overall severity of angioedema symptoms ≥ 20 mm) in angioedema signs between determination of eligibility, (Time -1 hour) and baseline (Time 0 hours).

Major exclusion criteria in both studies concerned history of allergic reactions to C1INH concentrates or any rabbit protein, diagnosis of acquired C1INH deficiency, and presentation or development of a life-threatening attack (an attack requiring immediate emergency procedures to prevent death, hypoxemia related injuries or other unfavourable outcomes).

Treatments

In both studies, patients were to present for evaluation within 5 hours and be treated within 1 hour after eligibility of the angioedema attack was confirmed. The patients received recombinant human C1 Inhibitor (rhC1INH, INN conestat alfa) by intravenous (iv) infusion.

Study C1 1304 Randomised Clinical Trial

Study treatment was:

- rhC1INH at 100 U/kg body weight

Study C1 1304 Open Label Extension

The initial treatment dose was 1 vial (2100 U resulting in 18-40 U/kg). At the discretion of the Investigator and depending upon the patient's clinical response, an additional iv dose of 1 (2100 U) or 2 (4200 U) vials could be administered within 4 hours from the initial dose. The maximum amount of rhC1INH that could be given to a patient for a single attack was 3 vials.

Study C1 1205 Randomised Clinical Trial

Study treatment was either:

- rhC1INH at 100 U/kg body weight
- rhC1INH at 50 U/kg body weight

Study C1 1205 Open Label Extension

The initial treatment dose was 50 U/kg. At the discretion of the Investigator and depending upon the patient's clinical response, an additional iv dose of 50 U/kg could be administered within 4 hours from the initial dose. The maximum amount of rhC1INH that could be given to a patient for a single attack was 100 U/kg.

In the double-blind RCT phase of each study, the corresponding volume of 0.9% sodium chloride solution was administered as a control. There was no reference therapy in the OLE phase of each study.

It is noted that only 1 adolescent took part in the randomised, double-blinded phase of one study. All other adolescents contributed results after the studies were converted to an open-label format after an interim analysis had convinced of efficacy.

The number of adolescents per RCT (randomised controlled trial) and OLE (open label extension) sections of the studies is given in the Table 1.

Table 1 Number of adolescent patients and attacks treated per study

Study	Number of adolescents	Number of attacks treated
C1 1205-01 RCT	1*	1
C1 1205-01 OLE	9	25
C1 1304-01 RCT	0	0
C1 1304-01 OLE	7	24

*Subject 1205-028-008, had two treated attacks with Ruconest. Attack 1 (rhC1INH (100 U/kg single dose)) was treated in the RCT stage and attack 2 (rhC1INH (50 U/kg single dose)) in the OLE stage. All other treated attacks happened during the OLE phases of the two studies.

Objectives

Main objectives of the integrated retrospective analysis of data from patients aged less than 18 years that took part in randomized controlled trials (studies C1 1205 RCT and C1 1304 RCT) and their respective open label extension (OLE) phases (studies C1 1205 OLE and C1 1304 OLE) was to:

- assess the safety, immunogenicity, tolerability, pharmacokinetics and pharmacodynamics of recombinant human C1 inhibitor (rhC1INH, INN: conestat alfa) in symptomatic adolescent patients with hereditary angioedema,
- assess the efficacy of rhC1INH in symptomatic adolescent patients with hereditary angioedema,

Outcomes/endpoints

Efficacy:

A patient reported visual analogue scale (VAS) was chosen to assess efficacy. VAS scores were recorded repeatedly throughout the study at defined time points and were measured at up to 4 different locations (abdominal, genitourinary, orofacial-pharyngeal-laryngeal or peripheral), depending on the affected locations. A series of VAS assessments were taken that varied for each location. To allow consistent evaluation of attacks at different anatomical locations, an overall severity VAS for each location was used. The last VAS question for each location indicated the overall severity of angioedema symptoms as felt by the

patient for that location. All VAS scores were measured as a continuous scale from 0 to 100 mm. For most of the VAS questions, including the overall severity VAS, 0 mm corresponded to 'No symptoms at all' and 100 mm corresponded to 'Extremely disabling'.

The primary efficacy endpoint was the time to the beginning of relief, assessed using overall severity VAS scores, where beginning of relief was defined as a decrease in VAS score of ≥ 20 mm (with persistence of the decrease at the next assessment time) at an eligible anatomical location compared to Baseline (Time 0, just prior to study medication infusion).

The secondary efficacy endpoint was the time to minimal symptoms, where 'minimal symptoms' was defined as an overall severity VAS score of < 20 mm in severity of symptoms at all locations.

A number of exploratory endpoints were included in the analysis, e.g. therapeutic failure, relapse of an attack.

Clinical pharmacology:

Blood samples were taken for functional C1INH, antigenic C1INH and C4.

Safety and tolerability

Safety and tolerability were assessed by evaluation of treatment emergent adverse events, vital signs, electrocardiogram, physical examination, safety laboratory parameters, and immunogenicity.

Sample size/patient population

The studies were planned to provide data describing the treatment of 50 angioedema attacks in at least 16 recruited adolescent patients.

Randomisation

The central randomization was carried out when the patient presented with an acute angioedema attack.

Study C1 1205-01:

The block size used was 3 with an allocation ratio of 1:1:1. There was no stratification factor used in the randomization.

Study C1 1304-01:

Treatment allocation was stratified by attack type ('submucosal' and 'peripheral') at the discretion of the Investigator. The block size was 2 with an allocation ratio of 1:1.

Only 1 adolescent patient took part in RCT (for 1 attack) remaining patients were enrolled for OLE studies

Statistical methods

Full Analysis Set (Modified Intention-To-Treat) (FAS [mITT]): defined as the set of patients who were randomized to one of the treatment groups and who took at least 1 dose of the study drug.

Safety Analysis Set: defined as the set of patients who received study drug and based on the actual treatment that the patient received.

The results for studies C1 1304 and C1 1205 were combined by pooling the data from both studies.

All 16 patients were included in the FAS (mITT) and the Safety Analysis Sets.

Results

Recruitment

First paediatric patient included in this analysis was enrolled on 17th February 2007 and last patient completed on 20th January 2010. Sixteen patients were recruited (8 male and 8 female), aged 14 to <18yrs at the time of first treatment. Nine of the patients participated in the study C1 1205 and remaining 7 took part in the study C1 1304. The study was conducted across 6 sites in the USA (9 patients), 3 sites in Israel (4 patients) and at 1 site in Romania (3 patients). In total 50 angioedema attacks were treated.

Patient demographics

Patient demographics are summarised in the following table:

Table 10 Demographic Characteristics (FAS [mITT])

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)
Age (years) at Admission					
Mean	16.1	16.3	16.1	16.2	16.3
SD	1.06	0.91	1.13	1.10	1.15
Range	14-17	14-17	14-17	15-17	15-17
Age at Admission					
< 18 years	16 (100%)	14 (100%)	8 (100%)	5 (100%)	3 (100%)
Sex					
Male	8 (50%)	6 (43%)	2 (25%)	0	0
Female	8 (50%)	8 (57%)	6 (75%)	5 (100%)	3 (100%)
Race					
Caucasian	15 (94%)	13 (93%)	8 (100%)	5 (100%)	3 (100%)
Black	1 (6%)	1 (7%)	0	0	0
BMI (kg/m ²) at Admission					
Mean	22.56	22.54	23.31	22.45	23.07
Range	18.5-27.4	19.0-28.1	19.6-29.3	19.4-28.8	19.4-28.6

Source: Table 14.1.2

FAS=full analysis set, mITT=modified, N=number of patients in the population, SD=standard deviation, BMI=body mass index.

None of the patients smoked or used alcohol. Seven patients were on maintenance therapy or prophylactic treatment at Screening; 3 patients received androgens, 3 patients received C1INH and 1 patient received androgens and C1INH previously. Two patients had received previous treatment with rhC1INH.

The 16 patients had experienced between 2 and 48 attacks per year prior to the study in which they were enrolled. The impact of these attacks ranged from minor (4 patients), through moderate (7 patients), to major (5 patients).

Conduct of the study

Baseline data

Of the 16 patients included in this integrated analysis, 14 patients had 2 or more attacks, 8 patients had 3 or more attacks, 5 patients had 4 or more attacks, and 3 patients had 5 or more attacks whilst aged < 18 years. (Some patients had treatment for further attacks aged ≥ 18 years, although these are excluded from this analysis).

Events are summarised by dose of product administered in the following table:

Table 9 Number of Treated Attacks: FAS (mITT)

Treatments Received	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)	Attack 6 (N=2)	Attack 7 (N=2)	Total (N=16)
rhC1INH (100 U/kg single dose)	1 (6%)	0	0	0	0	0	0	1 (2%)
rhC1INH (50 U/kg + add. dose)	1 (6%)	1 (7%)	0	0	0	0	0	2 (4%)
rhC1INH (50 U/kg single dose)	7 (44%)	7 (50%)	3 (38%)	3 (60%)	1 (33%)	1 (50%)	1 (50%)	23 (46%)
rhC1INH (18-40 U/kg + add. dose)	2 (13%)	3 (21%)	5 (63%)	2 (40%)	2 (67%)	1 (50%)	1 (50%)	16 (32%)
rhC1INH (18-40 U/kg single dose)	5 (31%)	3 (21%)	0	0	0	0	0	8 (16%)
Total	16 (100%)	14 (100%)	8 (100%)	5 (100%)	3 (100%)	2 (100%)	2 (100%)	50 (100%)

Source: Table 14.1.1 and Listing 16.2.5.1

FAS=full analysis set, mITT=modified intention-to-treat, N=number of patients in the population
In the 'Total' column, counts are presented for the number of attacks, and percentages are calculated out of the total number of attacks. This column includes the 2 patients treated for 7 attacks.

The 16 patients received rhC1INH treatment for a total of 50 acute attacks. Overall, 44 of the 50 attacks were at single locations (26 abdominal, 9 peripheral, 7 oro-facial-pharyngeal-laryngeal and 2 genito-urinary); the remaining 6 attacks were located as follows: 3 abdominal/peripheral, 2 peripheral attacks manifested at 2 separate locations, and 1 abdominal/oro-facial-pharyngeal-laryngeal.

Twenty three attacks (46%) were treated with a single dose of rhC1INH 50 U/kg, 16 attacks (32%) were treated with rhC1INH 18-40 U/kg with an additional dose, and 8 attacks (16%) were treated with a single dose of rhC1INH 18-40 U/kg. The remaining attacks were treated with rhC1INH 50 U/kg with an additional dose (2 attacks, 4%) and a single dose of rhC1INH 100 U/kg (1 attack, 2%).

Overall, 7 patients completed all follow-up visits after each attack, 8 patients did not complete all follow-up visits, and 1 patient withdrew consent (entered a different clinical study).

Concomitant Medication

Most patients (14 or 88%) reported using concomitant medications during the studies. The most frequently used types of concomitant medications were anti-gonadotropins. Concomitant medications are summarised in the following table:

Table 11 Concomitant Medications occurring in at least 10% of the Patients (Safety Analysis Set)

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)	Total (N=16)
Number of patients taking any concomitant medication	11 (69%)	9 (64%)	6 (75%)	4 (80%)	3 (100%)	14 (88%) [47]
Proteinase inhibitors	2 (13%)	3 (21%)	2 (25%)	2 (40%)	1 (33%)	3 (19%) [13]
Antigonadotropins and similar agents	4 (25%)	2 (14%)	1 (13%)	0	0	4 (25%) [11]
Other antihistamines for systemic use	2 (13%)	1 (7%)	1 (13%)	2 (40%)	1 (33%)	3 (19%) [10]
Tetracyclines	2 (13%)	2 (14%)	2 (25%)	2 (40%)	0	2 (13%) [10]
Propionic acid derivatives	2 (13%)	1 (7%)	1 (13%)	0	0	3 (19%) [7]
Other cold combination preparations	0	0	2 (25%)	1 (20%)	0	2 (13%) [5]
Other Antiemetics	0	1 (7%)	0	1 (20%)	0	2 (13%) [4]

Source: Table 14.1.3

N=number of patients in the population

Counting is by patient and not medication, with the exception of numbers in [] which denote medications.

If a medication was taken during more than 1 attack it was assessed as concomitant for all relevant attacks.

The total column includes the 2 patients treated for 7 attacks.

Outcomes and estimation

Primary end-points

The primary efficacy endpoint was the time to beginning of relief of symptoms at the location that showed the first response to treatment (overall severity VAS decrease of ≥ 20 mm from Baseline with persistence at next assessment time) in the FAS (mITT) set. Due to the low number of patients having more than 5 attacks (n=2), summaries are presented for the first 5 attacks experienced by the patients. One patient was excluded from the summary of Attack 1 for all VAS endpoints as she had no individual or overall VAS value at Attack 1. This patient was included in all other efficacy endpoints.

Median time (minutes) to beginning of relief of symptoms with persistence for each attack is shown in below table:

Table 3 Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of \geq 20mm with Persistence) (Adolescents):

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Table 14.2.1.1 Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of \geq 20mm with Persistence): Full Analysis Set (MITT)

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)
Time to beginning of relief of Symptoms with persistence (minutes)					
1st Quartile	31.0	37.0	32.5	30.0	15.0
95% CI	(30.0, 35.0)	(16.0, 60.0)	(30.0, 120.0)	(16.0, 84.0)	(15.0, 120.0)
Median	35.0	60.0	78.5	34.0	19.0
95% CI	(31.0, 62.0)	(37.0, 120.0)	(30.0, 241.0)	(16.0, 240.0)	(15.0, 120.0)
3rd Quartile	64.0	120.0	180.5	84.0	120.0
95% CI	(35.0, 130.0)	(60.0, 490.0)	(37.0, 719.0)	(30.0, 240.0)	(15.0, 120.0)

Source data: Listing 16.2.6.3. Generated on 27FEB2012 (15:33)

Values that are not estimable are displayed as '-'.
 Note: N=16 at Attack 1 for all efficacy endpoints and is reduced to N=15 for VAS endpoints as a result of Patient 3301 being excluded from the summary as they had no overall VAS values at Attack 1.
 Where there is no eligible location for a patient, the most severe location is considered an eligible location.

Due to low number of patients having more than 5 attacks (n=2) summaries are presented for the first 5 attacks experienced by the patients. The calculated time to beginning of relief of symptoms for the 2 patients with 7 treated attacks each were 231 and 15 minutes, respectively (Attack 6), and 62 and 120 minutes, respectively (Attack 7).

Only two adolescents received saline solution in the dataset used for this analysis. The time to beginning of relief (of symptoms) for these two saline-treated subjects was 245 and 496mins, both much longer than the times reported for the Ruconest-treated subjects.

The company provided corresponding data to allow for a direct comparison of the treatment effects seen in the adult and the adolescent populations.

The below table shows the results for the primary efficacy analysis for adults:

Table 2 Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of \geq 20mm with Persistence) (Adults):

Table 14.2.1.1.1 Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of \geq 20mm with Persistence): Full Analysis Set (MITT)

	Attack 1 (N=139)	Attack 2 (N=76)	Attack 3 (N=48)	Attack 4 (N=30)	Attack 5 (N=22)
Time to beginning of relief of Symptoms with persistence (minutes)					
1st Quartile	35.0	32.0	30.0	32.0	30.0
95% CI	(30.0, 55.0)	(30.0, 60.0)	(17.0, 37.0)	(22.0, 60.0)	(15.0, 61.0)
Median	65.0	63.0	60.0	60.0	64.0
95% CI	(60.0, 79.0)	(60.0, 67.0)	(35.0, 66.0)	(40.0, 114.0)	(30.0, 124.0)
3rd Quartile	128.0	120.0	120.0	242.0	125.0
95% CI	(120.0, 240.0)	(79.0, 240.0)	(62.0, 240.0)	(62.0, 465.0)	(67.0, 481.0)

Source data: Listing 16.2.6.3. Generated on 17DEC2015 (14:09)

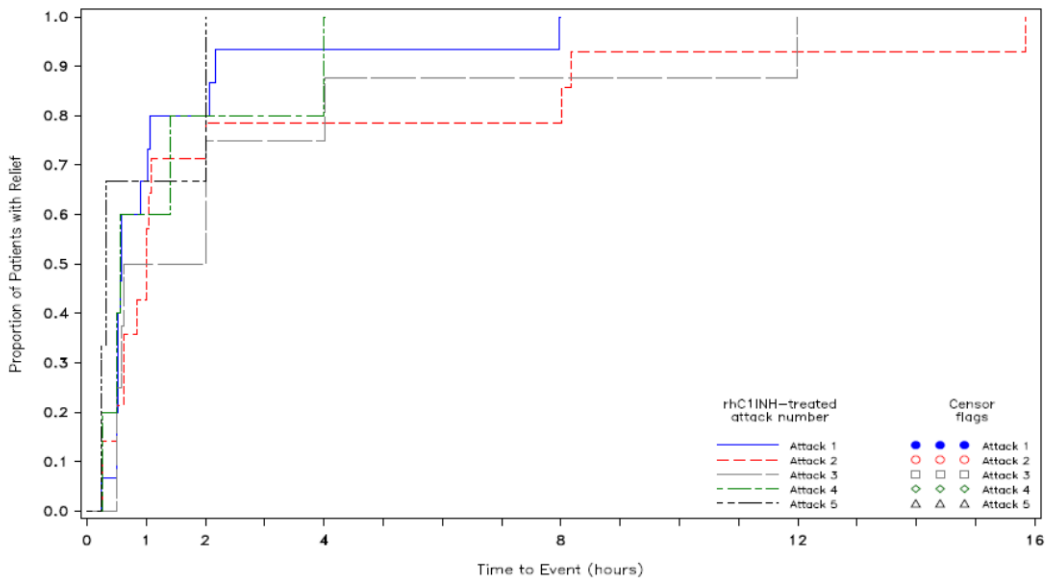
The median time to the beginning of relief of symptoms was 65 minutes (95% CI: 60.0-79.0) for adults as compared with 35 minutes (95% CI: 31.0-62.0) for adolescents for attack 1. Very similar results for subsequent treated attacks were seen in both adults and adolescents.

Furthermore, the results for time to beginning of relief on subsequent attacks (attacks 2-5) were comparable for both the adult and the adolescent population. There was therefore no detectable difference in efficacy between adults and adolescents in the response to Ruconest treatment. This is also evident in the Kaplan-Meier plots for each group:

Figure 5 Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms with Persistence (FAS [mITT]) (Overall VAS) (Adolescents)

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Figure 14.2.1.1 Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of ≥ 20 mm with Persistence): Full Analysis Set (MITT)

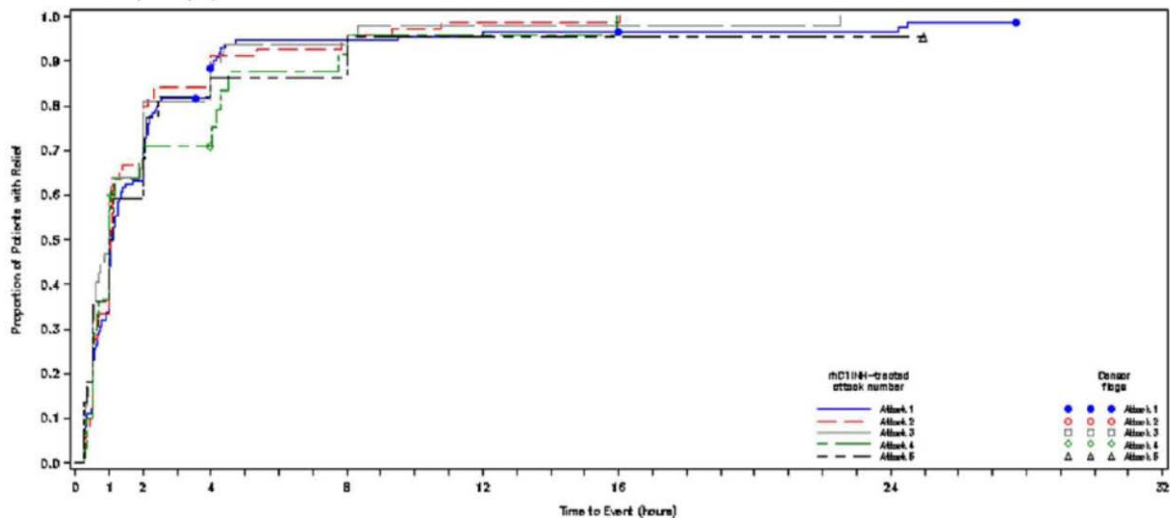


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 Source Data: Table 14.2.1.1.1

Figure 4 Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms with Persistence (FAS [mITT]) (Overall VAS) (Adults)

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Figure 14.2.1.1 Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of ≥ 20 mm with Persistence): Full Analysis Set (MITT)



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 Source Data: Table 14.2.1.1.1

The results presented above for adolescents and for adults contain data pooled from subjects taking part in studies C1 1205 or C1 1304 or their respective OLE phases. During the assessment the company provided the results for adults and adolescents separately for each of the studies to allow for a direct analysis of the results without the risk of any uncertainties arising from combining the sub-groups.

According to the provided data, the median time to beginning of relief of symptoms for adolescents taking part in the study C1 1205 was about 35mins and the median time for adults was about 60mins. The results excluded the data for one adolescent subject who (as the only one) took part in the RCT phase of the study C1 1205. The data for this subject were presented separately and were similar to those for the other adolescents in the study C1 1205, irrespective of dose (this subject received both 100U/Kg and 50U/Kg single dose for different events). The times to beginning of relief of symptoms for adolescents from the study C1 1304 were longer and showed more variability compared to adults, nonetheless the results for adolescents and adults could be considered sufficiently similar.

Time to Beginning of Relief by Dose

The median time to beginning of relief of symptoms with persistence (in minutes) is presented for the FAS (mITT) Population in Table 13. Although the numbers of participants are small, results suggest that a 50U/Kg single dose or additional dose shortens the time to the beginning of relief of symptoms (37mins median) compared to up to 40U/Kg single dose (120mins median).

Table 13 Median Time (minutes) to Beginning of Relief of Symptoms with Persistence (FAS [mITT]) and 95% CI (VAS Decrease of ≥ 20 mm; All Attacks)

	100 U/kg Single Dose (N=1)	50 U/kg Single or Additional Dose (N=9)	18-40 U/kg Single or Additional Dose (N=7)
Total number of attacks treated	1	25	23
Time to beginning of relief of symptoms with persistence	64.0 (-,-)	37.0 (31.0, 60.0)	120.0 (34.0, 130.0)

Source: Table 14.2.1.1.2

FAS=full analysis set, mITT=modified intention-to-treat, CI=confidence interval, VAS=visual analogue scale, N=number of patients in the population

Note: N=16 at Attack 1 for all efficacy endpoints and is reduced to N=15 for VAS endpoints as a result of Patient 1304-033-3301 being excluded from the summary as she had no overall VAS values at Attack 1.

Secondary end-points

The secondary efficacy endpoint was the time to minimal symptoms for an attack, assessed using VAS at all locations. Time to minimal symptoms was defined as overall severity VAS at all locations < 20 mm.

Table 4 and Table 5 (below) show median time to minimal symptoms for adult and for adolescents, respectively. As with the primary efficacy analysis, there was consistency in response to treatment for subsequent attacks in both adolescents and adults. The median times were shorter after all attacks for adolescents as compared with adults only.

Table 4 Median Time (Minutes) to Minimal Symptoms (FAS [mITT]) and 95% CI (Overall VAS Score) (Adults)

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Table 14.2.1.2.1 Time to Minimal Symptoms for an Attack Assessed Using VAS Scores (VAS <20mm): Full Analysis Set (MITT)

	Attack 1 (N=139)	Attack 2 (N=76)	Attack 3 (N=48)	Attack 4 (N=30)	Attack 5 (N=22)
Time to minimal symptoms (minutes)					
1st Quartile	124.0	125.0	120.0	239.0	123.0
95% CI	(79.0, 149.0)	(120.0, 240.0)	(67.0, 152.0)	(60.0, 242.0)	(30.0, 240.0)
Median	243.0	241.0	265.0	250.0	242.5
95% CI	(240.0, 256.0)	(240.0, 258.0)	(123.0, 485.0)	(240.0, 971.0)	(123.0, 335.0)
3rd Quartile	725.0	955.0	976.0	995.0	720.0
95% CI	(484.0, 970.0)	(480.0, 1380.0)	(483.0, 1394.0)	(451.0, 1440.0)	(244.0, -)

Source data: Listing 16.2.6.4. Generated on 17DEC2015 (14:09)

Values that are not estimable are displayed as '-'.

Table 5 Median Time (Minutes) to Minimal Symptoms (FAS [mITT]) and 95% CI (Overall VAS Score) (Adolescents)

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Table 14.2.1.2 Time to Minimal Symptoms for an Attack Assessed Using VAS Scores (VAS <20mm): Full Analysis Set (MITT)

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)
Time to minimal symptoms (minutes)					
1st Quartile	60.0	68.0	47.5	125.0	120.0
95% CI	(32.0, 130.0)	(56.0, 240.0)	(35.0, 240.0)	(60.0, 240.0)	(120.0, 127.0)
Median	130.0	189.5	180.0	141.0	120.0
95% CI	(63.0, 719.0)	(68.0, 960.0)	(45.0, 4333.0)	(60.0, 730.0)	(120.0, 127.0)
3rd Quartile	961.0	960.0	3450.0	240.0	127.0
95% CI	(130.0, 1450.0)	(139.0, 3041.0)	(120.0, 4333.0)	(125.0, 730.0)	(120.0, 127.0)

Source data: Listing 16.2.6.4. Generated on 27FEB2012 (15:33)

Values that are not estimable are displayed as '-'.

The company also submitted the comparison of data from adolescent and adults separately from each of the studies, showing that the results for time to minimal symptoms for adults and adolescents were comparable.

Time to Minimal Symptoms by Dose

Median time to minimal symptoms (in minutes) is presented for the FAS (mITT) Population in Table 15:

Table 15 Median Time (Minutes) to Minimal Symptoms (FAS [mITT]) and 95% CI (VAS < 20 mm; All Attacks)

	100 U/kg Single Dose (N=1)	50 U/kg Single or Additional Dose (N=9)	18-40 U/kg Single or Additional Dose (N=7)
Total number of attacks treated	1	25	23
Time to minimal symptoms	124.0 (-,-)	116.0 (60.0, 141.0)	240.0 (240.0, 730.0)

Source: Table 14.2.1.2.2

FAS=full analysis set, mITT=modified intention-to-treat, CI=confidence interval, VAS=visual analogue scale, n=number of patients with an observation, N=number of patients in the population

Note: N=16 at Attack 1 for all efficacy endpoints and is reduced to N=15 for VAS endpoints as a result of Patient 1304-033-3301 being excluded from the summary as she had no overall VAS values at Attack 1.

Where there is no eligible location for a patient, the most severe location was considered an eligible location.

Selected exploratory endpoints: Therapeutic Failure and Relapse of Attack

Therapeutic failure was defined for patients for whom the time to the beginning of the relief of symptoms was longer than 4 hours. In total, 3 patients experienced 5 therapeutic failures: 1 patient following attacks 1, 2 and 3 and 2 patients following attack 2. The patient who experienced therapeutic failure in 3 attacks received a single dose of rhC1INH 18-40 U/kg for each of attacks 1 and 2 and an additional dose of rhC1INH 18-40 U/kg for the treatment of attack 3 (total dose: 60.87 U/kg) prior to being assessed as a treatment failure.

Two patients who experience therapeutic failure for attack 2 received additional doses of rhC1INH 18-40 U/kg (total doses: 73.68 and 52.50 U/kg, respectively for the treatment of their second attacks prior to being assessed as treatment failures).

No patients experienced relapse of the attack within 24 hours according to VAS scores. One patient experienced relapse of the attack according to Investigator Score (early relapse at a peripheral location during Attack 2).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for Adolescent Patients in trial C1 1304

Title: A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study Of The Efficacy And Safety Of Recombinant Human C1 Inhibitor For The Treatment Of Acute Attacks In Patients With Hereditary Angioedema		
Study identifier	C1 1304 RCT + OLE	
Design	Randomized, Saline-controlled, double-blind, parallel group, multi-center clinical study, with an OLE phase (as per Protocol Amendment No. 3). During the double-blind phase of the study, HAE patients screened and found to be eligible were randomized to receive either rhC1INH or Saline in a ratio of 1:1 when they presented with an eligible acute angioedema attack. After the double-blind phase of the study, HAE patients with subsequent eligible acute angioedema attacks could be treated repeatedly with open-label rhC1INH. The assessment of the efficacy, safety and clinical laboratory variables took place at regular timepoints before and after study drug administration.	
	Duration of main phase:	JUL04-NOV07
	Duration of run-in phase:	not applicable
	Duration of extension phase:	SEP07-OCT09
Hypothesis	The objectives of the double-blind phase of the study were: <ol style="list-style-type: none"> 1. To demonstrate the efficacy of rhC1INH in the treatment of acute attacks in patients with HAE, and 2. To assess the safety and tolerability of rhC1INH in symptomatic patients with HAE. 	
Treatment groups	rhC1INH	rhC1INH 100 U/kg, one iv infusion, no adolescent patients randomized OLE phase initial dose 1 vial, 7 adolescent patients treated for 24 attacks
	Saline	NaCl 0.9%, one iv infusion, 0 randomised
Endpoints and definitions	Primary endpoint	Time to the beginning of relief based on patient's VAS scores. This variable will be based on the overall VAS for each eligible location (abdominal and/or facial-oro-pharyngeal-laryngeal and/or genito-urinary and/or peripheral). Time to the beginning of relief is defined as the first assessment time at which the overall VAS decreases by at least 20 mm with respect to baseline (t = 0 h). For single attacks involving more than one (eligible) location, time to the beginning of relief is based on a decrease of at least 20 mm for any location. For single attacks involving more than one (eligible; at least 50 mm at t = - 1 h) location, the location with the earliest response will be used for statistical analysis.

	Secondary endpoint	Time to resolution of clinical symptoms [minimal clinical symptoms] based on patient's VAS scores. This variable will be based on the overall VAS for each location. Time to complete resolution [minimal clinical symptoms] is defined as the first assessment time at which the overall VAS reaches a value of less than 20 mm for all locations.	
Database lock	28MAY2010		
Results and analysis			
Analysis description	Primary analysis		
Analysis population and time point description	<p>The primary efficacy endpoint was the time to beginning of relief of symptoms at the eligible location that showed the first response to treatment (VAS score decrease of ≥ 20 mm). The secondary endpoint was the time to minimal symptoms, where 'minimal symptoms' was defined as an overall severity VAS score of < 20 mm in severity of symptoms for all anatomical locations of an attack. These were summarized using 1st and 3rd quartiles and median time to event and Kaplan-Meier plots. Kaplan-Meier plots were presented showing the 2 treatment arms separately, and also showing the 2 treatment arms stratified, separately, by the type of attack.</p> <p>Statistical criteria were predefined for study success: primary endpoint $< 2.94\%$, secondary endpoint $< 10\%$ and supported by the analysis of therapeutic failure.</p>		
Descriptive statistics and estimate variability	Treatment group	18-40 U/kg Single or Additional Dose (N=7)	Saline x
	Number of subjects	7	1
	Total number of attacks treated	23*	1
	Time to beginning of relief of symptoms with persistence	120.0 (34.0, 130.0)	496.0 (NA,NA)
	Time to minimal symptoms	240 (240.0, 730.0)	988

*Patient 1304-033-3301 is excluded from the summary as there was no overall VAS scores at attack 1.

Table 2. Summary of Efficacy for Adolescent Patients in trial C1 1205

Title: A Randomized, Placebo-Controlled, Double-Blind Phase 2 Study Of The Safety And Efficacy Of Recombinant Human C1 Inhibitor For The Treatment Of Acute Attacks In Patients With Hereditary Angioedema		
Study identifier	C1 1205 RCT + OLE	
Design	Randomized, double-blind, Saline-controlled, parallel group, multi-center clinical study, with an OLE phase (as per Protocol Amendment No. 5). During the double-blind phase of the study, HAE patients screened and found to be eligible were randomized to receive rhC1INH at 50 U/kg, rhC1INH at 100 U/kg or Saline in a ratio of 1:1:1 when they presented with an eligible acute angioedema attack. After the double-blind phase of the study, HAE patients with subsequent eligible acute angioedema attacks could be treated repeatedly with open-label rhC1INH. The assessment of the efficacy, safety and clinical laboratory laboratory variables took place at regular timepoints before and after study drug administration.	
	Duration of main phase:	JUN05-JAN08
	Duration of run-in phase:	not applicable
	Duration of extension phase:	MAR07-JAN10
Hypothesis	OBJECTIVES: The objectives of the double-blind phase of the study were: <ol style="list-style-type: none"> 1. To assess the safety and tolerability of (rhC1INH) in symptomatic patients with HAE, and 2. To demonstrate the efficacy of rhC1INH in the treatment of acute attacks in patients with HAE. 	
Treatment groups	rhC1INH 50 U/kg	rhC1INH 50 U/kg, one iv infusion, no randomizations in RCT. 9 adolescent patients treated for 25 attacks in OLE
	rhC1INH 100 U/KG	rhC1INH 50 U/kg, one iv infusion, 1 randomized
	Saline	NaCl 0.9%, one iv infusion,

Endpoints and definitions	Primary endpoint	Time to beginning of relief based on patient's VAS scores, defined as the first assessment time at which the overall severity VAS has consistently decreased by at least 20 mm as compared to t=0 hrs. For single attacks involving more than one location, time to beginning of relief is based on a decrease of at least 20 mm for any (eligible) location. For single attacks involving more than one eligible location, the location with the earliest response will be used for statistical analysis. Analysis of the primary efficacy endpoint will be used to compare ehC1INH (at 100 U/kg and 50 U/kg combined or separately) versus placebo as well as to compare rhC1INH at 100 U/kg versus 50 U/kg.
	Secondary endpoint	Time to minimal clinical symptoms as defined as the first assessment time at which the overall VAS reaches a value of less than 20 mm for all locations. Analyses of this secondary endpoint will be used to compare rhC1INH at 100 U/kg versus 50 U/kg.

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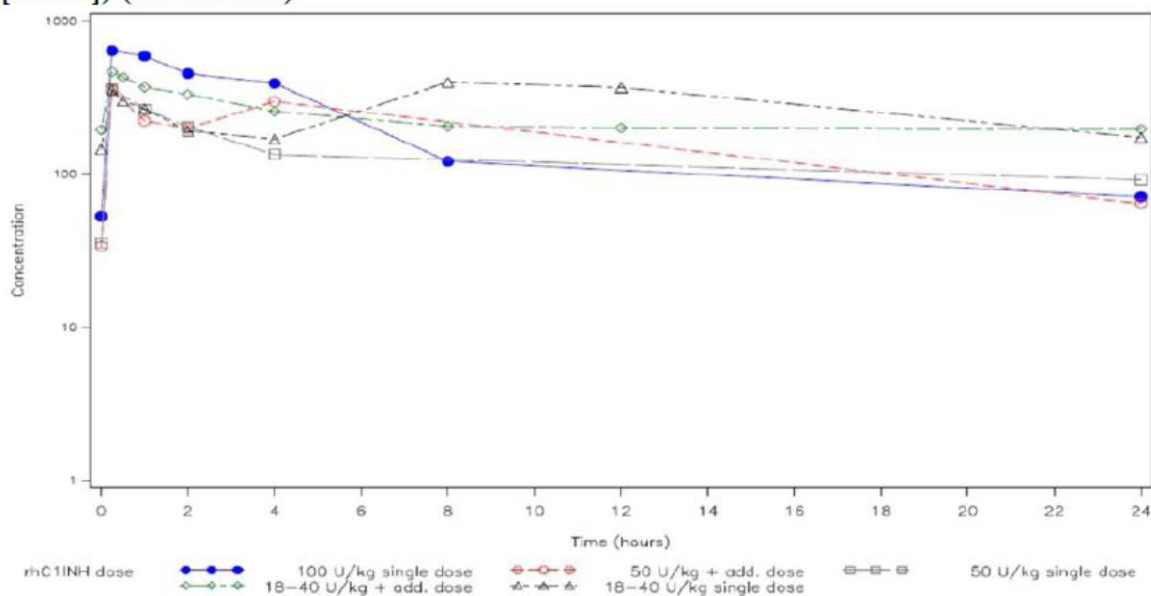
Results and analysis

Analysis description	Primary analysis			
Analysis population and time point description	The primary efficacy endpoint was the time to beginning of relief, assessed using overall severity visual analog scale (VAS) scores, where beginning of relief was defined as a decrease in VAS score of ≥ 20 mm (with persistence of the decrease in the next assessment time) at an eligible anatomical location compared to Baseline (Time 0, just prior to study medication infusion) If a patient had an attack at more than 1 (eligible) location, the earliest relief/resolution of these locations was considered.			
Descriptive statistics and estimate variability	Treatment group	rhC1 INH 50 U/kg	rhC1INH 100 U/kg	Saline
	Number of subjects	9	1	1
	Total number of attacks treated	25	1	1
	Time to beginning of relief of symptoms with persistence	37.0 (31.0, 60.0)	64.0 (-, -)	245.0 (NA, NA)
	Time to minimal symptoms	116.0 (60.0, 141.0)	124.0 (-, -)	2840

Pharmacokinetics

Pharmacokinetic (PK) data were collected in adolescents in analysed studies. The company has presented data demonstrating changes in concentration of antigenic C1INH in plasma following administration of the treatment. In majority of the patients PK concentrations of antigenic C1INH were maximal at the 15-minute time point (one patient in one attack had maximal concentrations of antigenic C1INH at the 30-minute time point) and declined slowly thereafter. Those patients, who received a repeated dose of rhC1INH for a single attack attained maximal concentrations of antigenic C1INH at the next blood sampling time after the end of the repeat infusion.

Figure 4 Mean Antigenic C1INH ($\mu\text{g/mL}$) Over Time (Logarithmic Scale) (FAS [mITT]) (All Attacks)



Source: [Figure 14.2.2.1.2](#)

The company also submitted the available data documenting C_{max} of antigenic C1INH in adolescents treated for number of attacks. Most data were collected for those patients who received rhC1INH 18-40 U/kg, either as a single or additional dose. For patients who received a single dose of rhC1INH 18-40 U/kg, individual antigenic C1INH C_{max} ranged from 183-639 $\mu\text{g/mL}$, with similar mean values of approximately 346 and 377 $\mu\text{g/mL}$ for Attacks 1 and 2, respectively. For patients who received a repeat dose of rhC1INH 18-40 U/kg, individual antigenic C1INH C_{max} ranged from 215-782 $\mu\text{g/mL}$, with mean values ranging from 383.00-522.20 $\mu\text{g/mL}$ for Attacks 1 to 5. Upon administration of a single dose of rhC1INH 50 U/kg, antigenic C1INH C_{max} was 361 $\mu\text{g/mL}$ based on the 1 patient with data. For the patient with PK data who received a repeat dose of rhC1INH 50 U/kg, antigenic C1INH C_{max} was 354 $\mu\text{g/mL}$.

Upon administration rhC1INH 100 U/kg, antigenic C1INH C_{max} was 641 $\mu\text{g/mL}$ based on the 1 patient with data.

Plasma concentrations of antigenic C1INH appeared to reflect the administered dose and seemed to be independent across the treatments for subsequent attacks.

Table 20 Antigenic C1INH ($\mu\text{g/mL}$) C_{max} by Dose and Attack (FAS [mITT])

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)
100 U/kg Single Dose					
n	1	-	-	-	-
Mean	641.00	-	-	-	-
Range	641.0-641.0	-	-	-	-
50 U/kg + Additional Dose					
n	1	-	-	-	-
Mean	354.00	-	-	-	-
Range	354.0-354.0	-	-	-	-
50 U/kg Single Dose					
n	-	1	-	-	-
Mean	-	361.0	-	-	-
Range	-	361.0-361.0	-	-	-
18-40 U/kg + Additional Dose					
n	2	3	5	2	2
Mean	472.50	436.33	522.20	383.00	466.00
Range	469.0-476.0	244.0-533.0	215.0-782.0	273.0-493.0	342.0-590.0
18-40 U/kg Single Dose					
n	5	3	-	-	-
Mean	346.00	377.33	-	-	-
Range	183.0-562.0	216.0-639.0	-	-	-

Source: Table 14.2.2.2

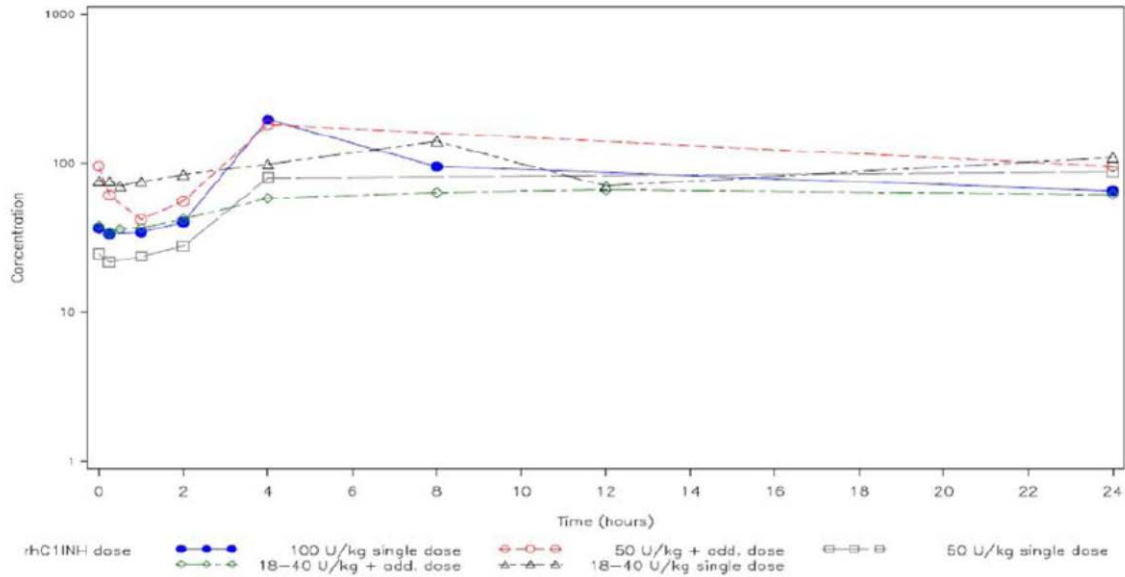
FAS=full analysis set, mITT=modified, N=number of patients in the population, n=number of patients with an observation

Pharmacodynamics

C1 esterase inhibitor prevents the proteolytic cleavage of complement component C4. Blood concentrations of complement components are low during an acute attack of hereditary angioedema because they are being consumed faster than they are generated. Indeed, a low blood concentration of C4 is a key diagnostic finding for hereditary angioedema. Exogenous C1 esterase inhibitor administered during an acute attack of hereditary angioedema may be expected to prevent further decrease in C4 concentration or even increase the levels of C4 in plasma.

Mean and individual patient C4 antigen concentrations were typically low at baseline and generally increased following treatment, although data were highly variable. Visual inspection indicates C4 antigen concentrations began to normalize by approximately 4 hours in the rhC1INH 50 U/kg single dose group and 18-40 U/kg plus additional dose group, and by 8 hours in the rhC1INH 100 U/kg single dose group. C4 antigen concentrations were more variable in the rhC1INH 18-40 U/kg single dose and 50 U/kg plus additional dose groups, although values appeared to normalize by 24 hours.

Figure 5 Mean C4 Antigen ($\mu\text{g/mL}$) Over Time (Logarithmic Scale) (FAS [mITT]) (All Attacks)



Source: [Figure 14.2.2.22](#)

The pattern of change in concentration of C4 in blood of adolescent patients following the administration of Ruconest was consistent with expected pharmacodynamic activity.

2.4.2. Discussion on clinical efficacy

The company provided pooled data from adolescents taking part in studies C1 1205, C1 1304 and their respective OLE phases compared to the results from the adult population. Although only 16 adolescents took part in the clinical studies, the results in this patient group demonstrated the marked and consistent reductions in time to relief of symptoms in comparison to placebo. The pooled results reported for time to beginning of relief of symptoms and time to minimal symptoms, as defined, for adolescents and adults were of similar magnitude and in the same direction, i.e. reduction in comparison to placebo.

However, the interpretation of the pooled results was to some degree difficult to interpret as the clinical studies used different posologies and, when converted to single arm studies, the posologies were further changed. Therefore, during the assessment the CHMP requested that the company provides the results for adults and adolescents separately for each of the studies/study phases, in order to allow for a direct analysis of the results without the risk of any uncertainties arising from combining the sub-groups. The submitted results show that the time to beginning of relief of symptoms as well as the time to minimal symptoms in either of the studies were similar between adolescents and adults and corresponded with the pooled results for adults and adolescents. This was considered reassuring by the CHMP.

Even though there were only 2 identified control subjects on saline, data provide re-assurance on the efficacy of Ruconest. From a methodological point of view it would have been preferred to have more patients under saline comparator to better establish a timeline on drug response for the placebo comparator group but taking into account ethical considerations in this life-threatening condition extrapolation based on results in adolescents from the open label phase of the studies and the comparability to adult data is acceptable.

Majority of adolescents participating in the analysed studies were administered either 50U/Kg or 18-40U/kg (1 vial) single dose of Ruconest, some received also and additional doses. Although numbers of participants were small, results suggest that 50U/Kg single dose or additional dose shortens the time to the beginning of relief of symptoms in comparison to 18-40U dose.

Three patients treated with Ruconest experienced therapeutic failure. However, it was noted during the assessment that the apparent therapeutic failures were few in number and occurred in the context of receiving less than the maximum possible dose of Ruconest. No patients experienced relapse of the attack within 24 hours according to VAS scores. One patient experienced relapse of the attack according to Investigator Score (early relapse at a peripheral location during Attack 2). However, there was a discrepancy between the outcomes reported by the patient and Investigator with the patient recording minimal symptoms.

In the light of limited PK data available for adolescents, a comparable pharmacokinetic behaviour of C11NH in adults and adolescents was demonstrated in order to support extrapolation of the positive B/R of C11NH in adults to adolescents. The company performed a population PK modelling to evaluate the potential differences in C11NH PK between the adolescent and adult populations. Due to the limited number of adolescent patients for whom PK data were available, only 8 individuals were included in the POPPK model. The weight range of these subjects was similar to adults, 46- 85 kg versus 45- 128 kg.

The analysis revealed that the effects of gender and age were adequately captured by the model. The correlation between predicted and observed C_{max} and AUC was assessed to be adequate. Moreover, the inclusion of age as a categorical covariate on the V, V_{max} and K_m parameters of the model resulted in a very small drop in OFV both with and without weight on V. This indicates that the PK of rhC11NH is consistent between adolescents and adults.

2.4.3. Conclusions on the clinical efficacy

Efficacy and PK results for adolescents are consistent with those seen in adults and indicate a beneficial effect of rhC11NH in the treatment of HAE attacks in adolescents.

2.5. Clinical safety

Introduction

The safety and efficacy of rhC11NH were established by 10 clinical studies of immunogenicity, PK, safety, and efficacy, and by nonclinical toxicity and pharmacology studies. At the time of the last PSUR (data lock point 28 April 2015), the total number of subjects who received Ruconest across all studies was 335 and the total number of administrations was 1032. Ruconest was marketed in 19 countries world-wide and no new safety concerns arose from the data presented.

Patient exposure

In total, 16 adolescent patients were exposed to Ruconest and received treatment for up to 7 attacks each.

The mean dose received by patients was similar across attacks, being in the range of 25-100 U/kg. Most attacks (64%) were treated with 1 dose of rhC11NH; of the 25 attacks treated with rhC11NH 50 U/kg, 23 attacks (92%) were treated with a single dose and 2 attacks (8%) were treated with an additional dose.

Of the 24 attacks treated with rhC1INH 18-40 U/kg, 8 attacks (33%) were treated with a single dose and 16 attacks (67%) were treated with an additional dose. One attack was treated with a single administration of rhC1INH 100 U/kg.

All treatments with multiple doses were given within the required 4 hours after the initial dose, with the exception of 1 patient, who received his second dose 4.75 hours after the start of his first dose infusion.

The extent of the patient exposure is summarised in the table:

Table 21 Extent of Exposure (Safety Analysis Set)

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)	Total (N=50)
Mean total volume administered, mL (Range)	47.6 (14-180)	43.4 (14-90)	44.5 (22-90)	51.4 (21-90)	48.7 (28-90)	44.8 (14-180)
Additional dose administered?						
Yes	3 (19%)	4 (29%)	5 (63%)	2 (40%)	2 (67%)	18 (36%)
No	13 (81%)	10 (71%)	3 (38%)	3 (60%)	1 (33%)	32 (64%)
Mean dose in U/kg (Range)	54.0 (25-100)	54.5 (30-100)	64.2 (49-99)	61.9 (50-91)	70.2 (50-91)	58.8 (25-100)
Mean interval initial dose-repeat dose in minutes (Range)	102.7 (65-163)	160.8 (75-285)	50.0 (22-75)	120.0 (10-230)	40.0 (10-70)	85.6 (10-285)

Source: Table 14.3.6

N=number of patients in the population

The total column includes the 2 patients treated for 7 attacks.

Adverse events

The safety set comprised 16 patients. There were no deaths, serious TEAEs or discontinuations due to TEAEs. Six patients (38%), all female, reported a total of 24 TEAEs.

3/16 (19%), 2/14 (14%), 2/8 (25%), 2/5 (40%), and 3/3 (100%) patients reported TEAEs during Attacks 1-5, respectively. The apparent increase in frequency of TEAEs with subsequent attacks was associated with a decrease in the number of patients with attacks.

Of the 2 patients who experienced 7 attacks each, only 1 patient experienced TEAEs after Attack 5 (nasopharyngitis and headache during Attacks 6 and 7, respectively).

All events were mild or moderate in severity; no patients experienced TEAEs which were considered severe. None of the events were considered to be probably or definitely related to study drug. One patient experienced vertigo and nausea which were considered to be possibly related to study drug.

Table 22 Treatment-Emergent Adverse Events (Safety Analysis Set)

	Attack 1 (N=16)	Attack 2 (N=14)	Attack 3 (N=8)	Attack 4 (N=5)	Attack 5 (N=3)	Total (N=16)
Number of Patients experiencing any Adverse Event	3 (19%)	2 (14%)	2 (25%)	2 (40%)	3 (100%)	6 (38%) [24]
SOC and AE Preferred Term						
Infections and Infestations	1 (6%)	1 (7%)	1 (13%)	0	1 (33%)	3 (19%) [6]
Influenza	0	1 (7%)	1 (13%)	0	0	1 (6%) [2]
Ear infection	0	0	0	0	1 (33%)	1 (6%) [2]
Nasopharyngitis	1 (6%)	0	0	0	0	1 (6%) [2]
Nervous system disorders	1 (6%)	1 (7%)	1 (13%)	1 (20%)	1 (33%)	2 (13%) [7]
Headache	1 (6%)	1 (7%)	1 (13%)	1 (20%)	1 (33%)	2 (13%) [7]
Respiratory, thoracic and mediastinal disorders	0	0	1 (13%)	1 (20%)	0	2 (13%) [2]
Pharyngolaryngeal pain	0	0	1 (13%)	1 (20%)	0	2 (13%) [2]
Skin and subcutaneous tissue disorders	1 (6%)	0	0	1 (20%)	0	2 (13%) [2]
Idiopathic urticaria	0	0	0	1 (20%)	0	1 (6%) [1]
Rash macropapular	1 (6%)	0	0	0	0	1 (6%) [1]
Gastrointestinal disorders	0	1 (7%)	0	0	1 (33%)	1 (6%) [2]
Abdominal pain	0	1 (7%)	0	0	0	1 (6%) [1]
Nausea	0	0	0	0	1 (33%)	1 (6%) [1]
Blood and lymphatic system disorders	0	1 (7%)	0	0	0	1 (6%) [1]
Anemia	0	1 (7%)	0	0	0	1 (6%) [1]
Ear and labyrinth disorders	0	0	0	0	1 (33%)	1 (6%) [1]
Vertigo	0	0	0	0	1 (33%)	1 (6%) [1]
Investigations	1 (6%)	0	0	0	0	1 (6%) [1]
Red blood cell sedimentation rate increased	1 (6%)	0	0	0	0	1 (6%) [1]
Reproductive system and breast disorders	1 (6%)	0	0	0	0	1 (6%) [2]
Ovarian cyst	1 (6%)	0	0	0	0	1 (6%) [2]

Source: Table 14.3.1.1

N=number of patients in the population, SOC=system organ class, AE=adverse event

Counting is by patient and not event, with the exception of numbers in [] which denote events.

The total column includes the 2 patients treated for 7 attacks.

TEAEs were most commonly reported in the Infections and Infestations SOC (6 events in 3 patients), with influenza, ear infection, and nasopharyngitis being reported at a similar and low frequency.

For TEAE in adults, the more common events were: (i) 23% reported Infections and infestations, (ii) 14% reported headache, (iii) 4% reported abdominal pain and (iv) 10% reported a skin disorder, mostly pruritus and erythema.

For TEAE in adolescents, the more common events were: (i) 19% reported Infections and infestations, (ii) 6% reported abdominal pain and (iii) 13% reported a skin disorder i.e. urticaria and rash.

Fifty eight percent of adults (78/141) had a TEAE whereas the corresponding rate for adolescents was 38% (6/16).

Laboratory findings

Treatment with rhC1INH did not result in clinically significant changes in routine clinical laboratory safety parameters.

No patient developed treatment-emergent anti-pdC1INH, anti-rhC1INH, or anti-HRI antibodies upon exposure to the study drug.

Five patients experienced abnormal changes in physical examination findings from Baseline:

- Patient experienced mild sinus arrhythmia (not clinically significant) at 24 hours after treatment for attack 1, slight facial edema at 24 hours after treatment for attack 2, and acne on day 22 relative to attack 3
- Patient experienced cerumen in right and left ear canals on day 90 following attack 2
- Patient experienced edema of the right hand on day 22 relative to attack 1
- Patient experience an acute facial attack of angioedema which was severe in intensity in day 22 relative to attack 2
- Patient experienced an acute attack of angioedema on left and right arms on day 22 relative to attack 1.
-

Serious adverse event/deaths/other significant events

There were no deaths or other SAEs in the adolescent population.

Post marketing experience

Ruconest is licensed for use in adolescents outside of the European Union. The company provided a summary of post-marketing evidence of continuing clinical safety in the adolescent population aged 14 to <18yrs. As of the end of 2015, there have been 20 patients under the age of 18 years treated with Ruconest in the US. For the adolescent population a total of four adverse events have been reported:

- Urticaria: 14yr old female, non-serious, possibly related. Patient recovered.
- Ear infection: 14yr old male, non-serious, causality not ascertained, outcome not known.
- Neck pain: 16yr old female, non-serious, unlikely related.
- Joint pain: 16yr old female, non-serious, unlikely related, outcome not reported. This subject also experienced an episode of lack of efficacy and difficulties with the giving device, considered non-assessable.

None of the reports suggest a new safety concern.

2.5.1. Discussion on clinical safety

Data on clinical safety in adolescents were presented to the CHMP at the time of initial marketing authorisation application and within the context of a combined population of adults and adolescents. Safety issues now reported in the integrated study reports do not give any particular reason for concern and are encompassed by the current SmPC.

There are limited adolescent events to make meaningful comparisons for the SOCs, however, the reports in adolescents appear to be similar to those of adults. The safety issues reported by the company from the post marketing setting do not give any particular reason for concern and are encompassed by the current SmPC.

2.5.2. Conclusions on clinical safety

The evidence of clinical safety in adolescents is limited to the data from 16 participating subjects but do not appear to be different from adults and are considered to be reflected appropriately in the SmPC.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The extension of the indication consists of an extension of the target population from adults only to adults and adolescents. The supportive clinical data were already present in the previous versions of the RMP. The last RMP was recently updated and assessed as part of the renewal application (EMA/H/C/001223/R/0023). The CHMP considered no RMP update necessary for this application.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

4.1 Therapeutic indications

Ruconest is indicated for treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

4.2 Posology and method of administration

(...)

Posology

- ~~Adults~~ Body weight up to 84 kg

One intravenous injection of 50 U/kg body weight.

- ~~Adults~~ Body weight of 84 kg ~~body weight~~ or greater

One intravenous injection of 4200 U (two vials).

(...)

- ~~Adults~~ Body weight up to 84 kg ~~body weight~~

For patients up to 84 kg calculate the volume required to be administered according to the formula below:

$$\text{Volume to be administered (ml)} = \frac{\text{body weight (kg) times 50 (U/kg)}}{150 \text{ (U/ml)}} = 6 \frac{\text{body weight (kg)}}{3}$$

- ~~Adults~~ Body weight of 84 kg ~~body weight~~ or greater

For patients of 84 kg or above the volume required to be administered is 28 ml, corresponding to 4200 U (2 vials).

Paediatric population

The safety and efficacy of Ruconest in children (age 0 to 12 years) has not yet been established. ~~Currently available data on adolescents (age 13 to 17 years) are described in section 5.1, but no recommendation on a posology can be made.~~

5.1 Pharmacodynamic properties

(...)

Paediatric population

Nine adolescent HAE patients (aged 13 to 17 years) were treated with 50 U/kg for 26 acute angioedema attacks, and 7 (aged 16 to 17 years) with 2100 U for 24 acute angioedema attacks. The efficacy and safety in adolescent patients was consistent with that seen in adults.

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.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Data from studies C1 1205 and C1 1304 were examined by separating results obtained on adolescents from adults with a view to claim the indication in adolescents.

A beneficial effect of treatment in the condition of hereditary angioedema would be a speedy resolution of signs and symptoms of an acute attack of angioedema. The primary end-point chosen by the company addresses timing to beginning of resolution of symptoms, recorded in minutes. A secondary endpoint was time to minimal symptoms, recorded in minutes.

For 7 adolescents who took part in study C1 1304 and who were administered Ruconest:

- The median time to beginning of relief of symptoms, as defined, of an attack was 120 minutes (95% CI 34, 130; 23 attacks treated). (One patient was given saline placebo and recorded a time to relief of symptoms, as defined, of the first attack of 496mins). By simple analysis, the reduction in time to relief of symptoms for study drug v. placebo is, therefore, about 6 hours.
- The median time to minimal symptoms was 240mins (95% CI 240, 730). [One patient was given saline placebo and recorded a time to minimal symptoms, as defined, of 988 mins]. By simple analysis, the reduction in time to minimal symptoms for study drug v. placebo is, therefore, about 12 hours.

For 9 adolescents who took part in study C1 1205 and who were administered Ruconest 50U/Kg:

- The median time to beginning of relief of symptoms, as defined, of an attack was 37 minutes (95% CI 31, 60). [One patient was given saline placebo and recorded a time to relief of symptoms, as defined, of 245mins]. By simple analysis, the reduction in time to relief of symptoms for study drug v. placebo is, therefore, about 6.5 hours.
- The median time to minimal symptoms was 116mins (95% CI 60, 141). [One patient was given saline placebo and recorded a time to minimal symptoms, as defined, of 2840 mins]. By simple analysis, the reduction in time to minimal symptoms for study drug v. placebo is, therefore, about 45 hours.

One adolescent in study C1 1205 was administered Ruconest 100U/Kg and returned a time to beginning of relief of symptoms of 64 mins and a time to minimal symptoms of 124mins.

Uncertainty in the knowledge about the beneficial effects

Uncertainties as to whether the efficacy will wane on long term repeated administration in subjects who develop antibodies against rhC1INH data is addressed by a registry as described in the RMP.

Risks

Unfavourable effects

No deaths occurred during any of the clinical studies. Six out of 16 adolescents (38%) had a treatment-emergent adverse event whereas 78 out of 141 adults (58%) reported a treatment-emergent adverse event and post marketing experience provided on further 20 adolescent patients do not suggest new safety concerns in this rare disease.

Uncertainty in the knowledge about the unfavourable effects

The safety database on adolescents is extremely limited but new safety concerns are not evident in the adolescent group compared to adults.

Effects Table

Table 1. Effects Table for Ruconest in management of adolescents ≥ 14 yrs with hereditary angioedema and presenting with an acute attack of angioedema

Short Description of Effect	Unit	Treatment	Placebo Control	Uncertainties/ Strength of evidence	References
Favourable Effects					
Median time to beginning of relief of symptoms	minutes (95% CI)	120 minutes (34, 130) 23 attacks treated in 7 subjects	Saline placebo control 1 subject 1 attack 496 minutes	Uncertainties related to single-arm design of study. Only 7 subjects exposed to Ruconest. Only 1 subject received saline placebo. Strength of evidence lies with consistent marked reduction in time to relief of symptoms for subjects administered Ruconest compared to placebo. Times appear similar to those recorded for adults.	1
Median time to minimal symptoms	minutes (95% CI)	240 minutes (240, 730)	988 minutes		1
Median time to beginning of relief of symptoms	minutes (95% CI)	37 minutes (31, 60) 25 attacks treated in 9 subjects	Saline placebo control 1 subject 1 attack 245 minutes	Uncertainties related to single-arm design of study. Only 9 subjects exposed to Ruconest. Only 1 subject received saline placebo. Strength of evidence lies with consistent marked reduction in time to relief of symptoms for subjects administered Ruconest compared to placebo. Times appear similar to those recorded for adults.	2
Median time to minimal symptoms	minutes (95% CI)	116 minutes (60, 141)	2840 minutes		2

Short Description of Effect	Unit	Treatment	Placebo Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects					
<p>There were no deaths, serious TEAEs or discontinuations due to TEAEs.</p> <p>Six patients (38%), all female, reported a total of 24 TEAEs.</p> <p>None of the events were considered to be probably or definitely related to study drug.</p> <p>One patient experienced vertigo and nausea which were considered to be possibly related to study drug.</p>				<p>Weaknesses in safety assessment: Only 16 patients and small numbers of incidents recorded. placebo control data only available on 2 subjects.</p> <p>Strength: novel adverse events / reactions not observed.</p>	3
					3
					3

Notes:

[1] study C1 1304. This study began as a randomised placebo-controlled trial using a posology of 100U/Kg Ruconest, one dose per acute attack.

This study was converted to a single-arm study using a posology of 2100 U (i.e. one vial) with provision for a second vial to be administered. It is understood that all adolescents entered this study as a single-arm study and that all received 2100U for each attack.

[2] study C1 1205. This study began as a randomised placebo-controlled trial using a posology of Ruconest 50U/Kg or 100U/Kg. This study was converted to a single-arm study with posology of 50 U/kg initial dose Ruconest, upon clinical response a repeat dose of 50 U/kg may be given.

One adolescent entered this study whilst still an RCT, was administered 100U/Kg Ruconest and returned a time to beginning of relief of symptoms of 64mins and a time to minimal symptoms of 124mins.

All other adolescents entered the study after it had become a single-arm study and all adolescents were administered 50 U/kg Ruconest during the single-arm phase.

[3] studies C1 1304 and C1 1205 combined.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Hereditary angioedema is a rare condition characterised by potentially life-threatening crises of acute angioedema. Early relief of symptoms in order to avert a life-threatening crisis is key in the treatment of attacks. Ruconest is intended for the treatment of acute attacks of angioedema in subjects with hereditary angioedema to reduce the time taken to achieve relief of symptoms.

With the caveats that both clinical studies C1 1205 and C1 1304 for adolescents followed a single-arm design and that adolescents represent a sub-group within each study, simple analysis of the results for adolescents show marked and consistent reductions in time to beginning of relief of symptoms and time to minimal symptoms compared to placebo. The effect was shown to be consistent in both, adults and adolescents.

The marked reduction in time to achieve relief of symptoms (either beginning of relief or minimal symptoms only) is considered to be very important because of the potentially life-threatening nature of the condition.

The importance of favourable effects is further supported by:

- continued availability of supply of Ruconest (produced by recombinant technology) in comparison to supply from donor plasma that may vary,
- not being a blood-derived product thereby removing the potential risk of exposure to blood-borne pathogens.

There were no deaths, serious TEAEs or discontinuations due to TEAEs in the clinical studies.

Six patients (38%), all female, reported a total of 24 TEAEs that were similar to those reported in adults i.e. urticaria, skin rash, abdominal discomfort and headache. None of the events were considered to be probably or definitely related to study drug.

One patient experienced vertigo and nausea which were considered to be possibly related to study drug.

There were too few adolescent subjects to conduct a comprehensive assessment of clinical safety: this is understood given the rarity of the condition of hereditary angioedema. Those adverse events / reactions that were reported are considered to be tolerable and relatively unimportant.

The consequences of antibody development is planned to be ascertained in an ongoing PASS as described in the RMP.

Benefit-risk balance

The potential life-saving consequence of exposure to Ruconest in the management of acute attacks of angioedema in subjects with hereditary angioedema far outweighs the unfavourable aspects, thus far limited to one patient experiencing vertigo and nausea which were considered to be 'possibly related' to study drug.

Discussion on the Benefit-Risk Balance

Although the total evidence of clinical efficacy is small as only 16 adolescents took part in the clinical studies which were (mostly) conducted in a single-arm experimental fashion, the marked and consistent reductions in time to relief of symptoms in comparison to placebo (administered during the placebo-controlled phases of the studies) and the similar magnitude of the effect in adults give overall assurance of clinical efficacy in adolescents. Furthermore a comparable pharmacokinetic behaviour of C1INH in adults and adolescents was demonstrated in order to support extrapolation of the positive B/R of C1INH in adults to adolescents.

There are outstanding concerns that clinical efficacy may wane over time but these have not been substantiated by the clinical programme now submitted which showed (apparent) consistent effect over the first five distinct episodes of acute angioedema. A long term follow up is being conducted via a registry.

The total evidence of clinical safety is limited, with the company reporting only one treatment emergent adverse event of vertigo and nausea that it considered to be related to study drug but the safety profile can be considered to be adequately managed with current risk minimisation and pharmacovigilance activities as described in the RMP. The sparseness of data comes in the context of a rare disease and safety as well as the immunological profile of Ruconest in particular in relation to development of neutralizing antibodies against C1 inhibitor is further under assessment within an ongoing PASS as described in the risk management plan.

The overall benefit-risk balance is considered to be 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 and IIIB

Extension of Indication to include adolescents in the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. As a consequence sections 4.1, 4.2, and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adolescents in the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. As a consequence sections 4.1, 4.2, and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Ruconest EMEA/H/C/001223/II/31 for further information.