26 March 2020
EMA/193472/2020
Committee for Medicinal Products for Human Use (CHMP)

Group of variations including an extension of indication assessment report

Procedure No. EMEA/H/C/001223/II/0053/G

Invented name: Ruconest

International non-proprietary name: conestat alfa

Marketing authorisation holder (MAH): Pharming Group N.V

This application is in the area of: (Non-)Clinical RMP

eCTD sequences related to the procedure: 0134, 0138

Note

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

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List of abbreviations

Ab	antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC0-3	area under the plasma concentration-time curve from Presentation to 3 hours post-infusion
BLQ	below the limit of quantification
C1INH	C1 esterase inhibitor
C4	plasma complement component 4
CI	confidence interval
Cmax	maximum plasma concentration of C1INH
CRF	case report form
CV	coefficient of variation
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EU	European Union
GCP	Good Clinical Practice
HAE	hereditary angioedema
hCG	human chorionic gonadotropin
HRI	host-related impurities
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IS	Investigator score(s)
ITT	Intention to Treat
iv	intravenous
KM	Kaplan-Meier
LLQ	lower limit of quantification
MID	minimally important difference
mins	minutes
OLE	open-label extension

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PT	preferred term
RCT	randomized controlled trial
rhC1INH	recombinant human C1 inhibitor 150 U/mL
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
t½	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TEQ	treatment effect questionnaire
Tmax	time to maximum plasma concentration of C1INH
USA	United States of America
WHO	World Health Organization
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Pharming Group N.V submitted to the European Medicines Agency on 25 October 2019 an application for a group of variations.

The following changes were proposed:

Variations 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 and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	I, IIIA and IIIB

Extension of indication to include children in the treatment of acute angioedema attacks with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. This is based on results from Study C1 1209 in children. In addition, final efficacy and safety data from the OLE phases of Studies C1 1304 and 1205 and the completed Study C1 1310 are submitted together with final study results of Studies C1 1207 and 3201, concerning prophylactic treatment of HAE patients. Consequently, the product information has been updated (sections 4.1, 4.2, 4.8, 5.1, 5.2).

Furthermore, the company is requesting an extension for the completion of registry Study C1 1412. The current RMP (V 18.0) states that completion of the final study report for Study C1 1412 is anticipated 31 March 2020. Although patient enrolment has increased, the study will not be completed on time. The MAH would therefore like to request an extension of the study completion date to submit the final report date for Study C1 1412 of 30 June 2022. In addition, as mentioned below, the RMP has also been aligned to RMP template version 2.0.1.

The product information has also been updated to align with the most recent QRD template, version 10.1.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet 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/0343/2018 on the agreement of a paediatric investigation plan (PIP) and the granting of a waiver.

At the time of submission of the application, the PIP P/0343/2018 was completed. The PDCO issued an opinion on compliance for the PIP EMA/PDCO/146070/2019.

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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	25 October 2019
Start of procedure:	2 November 2019
CHMP Rapporteur Assessment Report	20 December 2019
PRAC Rapporteur Assessment Report	20 December 2019
PRAC Outcome	16 January 2020
CHMP members comments	17, 23, 24 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2020
Request for supplementary information (RSI)	30 January 2020
PRAC Rapporteur Assessment Report	2 March 2020
PRAC members comments	04 March 2020
Updated PRAC Rapporteur Assessment Report	19 March 2020
CHMP Rapporteur Assessment Report	11 March 2020
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP Rapporteur Assessment Report	19 March 2020
Opinion	26 March 2020

2. Scientific discussion

2.1. Introduction

Rationale for the proposed change

The proposed application represents an update of the indication to include children in the treatment of acute angioedema attacks with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. The applied indication was: *Ruconest is indicated for treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.*

This application is based on results from Study C1 1209 performed in children of 2-13 years of age. Safety data from the OLE phases of Studies C1 1304 and 1205 and the completed Study C1 1310 are also submitted. Furthermore, the MAH provided final study results of Studies C1 1207 and 3201, investigating prophylactic treatment of HAE patients. Consequently, the product information has been updated.

Furthermore, the MAH is requesting an extension of the deadline for the completion of registry Study C1 1412. The current RMP (V 18.0) states that completion of the final study report for Study C1 1412 is anticipated 31 March 2020. Although patient enrolment has increased, the study will not be completed on time. The MAH would therefore like to request an extension of the study completion date in order to submit the final report date for Study C1 1412 of 30 June 2022.

2.1.1. Problem statement

Disease or condition/clinical presentation

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.

Management

The currently available treatments are described below

Firazyr (Icatibant) 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 in 2008 and received orphan designation. Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency.

Berinert 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 in 2009 in 23 European member states including Norway and Iceland.

Cinryze contains the active substance C1 inhibitor derived from human plasma. It was approved by a centralized procedure in 2011. It is indicated for treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).

Takhzyro (Lanadelumab) is a monoclonal antibody therapy for the prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. It was approved by a centralised procedure in 2018 and received orphan designation.

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

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP. There was no need to submit an updated ERA considering the population applied for in this extension of indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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:

Study	Study (Phase, Design, Type of control)	Objective(s) of the Study	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Administrations	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
	Submitted for extension of therapeutic indication (see clinical efficacy and safety)					
C1 1209	Phase 2 Single arm, Open label	Efficacy, safety, tolerability, immunogenicity, PK/PD,	Conestat alfa 50 U/kg (max 4200U) Slow IV injection	20 patients 73 administrations	Symptomatic children with HAE (age 2-13 years)	Single doses (1 attack)
	Submitted for changes in the SPC, Labelling or PL and change(s) to, the obligations and conditions of a marketing authorisation, including the RMP (see clinical safety)					
C1 1304 OLE	Phase 3 Open label extension	Efficacy, safety, tolerability, PK/PD	Conestat alfa 2100 U IV infusion	57 patients 194 administrations	Symptomatic patients with HAE	Single dose; option of 1 or 2 additional dose(s) (≥1 attack)
C1 1205 OLE	Phase 2 Open label extension	Efficacy, safety, tolerability,PK/PD	Conestat alfa 50 U/kg IV infusion	62 patients 168 administrations	Symptomatic patients with HAE	Single dose; option of additional dose (≥1 attack)
C1 1310	Phase 3 Randomized double blind placebo controlled	Efficacy, safety, immunogenicity	Conestat alfa 50 U/kg (maximum 4200 U) Placebo (saline) Slow IV injection	Conestat alfa: 43 patients Placebo: 31 patients Rescue medication: (open-label conestat alfa): 5 and 13 patients	Symptomatic patients with HAE	Single dose (1 attack)

					from conestat alfa and placebo group, respectively		
C1 1207*		Phase 2 Open label	Efficacy, safety, tolerability	Conestat alfa 50 U/kg Slow IV injection	25 patients: 8 doses: 22 patients 10 doses: 2 patients 11 doses: 1 patient ≥1 breakthrough attack: 6 patients	Asymptomatic patients with HAE	Once-weekly for 8 weeks; breakthrough attacks were treated; option of additional dose
C1 3201*		Phase 2 Randomized double blind placebo controlled	Efficacy, safety, tolerability	Conestat alfa 50 U/kg Placebo (saline) Slow IV injection	31 patients (including one patient with placebo only) / (527 administrations)	Asymptomatic patients with HAE	Twice-weekly conestat alfa, once-weekly conestat alfa + once-weekly placebo, or twice-weekly placebo; three 4-week periods; break-through attacks: ≤2 doses/24 hours

* This study concerns prophylactic treatment of HAE (not pertinent to the claimed indication). Only safety data are submitted for this variation.

Study C1 1209 was also previously assessed in procedure EMEA/H/C/001223/P46/020.

2.3.2. Pharmacokinetics and Pharmacodynamics

Methods

In study C1 1209 data was collected to characterize the Pharmacokinetics and Pharmacodynamics of Ruconest for children aged 2-13 years. The study is described in detail in the following section on clinical efficacy.

Pharmacokinetics were assessed by evaluation of functional C1INH concentrations over time for the first acute attack only. Functional C1INH pharmacokinetic concentrations were expressed as a percentage of normal, based upon a pool of plasma from healthy adult subjects (Standard Human Plasma sourced in Germany), which was originally set at 100%. The following PK parameters were derived (where appropriate) for C1INH activity in plasma from the concentration-time data using standard non-compartmental methods: maximum plasma concentration of C1INH (Cmax) and area under the plasma concentration-time curve from Presentation to 3 hours post-infusion (AUC0-3).

Pharmacodynamics were assessed by evaluation of plasma concentrations of C4 over time for the first acute attack only.

PK/PD was assessed using the ratio (2-4 hours post-dose: Baseline) of C4 versus the ratio (2-4 hours post-dose: Baseline) in functional C1INH for Attack 1 only.

Results

Pharmacokinetics

For all patients who received a single iv administration of rhC1INH for the first attack, concentrations of functional C1INH were maximal for the majority of patients at 5 minutes post-dose with individual values ranging from 62% to 168% of normal. At 2 to 4 hours post-dose, functional C1INH concentrations were lower than 5 minutes post-dose values but above Baseline (Presentation) values for the majority of patients (range 28% to 81% of normal, based upon 18/20 patients). As per study inclusion criteria, all 20 patients had concentrations of functional C1INH that were < 50% of normal at Baseline (Presentation). A total of 18/20 patients had concentrations of functional C1INH that were > 70% of normal (the lower limit of the normal range) at the 5 minutes and/or 2 to 4 hours post-dose time points.

Functional C1INH pharmacokinetic concentrations were expressed as a percentage of normal, based upon a pool of plasma from healthy adult subjects (Standard Human Plasma sourced in Germany), which was originally set at 100%. Due to an inadequate number of sampling time points; the only PK parameters calculated in this study were AUC0-3 and Cmax. Upon administration of a single iv dose of rhC1INH 50 U/kg for the first attack, arithmetic mean functional C1INH Cmax was 123.2% of normal (range 62% to 168%), and AUC0-3 was 170.87% of normal (range 95.20% to 243.58%).

At 2 to 4 hours post-dose, functional C1INH concentrations were lower than 5 minutes post-dose values but above baseline values for the majority of patients (range 28% to 81% of normal, based on 18/20 patients. A total of 18/20 patients had concentrations of functional C1INH > 70% of normal (the lower limit of the normal range) at the 5 minutes and/or 2 to 4 hours post-dose time points.

Table 2: Functional C1 Esterase Inhibitor (C1INH) (% of Normal) Over Time for First Attack Only (PK/PD Concentration Set)

	Presentation n=20	5 Minutes Post-dose n=19	2-4 hours Post-dose n=20
N > LLQ	1	19	19
Arithmetic mean	13.2	123.2	43.5
SD	5.14	28.32	16.15
CV (%)	39.1	23.0	37.1
Median	12.0	122.0	41.0
Min, max	12, 35	62, 168	12, 81
Geometric mean	12.7	119.8	40.5
Geometric CV (%)	24.3	25.5	42.4

Source: Table 14.2.2.1.1
C1INH = C1 esterase inhibitor, CV = coefficient of variation, LLQ = lower limit of quantification, n = number of patients with observation, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SD = standard deviation.
N > LLQ refers to the number of patients with C1INH concentrations above the LLQ.

Pharmacodynamics

For all patients who received a single iv administration of rhC1INH for the first attack, arithmetic mean and individual patient C4 concentrations generally decreased from Baseline (Presentation) values at 5 minutes post-dose before increasing above Baseline (Presentation) values at 2 to 4 hours post-dose, although individual patient data were variable.

Mean C4 concentrations at Presentation were comparable across attacks, with the exception of an increased mean C4 concentration at Attack 5, which was however highly variable (73 µg/mL; 7.25 - 187.00 µg/mL) and was measured only for 6 patients.

Table 3: C4 Concentrations (µg/mL) Over Time for First Attack Only (PK/PD Concentration Set)

	Presentation n=20	5 Minutes Post-dose n=19	2-4 hours Post-dose n=20
N > LLQ	16	14	18
Arithmetic mean	38.160	26.376	55.815
SD	36.4307	18.4498	51.5839
CV (%)	95.468	69.948	92.419
Median	24.700	21.400	37.650
Min, max	7.25,137.00	7.25, 71.00	7.25, 227.00
Geometric mean	26.293	20.495	39.218
Geometric CV (%)	109.231	88.457	109.291

Source: Table 14.2.2.2
C4 = plasma complement component 4, CV = coefficient of variation, LLQ = lower limit of quantification, n = number of patients with observation, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SD = standard deviation.
N > LLQ refers to the number of patients with C4 concentrations above the LLQ.

2.3.3. Discussion on clinical pharmacology

Blood samples for the assessment of PK and PD were collected prior to administration, directly following infusion (5 minutes post-infusion) and one sample between 2 and 4 hours post-infusion. For each sample for PK C1INH activity and for PD C4 were measured. C4 data was additionally collected at presentation of each subsequent acute HAE attack. For PK, only for the first attack, Cmax and AUC_{0-3} were calculated.

Pharmacokinetics

For the assessment of PK the functional C1INH activity was reported as percentage of normal based on a pool of plasma from healthy adult subjects which was originally set at 100%. The MAH clarified during the P46 procedure that a commercial standardized product was used (Standard Human Plasma sourced in Germany) and not a pool of samples from studies in healthy volunteers. The same standard was used for the analysis of PK samples in the adult studies.

The collected data showed an increase to 123% (62-168%) 5 minutes post dose and values approaching baseline at 2-4 h post dose (Table 11-8). These findings are consistent with the results for adult and adolescent patients, where the 50 U/kg dose also restored the C1INH level to normal for about 2 hours.

Pharmacodynamics

The data for a single dose indicate that the C4 concentrations decrease from baseline towards 5 minutes post-dose and then increase above baseline at 2-4 hours post-dose. The measurements are, however, very variable. Nevertheless, the results are comparable to the previously presented data for adult and adolescent patients.

2.3.4. Conclusions on clinical pharmacology

Overall, the results presented for the paediatric population are in accordance with the results obtained for the adult and adolescent patient population.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose response studies were submitted.

2.4.2. Main studies

The grouped variation is based on information obtained from different studies. The change of indication is based only on the results of study C1 1209 which is discussed in this section. All other submitted studies are briefly discussed in the introduction. Respective parts are discussed later in the clinical safety of this report as they only concern changes to the SmPC, Labelling or PL with regards to safety information and changes to the obligations and conditions of a marketing authorisation, including the RMP.

Title: Study C1 1209: Open-label, Phase 2, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in paediatric patients with hereditary angioedema, from 2 up to and including 13 years of age

Methods

This study was an open-label, Phase 2, non-comparative, multinational, multicenter clinical study in paediatric patients from 2 up to and including 13 years of age, with a confirmed diagnosis of HAE. Patients were eligible for treatment with rhC1INH if they presented to the clinic within 5 hours of onset

with an acute attack of at least moderate severity (Investigator score [IS] of at least three) without signs of spontaneous regression.

Patients received rhC1INH at a dose of 50 U/kg body weight up to a maximum of 4200 U. The reconstituted solution was administered as a slow intravenous (iv) injection over approximately 5 minutes. The patients remained in hospital and were closely monitored in the study center for at least 4 hours after study medication administration.

At the discretion of the Investigator and depending upon the patient's clinical response, an additional dose may have been given to patients following their initial dose as specified above. Not more than two doses were to be administered within 24 hours.

The minimum observation period was 4 hours, after which the patient could leave if the Investigator judged the patient's condition well enough for discharge from the hospital. The Investigator scheduled a telephone contact at 24 hours (± 4 hours) after study medication administration. Follow up visits were planned at Day 28 (± 3 days) and Day 90 (±7 days).

Patients could be treated for a maximum of 10 attacks, provided there was a minimum 24-hour interval between subsequent treated attacks, and as long as anti-rabbit epithelium (dander) immunoglobulin (Ig)E testing remained negative.

Safety (including immunogenicity), PK/PD, and efficacy variables were assessed at regular time points before and after administration of study medication.

Study participants

Inclusion Criteria

Consenting (parental/legal guardian permission) male or female patients from 2 up to and including 13 years of age with a clinical and laboratory confirmed diagnosis of HAE (Baseline C1 esterase inhibitor [C1INH] activity < 50% of normal) were eligible for enrolment. Patients were treated with study medication if they had an eligible attack that met the following criteria:

- Clinical symptoms of an acute HAE attack
- Onset of eligible symptoms within 5 hours from the moment at which medical evaluation to determine eligibility had occurred
- IS for at least one anatomical location at the time of initial evaluation of at least three (moderate severity or greater) without signs of spontaneous regression
- 24 hours or more had passed since the patient's last study treatment

Exclusion Criteria

Patients were not included in the study if they met any of the following criteria:

Screening

- A diagnosis of acquired C1INH deficiency (acquired angioedema)

A medical history of allergy to rabbits or rabbit-derived products (including rhC1INH, antisera), or positive anti-rabbit epithelium (dander) IgE test (cut off > 0.35 kU/L in ImmunoCap® assay [Phadia, Sweden] or equivalent.

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- Treatment with investigational drug in another clinical study in the last 30 days
- Any clinical significant abnormality in the physical examination and/or the routine laboratory assessments, that in the opinion of the Investigator made the patient unsuitable for participation in the study
- Patient or legal guardian whose decision to participate may have been unduly influenced by perceived expectation of gain or harm by participation, such as patient or legal guardian in detention due to official or legal order
- Any condition or treatment that in the opinion of the Investigator may have interfered with the evaluation of the study objectives

Treatment

- Any changes since Screening that would have excluded the patient based on the above exclusion criteria
- Ten HAE attacks previously treated with study medication
- Suspicion for an alternate explanation of the symptoms other than an acute HAE attack
- Use of any disallowed concomitant medication since onset of acute HAE attack (including narcotics, plasma-derived C1INH, fresh frozen plasma, bradykinin receptor antagonist, analgesics, anti-emetics, and/or non-steroidal anti-inflammatory drugs)
- Positive pregnancy test (urine or serum)

Treatments

Patients received rhC1INH at a dose of 50 U/kg body weight up to a maximum of 4200 U. At the discretion of the Investigator and depending upon the patient's clinical response, an additional dose may have been given to patients following their initial dose as specified above. Not more than two doses were to be administered within 24 hours.

Objectives

Primary:

- To assess the clinical safety, immunogenicity and tolerability of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old hereditary angioedema (HAE) patients.

Secondary:

- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old HAE patients
- To assess the efficacy of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old HAE patients

Outcomes/endpoints

Primary Endpoint:

The primary efficacy endpoint was the **time to beginning of relief** based on the Overall visual analog scale (VAS) score, where time of beginning of relief was assessed as the first time point at which the VAS score decreased by at least 20 mm at any eligible anatomical location compared to Baseline, with persistence of the decrease at the next time point.

Secondary Endpoint:

The secondary efficacy endpoint was the **time to minimal symptoms** based on the Overall VAS, defined as the time, in minutes, from time of infusion to minimal symptoms (i.e. the time at which the Overall VAS score fell below 20 mm for all locations where VAS Scores were recorded).

Exploratory Endpoints:

• Time to beginning of relief based on IS

• Time to minimal symptoms based on IS

• Time to beginning of relief based on the treatment effect questionnaire (TEQ)

• Time to minimal symptoms based on TEQ

• Time to complete resolution

• Therapeutic failure

• Receipt of a second dose

Sample size

63 patients were screened: six of these patients were considered screen failures and 57 patients were eligible for treatment and included in the Screening Analysis Set. 20 patients have been treated.

Randomisation and Blinding (masking)

This was an open label study therefore no randomisation or blinding was performed.

Statistical methods

The following analysis sets were defined:

- Screening Analysis Set: All patients screened for the study, who at Screening were eligible for treatment
- Safety Analysis Set: The set of patients who received at least one dose of the study medication
- Intention to Treat Analysis Set (ITT): The set of patients who received at least one dose of the study medication, and for whom any efficacy data was available
- Per Protocol (PP) Analysis Set: All patients in the ITT Analysis Set that had at least one attack without any major protocol violation that affected the efficacy assessments. Only data from the attacks without major protocol violations that affected the efficacy assessments were included for these patients.
- Pharmacokinetic (PK)/Pharmacodynamic (PD) Concentration Set: The subset of the Safety Analysis Set that had at least one PK/PD concentration measured

- Pharmacokinetic (PK)/Pharmacodynamic (PD) Analysis Set: The subset of the Safety Analysis Set that had sufficient plasma concentration data. A patient was seen as having sufficient plasma concentration data if at least the Cmax could have been calculated

For all continuous variables, summary statistics included the number of patients, mean, standard deviation (SD), median, minimum, and maximum values. For categorical variables, per category, the absolute counts (n) and percentages (%) of patients with data, and if appropriate, the number of patients with missing data, were presented.

Efficacy: The Intention to Treat (ITT) Analysis Set was the primary analysis set of interest in all efficacy analyses, and the primary, secondary, and exploratory efficacy analyses were repeated on the Per Protocol (PP) Analysis Set. Kaplan Meier (KM) analyses were performed for each of the time to event endpoints (time to beginning of relief and time to minimal symptoms defined using Overall VAS, IS, and TEQ, and time to complete resolution). Kaplan Meier analyses for time to beginning of relief and time to minimal symptoms using the Overall VAS score were repeated for first and last attacks. Kaplan Meier analyses for time to beginning of relief (IS and TEQ), time to minimal symptoms (IS and TEQ), and time to complete resolution were repeated for each attack. A bar chart was also presented to summarize therapeutic failure for both first and last attacks.

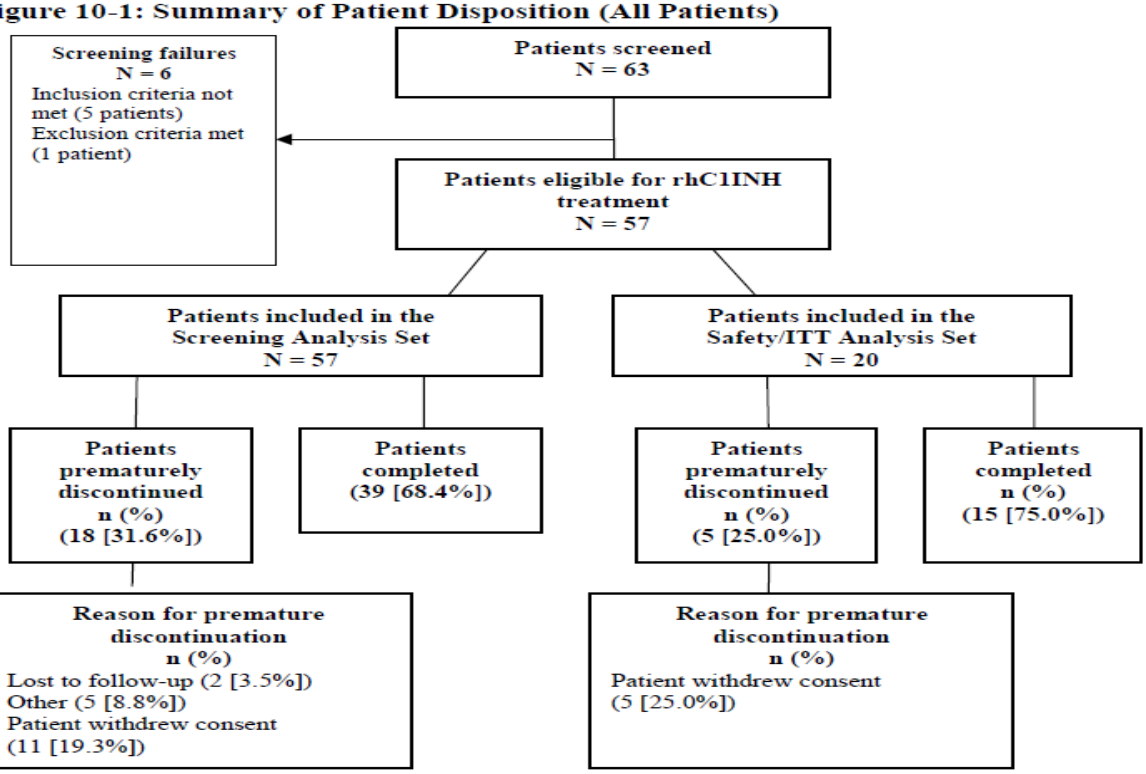
Pharmacokinetics (PK)/Pharmacodynamics (PD): PK (C1INH) and PD (C4) concentrations were summarized, listed, and presented in boxplots panelled by nominal time, and grouped by weight and panelled by nominal time. The ratio (2-4 hours: Baseline) in C4 versus the ratio (2-4 hours: Baseline) in functional C1INH was also summarized graphically.

Safety: AEs were summarized by attack for the Safety Analysis Set and were categorized by System Organ Class (SOC) and Preferred Term (PT). Laboratory parameters were summarized at each evaluation time point and as a change from Baseline. ECG, vital signs, diagnostic assay, and immunogenicity findings were summarized. Physical examination findings were listed.

Results

Participant flow

Figure 10-1: Summary of Patient Disposition (All Patients)



Source: Tables 14.1.1.1, 14.1.1.2, and 14.1.2
ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, rhC1INH = recombinant human C1 inhibitor 150 U/mL.

Recruitment

This was a multicenter study performed at 18 sites in the US, Israel. Italy, Poland, Romania, Germany, Macedonia, the Czech Republic, Slovakia and Hungary.

First patient recruited: 17 January 2012 (first patient first visit)

Last patient completed: 17 July 2017 (last patient last visit)

Conduct of the study

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations and the applicable regulatory requirements, including the ICH-E11 guideline "Clinical Investigation of Medicinal Products in the Paediatric Population".

Amendments

Four general protocol amendments have been implemented and one specific to the study sites in the Czech Republic.

Protocol Amendments 1 (ensure consistent evaluation of the VAS and TEQ efficacy parameter and Anti-rabbit IgE Ab testing was added to the immunology test panel at Day 28) and Protocol Amendment 2

(correct the IS to reflect the more redefined analysis of attack locations and Anti-rabbit IgE Ab testing was added to the analysis section for consistency with the change made in Protocol Amendment 1) were implemented before study initiation.

Protocol Amendment 3 (stipulate that pregnancies were to be reported as an SAE) was implemented after study initiation, and two patients were treated for a total of nine attacks under this protocol amendment only.

Protocol amendment 4 consisted in a) update of assessments made during the 4-5 hour period after Presentation of an attack to ensure any medications previously reported as taken on an as needed basis were re-assessed and recorded since the onset of symptoms, b) addition of a time window for completion of the VAS and TEQ questionnaires at the 8 hour (window = 1 hour) and 24 hour (window = 4 hours) time points after Presentation of the attack. C) other changes in time windows for telephone contact and follow up visit, d) Definitions for relapse and spontaneous regression were added.

One patient was treated under both Protocol Amendment 3 (four attacks) and Protocol Amendment 4 (two attacks). The remaining patients in the study were treated under Protocol Amendment 4 for a total of 58 attacks, of these, two patients were also treated under local Protocol Amendment 1 (Czech Republic patients only) for five of the 58 attacks.

Local amendment for the Czech Republic:

This amendment was introduced upon request of the Czech Republic Competent Authorities (SUKL) and includes country specific updates in the sections of blood sampling procedures to ensure compliance with the guidelines, extension of the reasons for withdrawal and the usage of contraception is removed because sexual intercourse between persons under the age of 15 is illegal in the Czech Republic.

Protocol deviations

All twenty patients (100%) in the Safety Analysis Set reported at least one protocol deviation during the study. The majority of reported protocol deviations were considered minor. The most common protocol deviations in the Safety Analysis Set included deviations in study procedures (20 [100%] patients) and deviations in the visit schedule (16 [80%] patients), all of which were considered minor (Table 10-2).

Major protocol deviations included:

- not completing the VAS at a particular time point for an eligible attack location (five patients),
- failure to verify inclusion/exclusion criteria prior to study treatment (two patients),
- inadvertent disclosure of patient identity or private information by the study site to unauthorized persons/agencies (one patient),
- SAE not reported in a timely manner (one patient),
- use of a disallowed concomitant medication/therapy (one patient).

Six patients reported major protocol deviations that caused HAE attack data to be excluded from the PP Analysis Set.

Table 4: Summary of Protocol Deviations (Safety Analysis Set)

	Total N=20 n (%)
Number of patients with at least one protocol deviation	20 (100.0)
Deviation category	
Inclusion/exclusion	2 (10.0)
Concomitant medication/therapy	1 (5.0)
Laboratory procedures	8 (40.0)
Study procedures	20 (100.0)
(S)AEs	1 (5.0)
Visit schedule	16 (80.0)
Efficacy ratings	11 (55.0)
Other	2 (10.0)

Source: Table 14.1.3
N = total number of patients, n = number of patients with observation, SAE = serious adverse event.

Baseline data

In the Safety Analysis Set, patient age at Presentation of Attack 1 ranged from 5 to 14 years, with a mean age of 8.20 years. There was a similar proportion of female (9/20 [45.0%]) and male (11/20 [55.0%]) patients, and the majority of patients were Caucasian (95.0%) compared to one (5.0%) Black patient. As patient age increased with increasing number of attacks, mean height, weight, and Tanner stage generally increased across attacks in the Safety, ITT, and PP Analysis Sets.

Table 5: Summary of Demographics and Baseline Patient Characteristics at Presentation of Attack 1 (Safety Analysis Set)

	Attack 1 N=20
Age at Presentation (years)	
n	20
Mean	8.20
SD	2.949
Min, max	5.0, 14.0
Gender	
Female	9 (45.0)
Male	11 (55.0)
Race	
Caucasian	19 (95.0)
Black	1 (5.0)
Height at Screening (cm)	
n	20
Mean	125.6
SD	25.78
Min, max	78, 167
Weight at Presentation (kg)	
n	20
Mean	34.81
SD	20.554
Min, max	16.0, 93.1
Weight group at Presentation	
Weight ≤ 30 kg	11 (55.0)
30 kg < Weight ≤ 60 kg	7 (35.0)
60 kg < Weight ≤ 84 kg	1 (5.0)
Weight > 84 kg	1 (5.0)
Tanner stage at Presentation	
Stage 1	13 (65.0)
Stage 2 or higher	7 (35.0)

Source: Table 14.1.4.2
min = minimum, max = maximum, N = total number of patients, n = number of patients with observation, SD = standard deviation.

Numbers analysed

Analysis Populations:

A total of 63 patients gave informed consent (parental/legal guardian permission) to enter the study: six of these patients were considered screen failures as they failed to meet an inclusion criteria or met an exclusion criteria for study entry, and 57 (90.5%) were eligible for treatment and included in the Screening Analysis Set. Twenty (31.7%) of these patients received at least one dose of study medication and were included in the Safety Analysis and ITT Analysis Sets. Of these 20 patients, 18 (28.6%) patients were included in the PP Analysis Set. Two (3.2%) patients were excluded for the following reasons: One patient only received one study treatment (Attack 1) and reported a major protocol deviation that affected the efficacy assessments (Attack 1, Day 0 VAS/TEQ 8 hr post-dose assessment was not performed as the patient was asleep). The second excluded patient only received one study treatment (Attack 1) and reported a major protocol deviation that affected the efficacy assessments (Attack 1, VAS/TEQ 8 hr post-dose assessments were not completed).

Six patients in the Safety and ITT Analysis Sets had study treatment data that were excluded from the PP Analysis Set due to major protocol deviations that affected the efficacy assessments. However, four of these patients were included in the overall PP Analysis Set as they had at least one other attack without a major protocol deviation that affected the efficacy assessments.

The PK/PD Concentration Set included 20 (31.7%) patients and the PK/PD Analysis Set included 19 (30.2%) patients (one patient was excluded as the 5 minutes post-dose C1INH and C4 assessment results were missing).

Exposure:

The planned volume of rhC1INH (50 U/kg body weight up to a maximum of 4200 U) was administered at every HAE attack administration and exposure to study medication was comparable across attacks.

A total of 3/73 attacks were treated with a second dose of rhC1INH during the study: attacks requiring a second dose were reported by 2/20 (10.0%) patients in the ITT Analysis Set (one patient received a second dose of rhC1INH for Attacks 3 and 8, and one patient received a second dose of rhC1INH for Attack 3).

Outcomes and estimation

Primary Efficacy Evaluation

The median *time to beginning of relief of symptoms* with persistence for the ITT Analysis Set estimated using KM analysis, based on Overall VAS decrease ≥ 20 mm, was approximately 60 minutes post-dose across repeated attacks. Results were generally similar in the PP Analysis Set. See table below.

Table 6: Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Beginning of Relief of Symptoms with Persistence Based on Overall Visual Analog Scale (VAS) Decrease ≥ 20 mm (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	19[a]	60.0 (35.0, 124.0)
Attack 2	12	11[a]	60.0 (30.0, 120.0)
Attack 3	9	9	62.0 (30.0, 75.0)
Attack 4	7	6[a]	61.5 (30.0, 125.0)
Attack 5	6	6	60.0 (30.0, 65.0)
Attack 6	5	5	65.0 (31.0, 240.0)
Attack 7	4	4	63.5 (60.0, 120.0)
Attack 8	4	4	60.0 (60.0, 66.0)
Attack 9	3	3	60.0 (36.0, 60.0)
Attack 10	3	3	120.0 (30.0, 128.0)
Last Attack[b]	12	12	60.0 (30.0, 120.0)
All Attacks[c]	20	20	60.0 (60.0, 65.0)

CI = confidence interval, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, rhC1INH = recombinant human C1 inhibitor 150 U/mL, VAS = visual analog scale.
[a] For Attacks 1, 2, and 4, Patient 01-01 received a rhC1INH dose infusion 5 minutes before the Presentation VAS assessment was completed; therefore, there was no Baseline VAS score to derive the VAS assessments at these time points.
[b] 'Last Attack' only included those patients who had more than one treated attack.
[c] 'All Attacks' was based on 73 attacks across 20 patients.
Time shown was the time to beginning of relief at any eligible location.

Secondary Efficacy Evaluation

The *median time to minimal symptoms* for the ITT Analysis Set estimated using KM analysis, based on Overall VAS decrease ≥ 20 mm, was approximately 120 minutes post-dose across repeated attacks. PP Analysis Set results were generally similar, with the exception of an increased median time to minimal symptoms for Attack 2 for the PP Analysis Set compared to the ITT Analysis Set (181.0 minutes versus 122.0 minutes). (refer to tale below)

Table 7: Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Minimal Symptoms Based on Overall Visual Analog Scale (VAS) Decrease ≥ 20 mm (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	20	125.0 (60.0, 240.0)
Attack 2	12	12	122.0 (60.0, 245.0)
Attack 3	9	9	120.0 (35.0, 485.0)
Attack 4	7	7	120.0 (30.0, 125.0)
Attack 5	6	6	120.0 (60.0, 495.0)
Attack 6	5	5	126.0 (120.0, 240.0)
Attack 7	4	4	180.0 (120.0, 487.0)
Attack 8	4	4	124.5 (60.0, 241.0)
Attack 9	3	3	120.0 (60.0, 249.0)
Attack 10	3	3	120.0 (60.0, 485.0)
Last Attack[a]	12	12	120.0 (60.0, 241.0)
All Attacks[b]	20	20	122.5 (120.0, 126.0)

CI = confidence interval, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, VAS = visual analog scale.
[a] 'Last Attack' only included those patients who had more than one treated attack.
[b] 'All Attacks' was based on 73 attacks across 20 patients.

Ancillary analyses

The median time to *beginning of relief of symptoms* based on IS for the ITT Analysis Set estimated using KM analysis, was approximately 60.0 minutes post-dose across repeated attacks. However, median values were lower for Attack 2 (median: 30.0 minutes [95% confidence interval (CI) 30.0 to 65.0 minutes]) and Attack 3 (median: 39.0 minutes [95% CI 30.0 to 75.0 minutes]), and higher for Attack 7 (median: 90.0 minutes [95% CI 60.0 minutes, upper limit of the 95% CI for the median not estimable]). Similar results were observed in the PP Analysis Set.

Table 8 : Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Beginning of Relief Based on Investigator Score (IS) (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	19[a]	60.0 (35.0, 65.0)
Attack 2	12	11[a]	30.0 (30.0, 65.0)
Attack 3	9	9	39.0 (30.0, 75.0)
Attack 4	7	6[a]	60.0 (30.0, 242.0)
Attack 5	6	6	60.0 (35.0, 60.0)
Attack 6	5	5	60.0 (30.0, 120.0)
Attack 7	4	4	90.0 (60.0, -)
Attack 8	4	4	60.0 (30.0, 64.0)
Attack 9	3	3	60.0 (30.0, 126.0)
Attack 10	3	3	60.0 (30.0, 64.0)
Last Attack[b]	12	12	60.0 (30.0, 64.0)
All Attacks[c]	20	20	60.0 (40.0, 60.0)

CI = confidence interval, IS = Investigator score, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, rhC1INH = recombinant human C1 inhibitor 150 U/mL.
[a] For Attacks 1, 2, and 4, Patient 01-01 received a rhC1INH dose infusion 5 minutes before the Presentation IS assessment was completed; therefore, there was no Baseline IS to derive the IS assessments at these time points.
[b] 'Last Attack' only included those patients who had more than one treated attack.
[c] 'All Attacks' was based on 73 attacks across 20 patients.
Time shown is the time to beginning of relief at any eligible location.
Values that were not estimable were displayed as '-'.

The *median time to minimal symptoms based on IS* for the ITT Analysis Set estimated using KM analysis varied across repeated attacks. The median time was approximately 120 minutes post-dose for Attacks 2, 3, 4, 5, 9, and 10; 180 minutes post-dose for Attacks 7 and 8; and 240 minutes post-dose for Attacks 1 and 6. PP Analysis Set results were generally similar, with the exception of an increased median time to minimal symptoms based on IS for Attack 2 for the PP Analysis Set compared to the ITT Analysis Set (183.5 minutes versus 127.0 minutes).

Table 9 Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Miminal Symptoms Based on Investigator Score (IS) (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	20	240.0 (120.0, 245.0)
Attack 2	12	12	127.0 (60.0, 245.0)
Attack 3	9	9	120.0 (60.0, 249.0)
Attack 4	7	7	120.0 (30.0, 245.0)
Attack 5	6	6	122.5 (60.0, 256.0)
Attack 6	5	5	240.0 (121.0, 240.0)
Attack 7	4	4	180.0 (120.0, -)
Attack 8	4	4	180.0 (60.0, 248.0)
Attack 9	3	3	120.0 (60.0, 247.0)
Attack 10	3	3	120.0 (60.0, -)
Last Attack[a]	12	12	123.0 (60.0, 240.0)
All Attacks[b]	20	20	126.0 (120.0, 240.0)

CI = confidence interval, IS = Investigator score, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation.
[a] 'Last Attack' only included those patients who had more than one treated attack.
[b] 'All Attacks' was based on 73 attacks across 20 patients.
Values that were not estimable are displayed as '-'.

The *median time to beginning of relief of symptoms based on TEQ* for the ITT Analysis Set estimated using KM analysis varied across repeated attacks. The median time was approximately 60 minutes post-dose for Attacks 1, 3, 4, and 5; approximately 120 minutes post-dose for Attacks 2, 6, 8, 9, and 10; and 180.5 minutes post-dose for Attack 7. PP Analysis Set results were generally similar, with the exception of an increased median time to minimal symptoms based on TEQ for Attack 4 for the PP Analysis Set compared to the ITT Analysis Set (90.0 minutes versus 65.0 minutes).

Table 10: Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Beginning of Relief Based on Treatment Effect Questionnaire (TEQ) (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	20	65.5 (60.0, 122.0)
Attack 2	12	12	125.0 (30.0, 243.0)
Attack 3	9	9	62.0 (30.0, 486.0)
Attack 4	7	7	65.0 (30.0, 122.0)
Attack 5	6	6	65.0 (30.0, 240.0)
Attack 6	5	5	127.0 (32.0, 240.0)
Attack 7	4	4	180.5 (60.0, 251.0)
Attack 8	4	4	125.5 (60.0, 242.0)
Attack 9	3	3	120.0 (60.0, 130.0)
Attack 10	3	3	120.0 (60.0, 487.0)
Last Attack[a]	12	12	122.5 (30.0, 242.0)
All Attacks[b]	20	20	120.0 (64.0, 122.0)

CI = confidence interval, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, TEQ = treatment effect questionnaire.
[a] 'Last Attack' only included those patients who had more than one treated attack.
[b] 'All Attacks' was based on 73 attacks across 20 patients.
Time shown was the time to beginning of relief at the most severe eligible location.

The *median time to minimal symptoms based on TEQ* for the ITT Analysis Set estimated using KM analysis varied across repeated attacks. The median time was 66 minutes post-dose for Attack 4; approximately 120 minutes post-dose for Attacks 2, 3, 9, and 10; approximately 180 minutes post-dose for Attacks 1 and 8; and approximately 240 minutes post-dose for Attacks 5, 6, and 7. PP Analysis Set results were generally similar, with the exception of increased median time to minimal symptoms based on TEQ for the PP Analysis Set compared to the ITT Analysis Set for Attack 1 (241.0 minutes versus

186.5 minutes), Attack 4 (93.0 minutes versus 66.0 minutes), and for All Attacks (240.0 minutes versus 133.5 minutes).

Table 11: Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Minimal Symptoms Based on Treatment Effect Questionnaire (TEQ) (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	20	186.5 (122.0, 260.0)
Attack 2	12	12	125.0 (60.0, 1440.0)
Attack 3	9	9	135.0 (30.0, 486.0)
Attack 4	7	7	66.0 (30.0, 122.0)
Attack 5	6	6	241.0 (60.0, 1442.0)
Attack 6	5	5	244.0 (240.0, 487.0)
Attack 7	4	4	240.5 (60.0, -)
Attack 8	4	4	181.0 (60.0, 251.0)
Attack 9	3	3	120.0 (60.0, 489.0)
Attack 10	3	3	120.0 (60.0, 1447.0)
Last Attack[a]	12	12	183.5 (60.0, 248.0)
All Attacks[b]	20	20	133.5 (123.0, 241.0)

CI = confidence interval, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation, TEQ = treatment effect questionnaire.
[a] 'Last Attack' only included those patients who had more than one treated attack.
[b] 'All Attacks' was based on 73 attacks across 20 patients.
Values that were not estimable are displayed as '-'.

The median time to complete resolution based on diary results for the ITT Analysis Set estimated using KM analysis varied across repeated attacks, with median values ranging from 100.0 minutes post-dose at Attack 9 to 1167.5 minutes post-dose at Attack 1. PP Analysis Set results were generally similar, with the exception of increased median time to minimal symptoms based on diary results for the ITT Analysis Set compared to the PP Analysis Set for Attack 1 (1167.5 minutes versus 270.0 minutes), Attack 4 (295.0 minutes versus 224.5 minutes), and All Attacks (262.5 minutes versus 230.0 minutes).

Table 12 Median Time (Minutes) and 95% Confidence Intervals (CIs) for Time to Complete Resolution Based on Diary Results (ITT Analysis Set)

	N	n	Median (95% CI)
Attack 1	20	20	1167.5 (180.0, 1687.0)
Attack 2	12	12	215.0 (120.0, 1833.0)
Attack 3	9	9	455.0 (50.0, 1930.0)
Attack 4	7	7	295.0 (55.0, 1465.0)
Attack 5	6	6	230.0 (99.0, 889.0)
Attack 6	5	5	230.0 (170.0, 535.0)
Attack 7	4	4	222.5 (65.0, 2287.0)
Attack 8	4	4	570.0 (58.0, 2204.0)
Attack 9	3	3	100.0 (33.0, 1607.0)
Attack 10	3	3	104.0 (48.0, 1599.0)
Last Attack[a]	12	12	260.0 (60.0, 1035.0)
All Attacks[b]	20	20	262.5 (220.0, 535.0)

CI = confidence interval, ITT = Intention to Treat, N = total number of patients, n = number of patients with observation.
[a] 'Last Attack' only included those patients who had more than one treated attack.
[b] 'All Attacks' was based on 73 attacks across 20 patients.

A total of 3/20 (15.0%) patients for 3/73 (4.1%) of attacks in the ITT Analysis Set had *therapeutic failure* during the study:

- Two patients at Attack 1 due to the VAS time to beginning of relief of symptoms occurring later than 4 hours after Baseline,

- one patient at Attack 2 due to taking a disallowed concomitant medication (paracetamol) within 45 minutes before administration of rhC1INH, which was noted as a protocol deviation.

None of the other patients in the ITT Analysis Set experienced therapeutic failure at any attack during the study. The majority of patients (90.0%) in the ITT Analysis Set did not receive a second dose of rhC1INH as treatment for any single HAE attack during the study. A total of 3/73 attacks were treated with a second dose of rhC1INH during the study: attacks requiring a second dose were reported by 2/20 (10%) patients in the ITT Analysis Set (one patient received a second dose of rhC1INH for Attacks 3 and 8, and one patient received a second dose of rhC1INH for Attack 3).

Summary of main study(ies)

The following table summarises 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 13: Summary of Efficacy for trial C1 1209

Title: C1-1209			
Study identifier	C1-1209		
Design	Open-label, Phase 2, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in paediatric patients with hereditary angioedema, from 2 up to and including 13 years of age		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		17. January 2012 -17. July 2017 not applicable not applicable
Hypothesis	OBJECTIVES: Primary: • To assess the clinical safety, immunogenicity and tolerability of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old hereditary angioedema (HAE) patients. Secondary: • To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old HAE patients • To assess the efficacy of rhC1INH in the treatment of acute angioedema attacks in 2-13 year old HAE patients		
Treatments groups	Ruconest		50 U/kg body weight up to a maximum of 4200 U, iv injection over a period of approximately 5 minutes 20 patients
Endpoints and definitions	Primary endpoint	time to beginning of relief based on VAS score	The primary efficacy endpoint was the time to beginning of relief based on the Overall visual analog scale (VAS) score, where time of beginning of relief was assessed as the first time point at which the VAS score decreased by at least 20 mm at any eligible anatomical location compared to Baseline, with persistence of the decrease at the next time point.

	Secondary endpoint	time to minimal symptoms based on VAS score	The secondary efficacy endpoint was the time to minimal symptoms based on the Overall VAS, defined as the time, in minutes, from time of infusion to minimal symptoms (i.e. the time at which the Overall VAS score fell below 20 mm for all locations where VAS Scores were recorded).
Database lock	14 September 2017		
Results and Analysis			
Analysis description	**Primary and Secondary Analysis**		
Analysis population and time point description	Intent to treat Following open-label treatment, patients remained in the study center for close monitoring for at least 4 hours after study medication administration. Treatment administration was followed for at least 90 days post-infusion or until another treatment for a subsequent HAE attack. Treatment for a subsequent attack reset the follow-up assessment schedule for an additional 90 days. Patients could be treated for a maximum of 10 attacks.		
Descriptive statistics and estimate variability	Treatment group	Ruconest All attacks	Ruconest First attack	Ruconest Last attack
	Number of subjects	20	20	12
	time to beginning of relief of symptoms (min)	60.0	60.0	60.0
	(95% CI)	(60.0, 65.0)	35.0, 124.0)	(30.0, 120.0)
	time to minimal symptoms (min)	120.0	125.0	120.0
	(95% CI)	(60.0, 241.0)	(60.0, 240.0)	(60.0, 241.0)

Supportive study(ies)

The additional supportive studies are briefly described later in the safety part of this report. In this grouped variation, they are mainly supporting additional changes related to safety in the SmPC. The SmPC amendments will be described in the later sections of this report (Safety and Product information).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study Design

The presented study C1 1209 is the only study planned to study paediatric patients between 2 and 13 years of age. It is an open-label, single arm study. Patients were treated with a single dose after presentation with an acute attack at the study centre. The patient remained in the study centre for close monitoring for at least 4 hours after study medication administration. Follow up was planned of at least 90 days or until a subsequent HAE attack occurred (reset of follow-up for additional 90 days). Patients could be treated for a maximum of 10 attacks. The general design is considered adequate.

Paediatric patients received rhC1INH at a dose of 50 U/kg body weight up to a maximum of 4200 U, which is according to the SmPC. It is the same dose that is recommended for adults and adolescents. No specific dose adjustment for paediatric patients is intended nor was any adjustment applied. The study continued until at least 20 patients had been treated with Ruconest for at least one acute HAE attack.

The inclusion and exclusion criteria for paediatric patients were in general similar to the phase III studies in adult patients and are overall acceptable.

However, one difference was noted: Only patients were included with an acute attack of at least moderate severity. This was defined by a so-called Investigator score [IS] of at least three. In contrast, the severity of the attack was estimated in the adult studies based on the VAS score (overall severity of angioedema symptoms of ≥ 50 mm at least 1 anatomical location at the time of evaluation (Time -1 hours). Upon request during the preceding P46 procedure, the MAH clarified that the IS score was selected because it was regarded as more objective to assess the severity at presentation in the paediatric population.

This explanation cannot be followed entirely as the VAS score has been applied successfully to paediatric patients before and the MAH used patient/parent(s)/legal guardian(s)-reported VAS scores for the primary endpoints. Further CHMP request, a comparison between IS (3 and 4 (no patients with IS 5 enrolled)) and VAS (≥50mm) for all attacks was provided. All patients with IS 4 had also a VAS ≥50mm. Considering all attacks, 70% of patients with IS 3 had also a VAS ≥ 50mm, with similar results over individual attacks.

In conclusion, the data indicate that both criteria are relatively comparable but patients with a minimal IS of 3 represent a slightly less severe affected population than based on the VAS criterion, which is considered acceptable to CHMP in this study setting.

Objectives and Endpoints

The primary objective was to evaluate the clinical safety and tolerability including immunogenicity in paediatric patients from 2 up to and including 13 years of age for the treatment of acute attacks of hereditary angioedema. Secondary objectives include the assessment of pharmacokinetics, pharmacodynamics and efficacy of Ruconest in this population.

The chosen endpoints for the assessment of clinical safety (AEs, clinical laboratory parameters, vital signs, electrocardiogram (ECG), physical examination), tolerability (immunogenicity), Pharmacokinetics (Ruconest concentrations, Cmax and AUC 0-3) and Pharmacodynamics parameters (C4 level) are acceptable. Please refer to the respective sections.

The endpoints for the efficacy assessment were grouped in primary, secondary and exploratory endpoints:

The primary endpoint was time to beginning of relief based on the Visual Analog Scale (VAS) score. The secondary endpoint was the time to minimal symptoms also based on the Overall VAS score. Both endpoints correspond to those chosen in the adult studies, where also the VAS score was used and the criteria were considered clinically relevant. The VAS score has also been used and was accepted in the evaluation of treatment of HAE attacks in other applications for marketing authorisation.

The exploratory endpoints besides time to complete resolution, therapeutic failure, and receipt of a second dose, measure also the time to the same events as the primary and secondary endpoints (beginning of relief, minimal symptoms) but are based on different scores: The Investigator Score (IS) and the treatment effect questionnaire (TEQ), which were both not applied in the adult studies. The MAH explained upon request during the preceding P46 procedure that due to the lack of an objective clinical or laboratory assessment method, the inclusion of different scores, combining patient reported outcomes

focussing on different aspects (VAS, TEQ) and an Investigator assessment tool (IS), should effectively measure the severity of an attack and any improvement induced by therapy.

The general study design is comparable to the studies in adult and adolescent patients and is considered acceptable for the objectives of the study.

Population characteristics

Height and weight are in a normal range for the screened and treated age group. Both increased with the number of treated attacks, which is in accordance with normal growth in children. Similar numbers of female (9) and male patients (11) were included which correspond to the general distribution between gender. Although no significant differences in incidence of HAE by race or ethnicity are known, only one patient was not Caucasian in the screening and the treated dataset. Also in the adult studies only a few non-Caucasian patients were included.

Age

The MAH intended to recruit children between 2 and 13 years of age. The 20 recruited and treated patients were however between 5 and 14 years old (mean 8.20) at presentation of attack 1. In the screening dataset patients' age ranged from 2-13 years.

The MAH discussed why no children between 2 and 4 years were treated. 20 children were enrolled in this age range but none were treated for events during the study. Only two presented in a study centre with untreated attacks at the age of 4 but did not meet the treatment criteria for this attack. No information is given on how many children between 2 and 4 years had events or their severity and if and how they were treated otherwise. The MAH explained that some parents had home treatment available and argued that this was preferable over a long drive to the centre. However, it is not clear how often this occurred or which alternative treatments have been used. Therefore, no treatment data is available for 2 to 4 year old patients.

However, the need for treatment of acute HAE attacks is also present for 2 to 4 year old patients. This is also reflected by the PIP requirement to conduct a study in paediatric patients from 2 years of age and above. It is acknowledged that feasibility of a study in this age group is limited. The availability of patients is limited in this orphan setting, other approved products for the treatment of HAE attacks in patients from 2 years of age are available and complying with all requirements in clinical trials might be an additional burden for the parents/caregivers. This might be especially true for very young children, as indeed observed in study C1 1209 (screened patients in this age group but no treatment data available).

The MAH was requested to address the lack of data in children 2 to 4 years of age and discuss the lower age limit of 2 years in the intended indication. A respective discussion has been presented by the MAH upon request including an additional literature review and popPK model with respective simulations:

Although the documentation of the literature search is missing, the review seems to be comprehensive and includes relevant data for this application and supports the difficulties to recruit patients in the age range of 2 to 4 years of age. Although episodes occur already at this age, attack frequency increase between 3 and 6 years of age and again later. Further, abdominal attacks in this age group may be more difficult to diagnose as the symptoms are often similar to other common paediatric diseases. It has also been seen in study C1 1209 that it is difficult to include this young patient population also due to existing treatment alternatives.

The popPK model predicted overall similar concentrations of Ruconest for adults, adolescents and children after administration of the recommended dose of 50 U/kg. Although a slight decrease in children < 5

years of age was predicted, this would still translate into 90% of children reaching maximum concentration of 0.7 U/mL. The MAH argued that in case this would lead to an insufficient clinical response, therefore an additional dose could still be administered. This argumentation is agreed and the second dose is also implemented in the SmPC.

Given the mode of action of Ruconest as enzyme replacement and assuming similar concentrations are achieved (as claimed by the popPK model and seen in children of 5-13 years), it is considered reasonable that the efficacy data derived from children (≥5 years), adolescents and adult patients can be extrapolated to younger children. Further, the registry study was also modified to include respective patients in order to gather data in the post marketing.

Efficacy data and additional analyses

All endpoints were presented combined for all attacks and for each attack separately as well as for the last attack of each patient. Since only five patients were treated for more than five HAE attacks, the results for these later attacks may be less reliable but are in general comparable to the previous attacks.

Primary endpoint

The median time to beginning of relief of symptoms based on Overall VAS decrease ≥ 20 mm, was approximately 60 minutes post-dose across repeated attacks. Those results are similar to the results achieved in the adolescent and adult patient population.

Secondary endpoint

The median time to minimal symptoms based on Overall VAS was approximately 120 minutes post-dose. The results are also consistent over repeated attacks. Similar to the primary endpoint, those results are similar to the results in adults and adolescents.

Exploratory endpoints based on IS and TEQ scores

The MAH used different scores for the exploratory endpoints to cover slightly different angles of evaluation (patient, investigator, different body area etc.). The results for time to beginning of relief and to minimal symptoms differ depending on the score. While the results based on VAS score for the beginning of relief are quite consistent at 60 minutes, the results based on the IS score seem to estimate the time in general a bit less (30-90 min) and based on TEQ score the time seems to be estimated longer (60 -180 min). In addition, the results for time to minimal symptoms do not correspond between the different scores. Therefore, the benefit of these scores for the evaluation of severity and improvement is rather limited, although they cover slightly different aspects.

Exploratory endpoint: time to complete resolution

The time to complete resolution was based on patient diaries as patients were usually released 4 hours after initiation of treatment. The results are highly variable, ranging from 33 to over 2000. Although the data are highly variable the median of different attacks suggests a time between 100 and 300 minutes (median over all attacks: 262.5 min), which seems consistent with the observations in the adult studies.

Although the data are limited, neither multiple affected regions, severity (measured as VAS score at baseline) nor age seem to have a relation to time to complete resolution.

Exploratory endpoints: Therapeutic failure, second dose.

Exploratory endpoints included also therapeutic failure and receipt of a second dose. It was noted that the patients classified as treatment failure did not receive a second dose, although the protocol states that a second dose can be administered if necessary. The MAH clarified upon request during the preceding P46 procedure that the respective patients showed a treatment effect after 4 hours and did therefore not receive a second dose.

A second dose was administered to two patients (10%) for three attacks, which is similar to results in adults (9% in study 1304).

The treatment of 3/73 attacks in three patients (15%) were considered as treatment failure: two due to the VAS time to beginning of relief of symptoms occurring later than 4 hours after Baseline (both at attack 1) and one patient due to a protocol violation (paracetamol within 45 min before treatment, during attack 2). The number and reasons for therapeutic failure are similar to the adult study: In the adult study 1304, 11% (10/90) of the patients treated with the same dose of 50 U/kg were considered as treatment failure at the first attack, which is similar to the rate observed in study C1 1209. The rates of treatment failure for subsequent attacks is much lower in children than in adults. The only treatment failure after attack one in children in study C1 1209 occurred at attack 2 and was due to a protocol deviation and not due to delayed effect. Other studies in adults showed rates of 13-22% of therapeutic failure for attacks 2-5, mainly due to beginning of relief occurring after 4 hours after baseline.

The results from study C1 1209 are consistent with the findings in previous clinical studies in adults and adolescents and demonstrate the efficacy of rhC1INH for the treatment of repeated acute HAE attacks in paediatric patients.

2.4.4. Conclusions on the clinical efficacy

Efficacy in children from the age of 5 years old have been demonstrated based on the clinical data. There was no data provided for children between 2 to 4 years of age. Extrapolation of the efficacy in children from the age of 2 years is accepted based on the mechanism of action, the provided population PK model and the available clinical data from the age of 5 years. The simulation results based on the population PK model were further considered acceptable to support the dose recommendation in young patients (2-4 years).

Additional efficacy data will be collected post marketing in the ongoing Registry Study C1 1412 in order to further characterise efficacy in this population. This is considered acceptable by CHMP.

2.5. Clinical safety

2.5.1. Introduction

Safety data for in total 20 paediatric patients was submitted from study C1 1209 to support the change of indication to include children between 2 and 12 years. The study was part of the paediatric investigation plan and was intended to include patients from 2-13 years of age. The part of the submitted variation procedure concerning the extension of indication is based solely on the provided data from study C1 1209.

Further, additional data was submitted from different clinical studies to update the safety profile and support the variation procedure part of this grouped variation concerning the update of the SmPC and PIL. The clinical studies include two open label extension (OLE) phase studies (C1 1304 OLE and 1205

OLE) of studies submitted with the initial application for marketing authorization, one additional randomized controlled trial including an OLE phase (C1 1310 RCT, OLE) and two studies performed for the prophylactic treatment of HAE patients (C1 1207 and 3201), which is not part of the current indication for Ruconest. The general information related to each study is described below in the respective section. The product information has been updated according to the new safety data.

The presented data for both variations, update of the safety part of the SmPC and extension of indication is discussed separately below.

2.5.2. Safety results for paediatric patients (study C1 1209)

Patient exposure

20 patients were treated for a total of 73 attacks. This was the first study including the paediatric population below 12 years of age using the same posology as the one recommended for adolescents and adults. Patients could be treated for a maximum of 10 attacks with a minimal interval between attacks of 24 hours.

Adverse events

Overall, in the Safety Analysis Set, 11 patients (55.0%) experienced at least one treatment-emergent adverse event (TEAE) after treatment with rhC1INH. The majority of TEAEs were of mild or moderate intensity, and not related to study treatment. Two patients (10.0%) reported TEAEs of severe intensity after study treatment for Attack 1 (abdominal pain [one patient] and vomiting [one patient]), and two patients (10.0%) reported TEAEs considered possibly related to study treatment (abnormal lymphocyte morphology events after study treatment for Attacks 1 and 2 [one patient] and Attack 4 [one patient]).

The only possibly related TEAE was "abnormal lymphocyte morphology events" and was reported four time for two patients after three attacks on a total of four occasions (attack 1,2 and 4 (twice)). The MAH clarified upon request during the preceding P46 procedure that all events occurred not immediately after treatment but a couple of days after (earliest 10 days) and that three of the four events occurred more than 30 days after treatment (31, 38, 55 days).

There was no evidence of an increase in the TEAE frequency across attacks, although a higher proportion of patients experienced TEAEs after study treatment for Attack 1 (8/20 patients [40.0%]) and Attack 4 (3/7 patients [42.9%]) compared to following treatment for the remaining attacks.

Eight patients (40%) experienced a subsequent attack that required treatment before completing the follow-up visits. The number of subsequent attacks ranges from 1 up to 9.

A total of 10/20 patients (50.0%) experienced TEAEs within 24 hours of completion of rhC1INH infusion and 8/20 patients (40.0%) experienced TEAEs within 28 days of completion of rhC1INH infusion. The most common TEAEs across all attacks were in the SOCs of infections and infestations (7/20 patients [35.0%]), gastrointestinal disorders (4/20 patients [20.0%]), and investigations (3/20 patients [15.0%]), and included nasopharyngitis, vomiting, viral infection, and abnormal lymphocyte morphology.

Serious adverse event/deaths/other significant events

There were no deaths during the study.

Overall, in the Safety Analysis Set, three patients experienced nine treatment-emergent SAEs (TESAEs) that occurred after study treatment for Attacks 1, 2, or 4. The most common TESAEs were grouped as SOC infections and infestations and included bronchitis, pneumonia, tonsillitis, and viral infection.

No AEs of special interest were reported during this study (such as type I hypersensitivity reactions against IgE, type III hypersensitivity reactions against rhC1INH, induction of acquired angioedema, or thromboembolic complications).

Laboratory findings

Treatment with rhC1INH did not result in any significant trends in routine clinical laboratory safety parameter data across attacks. For two patients clinically significant abnormalities during the study were reported (one patient had a high value for erythrocyte sedimentation rate at Day 28 after treatment for Attack 3, and one patient had a high value for monocytes and low value for white blood cell count on Day 28 after treatment for Attack 10).

Two patients (10.0%) in the Safety Analysis Set reported TEAEs of abnormal lymphocyte morphology that were considered possibly related to rhC1INH (one patient after study treatment for Attacks 1 and 2, and one patient at two occasions after study treatment for Attack 4). The MAH clarified upon request that all events occurred not immediately after treatment but a couple of days after (earliest 10 days) and that three of the four events occurred more than 30 days after treatment (31, 38, 55 days).

Most abnormal physical examination findings reported during the study were related to HAE or unrelated to study drug (e.g. caries).

Most patients had normal ECG results at Presentation of attack and post-infusion. Abnormal but not clinically significant ECG results were detected for four patients. The ECG values returned to normal for all but one patient, which experienced slight sinus tachycardia which was also present at Presentation of attack.

There were no further clinically meaningful changes in any of the vital signs parameters during the study. As patient age increased with increasing number of attacks, mean weight at Presentation generally increased across attacks.

Immunogenicity

Hypersensitivity to host related impurities (HRI) is an identified risk for Ruconest, also included in the SmPC. Therefore, patients were excluded if a history of allergy to rabbits or rabbit-derived products was known. An additional assessment of immunogenicity reaction was also performed in study C1 1209. The assessment of immunogenicity reactions was performed based on the blood samples collected also for the PK and PD analysis. The samples were tested for anti- C1INH and anti-HRI antibodies (Abs). Sporadic, transient immune responses to rhC1INH and HRI were observed, but with no associated clinical findings. Two patients had confirmed Abs against C1INH at screening or presentation of attack. Eight patients experienced confirmed anti-HRI Abs. None of the patients developed neutralizing Abs to C1INH and no impact of immunogenicity on clinical efficacy or safety was observed. No AEs concerning anaphylactic reactions were observed by any patient in this study.

Discontinuation due to adverse events

There were no discontinuations due to TEAEs during the study.

Five patients discontinued the study prematurely; all withdrew their consent. The reported reasons include: too old for the study, no longer interested to continue, left the country, personal reasons and preferred to treat attacks otherwise.

2.5.3. Safety results from additional studies

Data from studies C1 1304 OLE, C1 1205 OLE and from the completed Study C1 1310 (RCT and OLE) have been submitted for this variation procedure. Additional safety data are included from Studies C1 1207 and 3201 for the prophylactic treatment of HAE patients, which are not included in the current indication for Ruconest. The product information has been updated accordingly.
All studies are described briefly below.

a) Study C1 1304 OLE: 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: Open Label Extension (OLE) phase.

Of note the results of the double-blind phase have been assessed during the initial marketing authorization. In this application, the MAH is providing in this application the open label phase for review.

Methods
The study was performed in Italy, Spain, UK, Israel, Romania and Argentina from 06 September 2007 until 13 October 2009 (First patient treated - Last patient completed).
The open label extension study included 57 patients ≥ 16 years of age that have received in total 194 OLE treatments.

Study objective
The objectives of the OLE phase of the study were to assess the safety, tolerability, and efficacy as well as pharmacokinetics (PK) and pharmacodynamics (PD) of rhC1INH in the open-label treatment of subsequent attacks of HAE.

Study participants/Inclusion criteria
During the double-blind phase of the study, hereditary angioedema (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 in the OLE phase of the study. In addition, screened patients with an eligible acute angioedema attack who had not previously participated in the double-blind phase of the study could be treated in the OLE phase.

Treatments
In the OLE phase, the treatment consisted of a fixed dose of 2100 U per attack with the provision to administer one or two additional vials within 4 hours after administration of the first vial. Patients received study medication by slow iv injection in 2-3 minutes. The maximum amount of rhC1INH that could be given to a patient for a single attack was 3 vials (6300U).

Study endpoints
Although the efficacy results of this study are not part of this assessment the endpoints are briefly described here for completeness:

- The primary efficacy endpoint was the time to the 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 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 one eligible location, the earliest relief of these locations was considered.

- 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 for all anatomical locations of an attack.
- The main exploratory efficacy variables were therapeutic failure and time to the beginning of relief based on Investigator's score (IS).

Safety and Tolerability: Safety and tolerability were assessed by evaluation of treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG), physical examination, safety laboratory parameters and immunogenicity.

b) Study C1 1205 OLE: Randomized, Placebo-Controlled (saline), Double-Blind Phase II Study of the Safety and Efficacy of Recombinant Human C1 Inhibitor for the Treatment of Acute Attacks in Patients with Hereditary Angioedema:

The results of the double-blind phase have been a part of the data submitted for the initial marketing authorization.

Methods

The OLE phase of the study was performed in America and Canada from 01 March 2007 until 20 January 2010 (First patient treated - Last patient completed).

Study objectives

The objectives of the OLE phase of the study were to assess the safety, tolerability and effects of rhC1INH in treating subsequent attacks of HAE.

Study participants

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 treatment in the double-blind phase of the study, patients with subsequent eligible HAE attacks could be treated on an unlimited number of occasions with open-label rhC1INH (50 U/kg). Furthermore, after the double-blind phase of the study closed, the OLE phase of the study was open for HAE patients that presented with an eligible angioedema attack, whether or not they had participated in the randomized controlled phase of the study. New patients could also be screened and treated in the OLE phase.

Treatments

In the OLE phase, treatment consisted of rhC1INH at 50 U/kg per attack with the provision to administer an additional 50 U/kg dose within 4 hours after administration of the first treatment.
Patients received study medication by slow iv injection at an approximate rate of 6mL/min. The maximum amount of rhC1INH that could be given to a patient for a single attack was 100 U/kg.
This study included 62 patients ≥ 12 years that received in total 168 treatments.

Study endpoints

Although the efficacy results of this study are not part of this assessment the endpoints are briefly described here for completeness:

- The primary efficacy endpoint was the time to the 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 at 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

- 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 for all anatomical locations of an attack.
- The main exploratory efficacy variables were therapeutic failure and time to the beginning of relief based on Investigator's score (IS).

Safety and Tolerability: Safety and tolerability were assessed by evaluation of treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG), physical examination, safety laboratory parameters and immunogenicity.

C) Study C1 1310 RCT and OLE: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension Evaluating the Efficacy, Safety and Immunogenicity of Recombinant Human C1 Inhibitor for the Treatment of Acute Attacks of Angioedema in Patients with HAE.

Methods

This study was conducted in a total of 26 centers in 10 countries from 30 January 2011 (FPFV) until 26 September 2012 (RCT LPLV) and 07 March 2013 (OLE LPLV).
A total of 75 eligible patients (≥13 years of age (≥18 years for patients outside the United States or Canada)) were centrally randomized (3:2) to receive either intravenous (iv) rhC1INH or saline in a double-blind fashion (44 rhC1INH; 31 saline). 73 patients completed the scheduled visits in the RCT Phase (42 rhC1INH; 31 saline) and 44 patients entered the Entered OLE Phase.

Study Objectives:

- To evaluate efficacy and safety of rhC1INH at a dose of 50 IU/kg when used for the treatment of acute angioedema attacks in patients with HAE
- To assess efficacy, safety and immunogenicity of rhC1INH when used for the repeat treatment of acute angioedema attacks in patients with HAE

Treatment

A dose consisted of rhC1INH 50 IU/kg for patients <84 kg, or a dose of rhC1INH 4200 IU (2 vials) for patients ≥84 kg administered as slow IV injection over a period of approximately 5 minutes
Each patient started with a screening visit and was followed for at least 90 days after treatment or until another open-label treatment for a subsequent HAE attack. Treatment for a subsequent attack reset the follow-up assessment schedule for an additional 90 days.
Rescue medication (open-label rhC1INH) may have been provided under respective circumstances.

Study endpoints

Although the efficacy results of this study are not part of this assessment the endpoints are briefly described here for completeness:

- Primary Endpoint: The primary efficacy endpoint was the time to beginning of relief of symptoms at the primary attack location (based on Treatment Effect Questionnaire [TEQ]).
- Secondary Endpoint: The secondary efficacy endpoint was the time to minimal symptoms at all locations based on TEQ.
- In addition, several exploratory endpoints were defined including evaluation based on different

scores, treatment failure etc.

Safety: Safety was assessed by evaluating adverse events (AEs), clinical laboratory parameters, immunogenicity, immunoglobulin E (IgE) testing, vital signs, physical examination, change in weight, Wells score, and ultrasound.

d) Study C1 1207 An Open-label exploratory Phase II study of the safety and Prophylactic Effect of a weekly 50 U/kg rhC1INH treatment in Asymptomatic patients with hereditary C1INH deficiency (HAE).

Methods

25 patients (≥18 years) were treated in three sites Romania, Israel and Poland from 26 August 2009 (FPFV) until 19 April 2010 (LPLV).
The patients received once weekly administration of rhC1INH at 50 U/kg for 8 weeks, with a 2 weeks run-in period before the first administration and a 42 days follow-up period after the last administration.

Study objectives

- Primary objective: To evaluate the occurrence of HAE attacks under prophylactic administration of rhC1INH (50 U/kg, once a week)
- Secondary objectives: To evaluate the PK/PD parameters, safety and immunogenicity on repeated administration of rhC1INH

Study endpoints

Although the efficacy and PK/PD results of this study are not part of this assessment the endpoints are briefly described here for completeness:
- Efficacy: Incidence of documented HAE attacks during treatment period
- Pharmacokinetics/ Pharmacodynamics: - AUC0-4, Cmax and Tmax of functional C1INH, antigenic C1INH and C4

Immunology: Antibodies against C1INH, host related impurities, rabbit dander and cow milk

Safety: Safety was assessed by evaluating Adverse events, thrombogenic effects, Vital signs, Significant changes from baseline of routine haematology and biochemistry blood test results and recorded ECG data.

e) Study C1 3201: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Period Crossover Study to Evaluate the Efficacy and Safety of Recombinant Human C1 Inhibitor in the Prophylaxis of Angioedema Attacks in Patients with Hereditary Angioedema (HAE)

Methods

32 patients (≥13 years) were treated in 12 sites in eight countries from 29 December 2014 (FPFV) until 3 May 2016 (LPLV). Eligible patients with a history of frequent HAE attacks (⩾ 4 attacks per month for 3 consecutive months) were enrolled and randomized to one of six treatment sequences in an equal allocation ratio. Each patient was to receive three 4-week periods of study treatment twice weekly, according to the assigned treatment sequence, with a 1-week washout period between treatment periods

Study objectives:
- The primary objective of this study was to evaluate the efficacy of recombinant human C1 inhibitor (rhC1INH) in the prophylaxis of angioedema attacks in patients with HAE.

- The secondary objective was to evaluate the safety and immunogenicity of recombinant human C1 inhibitor (rhC1INH) in the prophylaxis of angioedema attacks in patients with HAE.

Treatments

Patients received hC1INH 50 IU/kg (to a maximum of 4200 IU for patients ⩾ 84 kg) or placebo (saline), administered as a slow IV injection at the study center over approximately 5 minutes (⩽ 10 minutes), twice weekly according to the assigned treatment sequence.

Study endpoints

Although the efficacy results of this study are not part of this assessment the endpoints are briefly described here for completeness:

- Primary Endpoint: Monthly HAE attack rate, defined as the number of HAE attacks during each treatment period normalized by the number of days the patient participated in that period.
- Secondary Endpoint: Clinical response, defined as a ⩾50% reduction in the number of attacks from treatment with placebo to treatment with rhC1INH. The number of attacks is normalized by the number of days the patient participated in that period.
- In addition, several exploratory endpoints were defined including reduction, duration, severity or absence of the attacks, etc.

Safety: Safety was assessed by evaluating adverse events (AEs), clinical laboratory parameters (hematology, biochemistry, coagulation), immunogenicity, vital signs, and physical examination.

Patient exposure

Study C1 1304 OLE: This study included 57 patients received in total 194 OLE treatments.

Study C1 1205 OLE: This study included 62 patients that received in total 168 treatments.

Study C1 1310 RCT: In this study, 74 patients were treated for an HAE attack (primary attack location: 45% peripheral, 38% abdominal, 11% facial, and 7% oropharyngeal-laryngeal), with 56 patients exposed to rhC1INH either as randomized therapy or rescue medication. Including rescue medication, the mean (SD) total dose of rhC1INH administered during the RCT Phase was 52.74 (11.278) IU/kg for patients <84 kg and 50.00 (19.609) IU/kg for patients ≥84 kg.

Study C1 1310 OLE: During the OLE Phase, 44 patients were treated for 224 attacks; an additional dose of rhC1INH was administered for nine of 224 attacks.
In total, the safety database including the presented studies amounts to 201 symptomatic patients treated for 691 attacks. In addition, in the RCT trials four patients received rescue medication in the placebo group and are subsequently also included in the all safety dataset.

In studies C1 1207 and C1 3201 25 and 32 patients received prophylactic treatment with Ruconest.

Adverse events

Overall, 117 (57%) patients reported at least 1 TEAE (C1 1304 OLE: 27 (47%), C1 1205 OLE: 39 (63%), C1 1310 RCT: 18/56 [32%] OLE: 30 (68%)). There was no increase in TEAEs with repeated treatments. Most events were mild to moderate in severity in all presented studies.
Severe AEs were reported in a few patients in all studies and none were considered to be treatment related (C1 1304 OLE: 3 AEs in 3 patients; C1 1205 OLE: 14 AEs in 7 patients; C1 1310 RCT: 3 AEs in 3 patients (2 Ruconest, 1 placebo); OLE: 9 AEs in 6 patients)

In studies for the prophylactic treatment:
In study C1 1207 a total of 30 treatment-emergent adverse events were observed in 13 patients (52%). Most were mild or moderate but two events were of severe intensity: appendicitis and laryngeal edema. The later event resulted in the death of the respective patient. The event was judged as not related to study drug. Based on the narratives provided by the MAH this can be followed.
In study C1 3201 24 TEAEs were reported for 10 patients (34.5%) during twice weekly treatment, 18 TEAEs in 13 patients (44.8%) during once weekly treatment, and 15 TEAEs in 8 patients (28.6%) during placebo treatment. Almost all TEAEs were of mild or moderate severity. Two events were reported as severe: Abdominal pain during twice weekly treatment and Nasopharyngitis during once weekly treatment.

The most frequently reported SOCs in all studies (including the studies for prophylactic treatment) were Gastrointestinal disorders (abdominal pain, nausea, diarrhoea), Infections and infestations (nasopharyngitis, upper respiratory tract infection) and Nervous System Disorders (headache, dizziness). Those adverse events are adequately mentioned in the SmPC.

Treatment related TEAEs
Four (C1 1304 OLE) and eight (C1 1205 OLE) patients experienced possible related TEAE, as determined by the investigator, but none of them required any treatment. The reported AEs include:
diarrhoea (3 events), nausea (2 events), paresthesia (2 events), vertigo, dysuria, vesicular rash, dizziness, persistent increase of gamma-GT, headache, throat irritation, abdominal discomfort and hypersensitivity (1 event each).
In the RCT phase of study 1301 only one patient in the rhC1INH group experienced TEAEs assessed as related to treatment by the Investigator, which were headache, skin burning sensation and back pain.
In the OLE phase, four (9%) patients experienced a total of 15 treatment-related TEAEs during the OLE Phase including flatulence (4 events), diarrhea (3 events), lacrimation increased (2 events), back pain, chills, fatigue, nasopharyngitis, pruritus, and rash (1 event each).
Study C1 1207: four events were considered possibly drug-related by the investigator. All these events were of mild intensity: dry mouth, dizziness, hypotension, anxiety.

Study C1 3201: related TEAEs (relationship possible or probable) were reported for 2 patients during twice weekly treatment: Fatigue (mild and possibly related) and headache (mild and possibly related).

Overall, the described (possibly) treatment-related AEs have been currently - and are also with the applied changes - appropriately reflected in the SmPC.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths due to TEAEs in any of the additionally presented studies.

One patient died in study C1 1207 (for prophylactic treatment) due to laryngeal oedema, which was considered as not related to study drug.

Serious adverse events

Study C1 1304
Two SAEs (acute myocardial infarction 70 days post treatment and tonsillitis) were reported and both

were considered not related. One other significant adverse event of spontaneous abortion was considered unlikely related to study medication.

Study C1 1205
Twenty serious TEAEs were reported in 10 patients. Thirteen SAEs were HAE attacks (11 single HAE attacks and 2 HAE attacks combined with other SAEs) reported in 8 patients. The other 7 treatment-emergent SAEs were reported in 4 patients included: 1 patient with severe vertigo, 1 patient with a severe pneumonia and peripheral oedema, 1 patient with a moderate "hypersensitivity reaction", and 1 patient experiencing an urinary tract infection with sepsis on two occasions (mild and severe, respectively). All SAEs resolved and none was related to treatment in the Investigator's opinion except for the "hypersensitivity reaction", which was deemed to be possibly-related to treatment. Laboratory data suggest that the event was not an IgE-mediated reaction.

Study C1 1310 RCT
Three patients experienced a total of five SAEs during the RCT Phase, only one of which was treatment-emergent (severe abdominal hernia 79 days after administration of study medication). The event was assessed as not related to the study drug by the Investigator.

Study C1 1310 OLE

One patient experienced a serious TEAE of a new HAE attack approximately 25 days after the last administration of rhC1INH (for Attack 13). The attack was moderate in severity, required hospitalization and resolved after 52.5 hours. The Investigator considered the event to be not related to study drug.

Study C1 1207
Two serious adverse events were reported in two patients: laryngeal oedema and acute appendicitis. The reported SAE of laryngeal oedema was fatal. Both SAEs events were considered as not related to study drug. Based on the narratives provided by the MAH this can be followed.

Study C1 3201
A single treatment-emergent SAE was reported during twice weekly treatment (Phimosis), and was judged as being unrelated to the study drug. The event was an SAE due to a brief hospitalization.

AEs of special interest

AEs of special interest were defined as type I hypersensitivity reactions against IgE, type III hypersensitivity reactions against rhC1INH, induction of acquired angioedema, or thromboembolic complications. No such events occurred in any of the presented studies.

Laboratory findings

Treatment with rhC1INH did not result in clinically relevant mean changes in vital signs, ECG, and routine clinical laboratory safety parameters in all studies. Occasional clinically relevant changes were reported but all considered as not related to study drug.
In Study 1310, D-dimer concentrations were measured at Baseline, 2 h, and Day 7 following study drug administration in the RCT and OLE Phases of the study. In the RCT Phase of Study 1310, Baseline and 2-h D-dimer concentrations were elevated in both the rhC1INH and saline groups. By Day 7, median values decreased in both groups. Similar trends were observed in the ongoing OLE Phase of this study. As reported in the literature, the early high D-dimer concentrations likely reflect the ongoing HAE attack, which is associated with activation of both coagulation and fibrinolysis. Finally, no thromboembolic events were reported in the study.

Immunogenicity

In the integrated immunosafety analysis, antibodies against conestat alfa, plasma-derived C1-INH, and HRI were assessed in samples collected from 205 patients with HAE treated for 704 acute attacks participating in Studies C1 1202/1203, and the RCT and OLE phase of C1 1304, 1205, and 1310. Of the 1784 planned samples (excluding placebo-treated attacks), 1696 samples (95%) were collected and analyzed.
It showed that the frequency of initial ELISA results above cut-off for antibodies against C1-INH was low and was similar for pre-exposure (Attack 1 at screening: 2%, Attack 1 at baseline: 1%) and post-exposure (1-3%) samples. Results above cut-off tended to be isolated or transient occurrences.

Although no information in the SmPC was updated based on immunogenicity data the data from from studies C1 1207 and C1 3201 in asymptomatic patients is added here for completeness:
C1 1207: Occasional antibodies to C1INH were observed, but no neutralizing antibodies. Antibodies to Host Related Impurities were found at any point in time in 11/25 patients without associated clinical symptoms.

Study C1 3201: For anti-HRI, positive results were observed for 19 patients (67.9%) at the last study visit (follow-up), of which 18 were confirmed.
None of the results for IgE against rabbit epithelium were positive.
For rhC1INH-specific IgG, positive results were observed 4 patients at follow-up (14.3%, all confirmed).
For rhC1INH-specific IgM, no positive results were observed at follow-up.
No neutralizing antibodies were observed. Observed anti-C1INH and anti-HRI antibodies were not associated with adverse clinical findings.

Discontinuation due to adverse events

There were no discontinuations due to adverse events in the study.

2.5.4. Discussion on clinical safety

Clinical safety in children (study C1 1209)

Study C1 1209 included 20 paediatric patients between 5 and 14 years. Although children between 2 and 4 years of age were screened, none were treated during the study resulting in a lack of data for this population. The need for treatment of acute HAE attacks is also present for 2 to 4 years old patients. This is also reflected by the PIP requirement to conduct a study in paediatric patients from 2 years of age and above. It is acknowledged that feasibility of a study in this age group is limited.

Upon further request the MAH provided arguments why data derived from older patients (>5 years) could be extrapolated to the young children (2-4 years). Although such extrapolation might be possible for efficacy of Ruconest, some safety concerns remain which could not be derived from older patient populations. The MAH agreed that it is not possible to determine the risk and potential clinical presentation of hypersensitivity to rabbit antigens in children (2-4 years) due to the lack of data. Further, there is no literature to support any assumption in this matter.

However, the immunogenicity results of children between 5 and 14 years of age were consistent with the data observed in previous studies in adults and adolescents. Only sporadic, transient immune responses to rhC1INH and HRI were observed, but with no associated clinical findings. Hypersensitivity to host related impurities (HRI) is already an identified risk for Ruconest and included in the SmPC in section 4.4.

Consequently, it is agreed with the MAH to introduce additional recommendations of monitoring of potential hypersensitivity reactions in all children, including also those between 2 and 5 years of age during and after the treatment, considering the absence of clinical data in this population. This is also in line with current recommendations for the adult and adolescent populations.

Patients could be treated for subsequent attacks before the follow up visits were completed, resulting in the reset of the follow up schedule based on the most recent treatment. This procedure had no influence on efficacy and safety data, since no trends have been observed across attacks. However, the available data is rather limited with eight patients and no definite conclusion can be drawn.

Adverse events (AEs)

11 patients (55.0%) experienced at least one treatment-emergent adverse event (TEAE) most of mild or moderate intensity, and not related to study drug. Only two were reported as of severe intensity (abdominal pain and vomiting). These TEAEs have also been observed in similar frequency in the adult studies and have already been included in the SmPC.

The only possibly related TEAE that occurred in study C1 1209 was "abnormal lymphocyte morphology events". In total four events were reported for two patients. The event was not reported in the adult studies, however, it is not clear whether lymphocyte morphology was investigated. A few cases of low lymphocyte counts were reported in the adult studies but balanced between treatment arms and all were considered not clinically significant. All events occurred not immediately after treatment but at least 10 days later. Overall, the MAH´s evaluation that these events are not related to treatment is supported.

No deaths occurred during the study. Nine SAEs were reported for a total of three patients which were mainly infections and infestations, e.g. bronchitis, pneumonia, tonsillitis, and viral infection.

AEs of special interest were defined according to the known safety profile of Ruconest but none occurred during the study.

Discontinuations

Five patients discontinued the study prematurely; all withdrew their consent. No patients discontinued due to TEAEs.

Additional data provided for patients who stated that they withdrew their consent indicated that the treatment was effective and no AEs occurred around the time of their decision. Therefore, no concern arises that their withdrawal of consent was related to safety or signs of lack of efficacy.

Laboratory values

No clinically relevant changes possibly related to study drug in vital signs or physical examinations were observed during the study and no trends in laboratory values were observed across attacks.

Immunogenicity

Hypersensitivity to host related impurities (HRI) is an identified risk for Ruconest, also included in the SmPC. Therefore, patients were excluded if a history of allergy to rabbits or rabbit-derived products was known. In study C1 1209 sporadic, transient immune responses to rhC1INH and HRI were observed, but with no associated clinical findings. Furthermore, none of the patients developed neutralizing Abs to C1INH and no impact of immunogenicity on clinical efficacy or safety was observed. No AEs concerning anaphylactic reactions were observed by any patient in this study.

Overall, the reported safety profile observed in the paediatric population is consistent with the known safety profile for adult patients.

Update of safety data based on additional data from other studies

In this grouped variation procedure, amendments to the product information based on updated safety data were introduced. For this purpose, data from two open label extension (OLE) phases of randomized controlled studies presented at the initial marketing authorization procedure and from an additional study (RCT with OLE) have been submitted. Additional safety data are included from two studies for the prophylactic treatment of HAE patients, which are not included in the current indication for Ruconest.

With the above safety data, the total safety database increased to 205 patients treated for 691 attacks. In addition, 57 asymptomatic patients received prophylactic treatment with Ruconest.

One patient died in study C1 1207 (for prophylactic treatment) due to laryngeal oedema, which was considered not related to study drug. Overall, the occurrence of SAEs is limited and both frequency and AEs are consistent with the previously presented safety profile.

Minor changes of the SmPC were considered necessary resulting from the above submitted data: dizziness has been added to the list of uncommon adverse events and included in section 4.7. Other changes related to the frequency of nausea (change from uncommon to common) and headache (change from common to uncommon) in section 4.8 of the SmPC.

In addition to the changes of frequencies of adverse events in section 4.8 of the SmPC, the MAH updated the number of treated patients and attacks in section 5.1 of the SmPC.

In addition, minor update in the figures for study C1 1205 were introduced in the SmPC section 5.1 by the MAH which are agreed upon.

2.5.5. Conclusions on clinical safety

Extension of indication

The presented study C1 1209 was appropriately designed for the intended objectives and the presented results indicate similar efficacy and a similar safety profile in children compared to the results observed in adult and adolescent patients

The safety data in children from the age of 5 years support an approval in this patient population. Extrapolation of the safety data to younger patients (2-4 years) can be accepted provided that further safety data will be provided post approval, to which the MAH agreed. The registry protocol of Study C1 1412 has been appropriately modified to include collection of data in children from 2 to 4 years.

The need for monitoring of safety in patients from 2 to 4 years of age is essential considering the absence of safety data in this population.

Information on the lack of clinical data in children less than 2 years is also introduced in section 4.2 of the SmPC.

Variation to update the safety data in section 4.8 and 5.1 of the SmPC

The additional safety data presented for adult and adolescent patients are consistent with the data presented for the initial marketing authorization. No new or unexpected safety concerns have been

identified. The requested amendments on the frequency of ADRs in the SmPC section 4.8 and correction of figures and update of information in section 5.1 are acceptable.

Additionally the delay in submission of the final study results of the registry study C1 1412 is agreed. Final results will be submitted by June 2022.

2.5.6. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the indication in the children population and on the basis of the limited safety data, the CHMP is of the opinion that the already existing entry in the EURD list for conestat alfa needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 28/10/2020.

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 19.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

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.

Safety concerns

Summary of safety concerns	
Important identified risks	• Allergic reactions in patients with rabbit allergy • Off-label use • Lack of efficacy
Important potential risks	• Allergic reaction due to the formation of IgE antibodies against rabbit allergens • Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies • Induction of acquired angioedema due to the formation of anti-C1-INH antibodies • Thromboembolic complications • Medication error • Adverse events with self or home administration
Missing information	• Data on pediatric patients aged 2 up to 5 years • Data on pregnant and breastfeeding women

Pharmacovigilance plan

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not Applicable				
Category 3 – Required additional pharmacovigilance activities (by the competent authority)				
Data collection from participation in the Ruconest registry (C1 1412) *Ongoing*	To observe adverse events and insufficient efficacy, and to assess the immunological profile following single and repeat treatment with Ruconest in patients diagnosed with HAE.	- to expand the safety database for Ruconest - serious allergic reactions or anaphylaxis	Regular updates	Data will be reviewed on an ongoing basis as part of signal detection and reported within the DSUR, PSUR and RMP updates.
			Final report	31/06/2022
Effectiveness evaluation of educational materials for Ruconest (PHARM/EU/ aRMM/01) *Planned*	To evaluate the usefulness and HCPs awareness of the educational materials for Ruconest and whether key safety messages are understood by the prescriber and communicated to their patients. To evaluate whether the reporting rate of adverse events related to hypersensitivity reactions after administration of Ruconest has changed.	- to measure the effectiveness of the educational materials	Regular updates	Study progress will be reported in the PSUR and RMP updates.
			Final report	31/01/2021

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Allergic reactions in patients with rabbit allergy	Routine risk minimization measures: *SmPC section 4.2, 4.3 and 4.4* *PL section 2* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Off-label use	Routine risk minimization measures: *SmPC section 4.1 and 4.2* *PL section 1 and 3*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Lack of efficacy	Routine risk minimization measures: *SmPC section 4.2* *PL section 3* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Allergic reaction due to formation of IgE antibodies against rabbit allergens	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Induction of acquired angioedema due to the formation of anti-C1-INH antibodies	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Thromboembolic complications	Routine risk minimization measures: *Not applicable*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Medication error	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Adverse events with self or home administration	Routine risk minimization measures: *SmPC section 4.4* *PL section 3* *Legal status: prescription only medicine* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Data on pediatric patients aged 2 up to 5 years	Routine risk minimization measures: *SmPC section 4.2 and 4.4* *PL section 2*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Data on pregnant and breastfeeding women	Routine risk minimization measures: *SmPC section 4.6* *PL section 2* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Pregnancy notification form* *Pregnancy outcome form* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*

2.7. Update of the Product information

Variation C.1.6: Extension of indication in children from the age of 2 years and above

This application includes an update on the indication to introduce the use of Ruconest in paediatric patients with acute angioedema attacks from the age of 2 years. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet is updated accordingly.

Variation C.1.4: Final study results of adult and adolescent clinical data.

An update of section 4.8 of the SmPC to amend frequencies of selected adverse drug reactions is introduced together with correction on figures and updated of information in section 5.1 of the SmPC.

Variation C.1.11

The delay in submission of the final study results of the registry study C1 1412 is agreed. Final results will be submitted by June 2022.

Changes were also made to the Product Information to bring it in line with the current Agency/QRD template version 10.1, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

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 MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ruconest. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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 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 attacks occur 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 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.

3.1.2. Available therapies and unmet medical need

Ruconest is approved for treatment of treatment of acute angioedema attacks in adult and adolescent patients

Several other therapies are available in the European Union for the treatment of acute HAE attacks in patients from 2 years of age:

Firazyr is a synthetic decapeptide with a structure similar to bradykinin and is a selective competitive antagonist at the bradykinin type 2 receptor. Firazyr is currently indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency.

Berinert is an extract of human plasma that contains the active substance: human C1-esterase inhibitor. Berinert is currently indicated for management of hereditary angioedema types I and II.

Cinryze contains the active substance C1 inhibitor derived from human plasma. It is currently indicated for treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).

Takhzyro (lanadelumab) is a monoclonal antibody therapy approved for the prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

3.1.3. Main clinical studies

Clinical data from study C1 1209 were submitted for the **paediatric population**. It was an open-label, Phase 2, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in paediatric patients with hereditary angioedema, from 2 up to and including 13 years of age. 20 patients were treated for a total of 73 attacks from 5 years of age. No dose modification was introduced compared to the posology recommended in the SmPC for adolescents and adults. However clarification on the timing of the second dose administration is introduced in section 4.2. Patients could be treated for a maximum of 10 attacks with a minimal interval between attacks of 24 hours.

Updated safety data for the **adolescent and adult population** were provided in order to support the update of section 4.8 of the SmPC. Data from two open label extension (OLE) phases of randomized controlled studies presented at the initial marketing authorization procedure and from an additional study (RCT with OLE) have been submitted. Additional safety data were included from two studies investigating the use as prophylactic treatment of HAE patients.

3.2. Favourable effects

The following favourable effects have been observed in study C1 1209 in the **paediatric population**:

The median *time to beginning of relief of symptoms* with persistence based on Overall VAS decrease ≥ 20 mm was 60 minutes (mean) post-dose across repeated attacks. This was the primary endpoint in study C1 1209. Time to beginning of relief of symptoms has also been included as exploratory endpoint measured based on Investigator score (IS) (60 minutes) and treatment effect questionnaire (TEQ) (60 – 180 minutes at different attacks).

The median *time to minimal symptoms* based on Overall VAS decrease ≥ 20 mm was approximately 120 minutes post-dose across repeated attacks. This was defined as the primary endpoint in study C1 1209. Time to minimal symptoms has also been included as exploratory endpoint measured based on Investigator score (IS) (120-180 minutes) and treatment effect questionnaire (TEQ) (60 – 180 minutes at different attacks).

The *median time to complete resolution* based on diary results varied across attacks, with median values ranging from 100.0 minutes post-dose at Attack 9 to 1167.5 minutes post-dose at Attack 1.

A total of 3/20 (15.0%) patients for 3/73 (4.1%) of attacks in the ITT Analysis Set had *therapeutic failure* during the study: Two patients due beginning of relief of symptoms occurring later than 4 hours after treatment and one patient due a protocol deviation (disallowed concomitant medication).

A total of 3/73 attacks were treated with a *second dose* of rhC1INH during the study. These attacks requiring a second dose were reported for 2/20 (10%) patients.

3.3. Uncertainties and limitations about favourable effects

No placebo control arm was implemented in the study.

The primary and secondary endpoints (time to beginning of relief of symptoms and time to minimal symptoms) have been measured with the overall visual analog scale (VAS) and additionally as

exploratory endpoints with two different scores covering different aspects of treatment and possible benefit. Although the different perspectives are endorsed in general, all three scores are based on the patients' subjective perception and the results differ between 60 and 180 minutes depending on the score. However, the overall VAS score has also been applied in the adult population with similar results to the paediatric population.

The time to complete resolution was based on patient diaries and the results are highly variable, ranging from 33 to over 2000. Nevertheless, the data appear consistent with the variable disease manifestations (location, severity) and with the results observed in the adult and adolescent patients.

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

The ongoing registry study has been updated to gather data on this population in the post marketing. Extrapolation of the efficacy data to the younger patients of 2 to 4 years of age is considered acceptable based on the mechanism of action and existing knowledge in the literature, the provided PK analysis including a population PK model and the provided clinical data in older children.

3.4. Unfavourable effects

The following unfavourable effects have been observed in study C1 1209 in the **paediatric population**:

Three patients experienced nine serious adverse events (SAEs). The most common SAEs were grouped as SOC infections and infestations including bronchitis, pneumonia, tonsillitis, and viral infection.

Eleven patients (55.0%) experienced at least one treatment-emergent adverse event (TEAE) after treatment with rhC1INH. There was no evidence of an increase in the TEAE frequency across attacks. Two patients (10.0%) reported TEAEs of severe intensity after study treatment (abdominal pain and vomiting). Two patients (10.0%) reported three events of abnormal lymphocyte morphology, which were considered possibly related to study treatment. No other events were reported as possibly treatment related. The most common TEAEs were infections and infestations (7/20 patients [35.0%]), gastrointestinal disorders (4/20 patients [20.0%]), and investigations (3/20 patients [15.0%]).

The immunogenicity results of children between 5 and 14 years of age were consistent with the data observed in previous studies in adults and adolescents. Only sporadic, transient immune responses to rhC1INH and HRI were observed, but with no associated clinical findings. Hypersensitivity to host related impurities (HRI) is already an identified risk for Ruconest and included in the SmPC in section 4.4.

In the additional studies performed in the **adult and adolescent population** the presented results for adverse events, laboratory findings as well as the immunogenicity results were consistent with the safety profile presented at the initial marketing authorization.

One patient died in study C1 1207 (for prophylactic treatment) due to laryngeal oedema, which was considered not related to study drug.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety database for the paediatric population is limited with 20 patients treated for 73 attacks. No safety data in children 2 to 4 years of age are available,

Although no concerns due to antibody formation were evident, no data is available for long term repeated administration. However, this is addressed by the ongoing registry C1 1201 as described in the RMP which will collect further data post marketing.

3.6. Effects Table

Table 14: Effects Table for Ruconest in the paediatric population

Effect	Short description	Treatment	Control	evidence	References
Favourable Effects					
median time to beginning of relief of symptoms	Overall VAS decrease ⩾ 20 mm	60 min	NA	*)	C1 1209
median time to minimal symptoms	Overall VAS decrease ⩾ 20 mm	120 min	NA	*)	C1 1209
median time to complete resolution	based on diary results	100.0 - 1167.5 min	NA	*)	C1 1209
therapeutic failure		3 patients 3 attacks	NA	*)	C1 1209
Treatment with second dose		2 patients 3 attacks	NA	*)	C1 1209
Unfavourable Effects					
SAE	infections and infestations	3 patients 9 SAEs	NA	*)	C1 1209
Possibly treatment related AEs	abnormal lymphocyte morphology	2 patients 3 events	NA	*)	C1 1209

Abbreviations: NA – not applicable

Notes: *) Uncertainties: Open label study, No placebo control, Limited safety set of 20 patients; Strength: Similar endpoints have been used in the adult studies with similar results.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary and secondary endpoints (time to beginning of relief of symptoms and time to minimal symptoms) are adequate to reflect a clinically relevant benefit for the patient suffering an attack. The exploratory endpoint time to complete resolution is also considered relevant in this context. Both exploratory endpoints – treatment failure and second dose – are adequately chosen to reflect other important aspects of the treatment related to HAE attacks.

Although the efficacy and safety data presented for the paediatric population are limited with 20 patients aged 5 to 14 years old treated for 73 attacks, since HAE is an orphan disease, they are considered sufficient to support authorisation. The efficacy and safety results submitted in the children population have been consistent with the results in the adult and adolescent populations.

No data are available in patients 2 to 4 years of age. The MAH tried to included patients in this age group but the availability of patients is limited in this orphan setting. In addition, other approved products for the treatment of HAE attacks in patients from 2 years of age are available and complying with all requirements in clinical trials might be an additional burden for the parents/caregivers.

In order to support the extrapolation of efficacy and safety data from older children to younger children aged 2 to 4 years where no clinical data are available the pharmacokinetic parameters of Ruconest in children were analysed and a population PK analysis presented. The results of the PK analysis as well as the predictions of the model are consistent with the results in adults and adolescents. The presented population PK model. predicted overall similar concentrations of Ruconest for adults, adolescents and children after administration of the recommended dose of 50 U/kg. Although a slight decrease in children < 5 years of age was predicted, this would still translate into 90% of children reaching maximum concentration of 0.7 U/mL. In case of an insufficient clinical response, an additional dose could be administered as recommended in the SmPC.

The uncertainties discussed for the favourable effects concerning the size of the safety database and the minimal age of paediatric HAE patients also apply to the unfavourable effects.

The reported adverse events are manageable and consistent with the safety profile established for the adult and adolescent populations. Further, no new safety concerns have been identified with the safety data provided in children from the age of 5 years.

Remaining uncertainties concerning efficacy and safety due to antibody development with long term repeated treatment are addressed by an ongoing registry as described in the RMP. Due to the absence of clinical safety data in the 2 to 4 years of age population, it is important to closely monitor symptoms of hypersensitivity during and after administration of Ruconest. This is requested in section 4.4 of the SmPC for all patients.

3.7.2. Balance of benefits and risks

No direct evaluation of the treatment benefit in children 5-14 years of age can be performed since the presented study was performed as an open label single arm study. Nevertheless, the obtained results are consistent with the results observed in adult and adolescent populations. Given the mode of action of Ruconest as enzyme replacement and assuming similar concentrations are achieved, it is acceptable to consider that efficacy data derived from children (≥5 years), adolescents and adult patients could be extrapolated to younger children from the age of 2 years.

Taking into account available data on efficacy and safety in patients 5 years and above, the presented popPK data, the mode of action, appropriate modifications to the SmPC and the proposed measures for gathering post marketing data, it is considered acceptable to amend the indication to include children from 2 years of age. Clarification is introduced in section 4.2 with regards to the timing of administration of a second dose if needed, this is supported by the PK data in children and in adult/adolescents.

The safety profile in the paediatric population is manageable and overall consistent with the safety profile established for the adult and adolescent populations.

Remaining uncertainties concerning efficacy and safety due to antibody development with long term repeated treatment are addressed by the ongoing registry study C1 1412 as described in the RMP. Monitoring of potential hypersensitivity reactions for all patients during and after the treatment is recommended in section 4.4 of the SmPC.

Several studies providing additional safety data for the adolescent and adult population consistent were also submitted in this grouped variation supporting the requested update of section 4.8, 5.1 of the SmPC.

Additionally, the submission of the final study results of the ongoing registry study C1 1412 has been delayed up to June 2022.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Ruconest is positive in children from the age of 2 years and above.

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:

Variations 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, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	I, IIIA and IIIB

Extension of indication to include the population of children from 2 years of age for the treatment of acute angioedema attacks with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency. This indication is based on results from Study C1 1209 in the children population.

Final efficacy and safety results from the Open Label Extension phases of Studies C1 1304, C1 1205, C1 1310 for treatment of HAE attacks and studies C1 1207 and C1 3201, investigating prophylactic treatment of HAE patients are also submitted to support update of sections 4.8, 5.1 of the SmPC. Furthermore, the submission of the final report for Registry Study C1 1412 included in the RMP is extended to 30 June 2022. The RMP has also been aligned to RMP template version 2.0.1.

Additionally, the product information has been updated to align with the most recent QRD template, version 10.1.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric

Investigation Plan PIP P/0343/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ruconest is not similar to Firazyr and Takhzyro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See attachment 2.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Ruconest-H-C-001223-II-0053-G.