



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Evaluation of Medicines for Human Use

## CHMP assessment report

**Ruconest**

**International Nonproprietary Name: conestat alfa**

**Procedure No. EMEA/H/C/001223**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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## Table of contents

## Page

<b>1. Background information on the procedure .....</b>	<b>3</b>
1.1. Submission of the dossier.....	3
1.1.1. For new centralised dossiers orphan medicinal products .....	3
1.1.2. Information on paediatric requirements .....	3
1.1.3. Information relating to orphan market exclusivity .....	3
1.1.4. Licensing status: .....	4
1.2. Steps taken for the assessment of the product .....	4
<b>2. Scientific discussion .....</b>	<b>4</b>
2.1. Introduction .....	4
2.2. Quality aspects .....	6
2.2.1. Introduction .....	6
2.2.2. Active substance .....	7
2.2.3. Finished Product.....	9
2.3. Non-clinical aspects.....	10
2.3.1. Introduction .....	10
2.3.2. Pharmacology .....	11
2.3.3. Pharmacokinetics .....	11
2.3.4. Toxicology .....	13
2.3.5. Ecotoxicity/environmental risk assessment.....	17
2.3.6. Discussion on non-clinical aspects.....	17
2.3.7. Conclusion on the non-clinical aspects .....	18
2.4. Clinical aspects .....	18
2.4.1. Introduction .....	18
2.4.2. GCP.....	20
2.4.3. Pharmacokinetics .....	20
2.4.4. Pharmacodynamics.....	22
2.4.5. Discussion on clinical pharmacology .....	23
2.4.6. Conclusions on clinical pharmacology .....	24
2.4.7. Clinical efficacy .....	24
2.4.8. Discussion on clinical efficacy .....	41
2.4.9. Conclusions on the clinical efficacy .....	43
2.4.10. Clinical safety.....	43
2.5. Discussion on clinical safety.....	48
2.6. Conclusions on the clinical safety.....	49
2.7. Pharmacovigilance.....	49
2.7.1. Detailed description of the pharmacovigilance system.....	49
2.7.2. Risk management plan.....	49
2.7.3. Benefit-risk balance .....	54
2.7.4. Similarity with authorised orphan medicinal products.....	57
2.7.5. Recommendation.....	57

# **1. Background information on the procedure**

## ***1.1. Submission of the dossier***

The applicant Pharming Group N.V. submitted on 03 September 2009 an application for Marketing Authorisation to the European Medicines Agency for Ruconest, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 27 April 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies

The applicant applied for the following indication:

Treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

### **1.1.1. For new centralised dossiers orphan medicinal products**

The applicant Pharming Group N.V. submitted on 03 September 2009 an application for Marketing Authorisation to the European Medicines Agency through the centralised procedure for Ruconest, which was designated as an orphan medicinal product EU/3/01/036 on 11 May 2001. Ruconest was designated as an orphan medicinal product in the following indication: Treatment of angioedema caused by C1 inhibitor deficiency. The calculated prevalence of this condition was approximately 2.1 in 10,000 EU population.

In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 September 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 9 September 2010.

### **1.1.2. Information on paediatric requirements**

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision P/132/2009 for the following condition:

Hereditary angioedema

on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

### **1.1.3. Information relating to orphan market exclusivity**

#### ***1.1.3.1. Similarity***

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

#### **1.1.3.2. Protocol assistance**

The applicant received Protocol Assistance from the CHMP on 21 November 2003. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

#### **1.1.4. Licensing status:**

The product was not licensed in any country at the time of submission of the application.

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

Rapporteur: **Ian Hudson** Co-Rapporteur: **Kristina Dunder**

#### **1.2. Steps taken for the assessment of the product**

- The application was received by the Agency on 03 September 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009.
- During the meeting on 18-21 January 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 January 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 March 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 April 2010.
- During the CHMP meeting on 17-20 May 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 24 May 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 June 2010.
- During the meeting on 21-24 June, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ruconest on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 June 2010.
- On 9 September 2010 the applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products.

#### **For new centralised dossiers orphan medicinal products**

- The CHMP adopted a report on similarity of Ruconest with Firazyr on 21 January 2010.

Note: The product was previously known as Rhucin.

## **2. Scientific discussion**

### **2.1. Introduction**

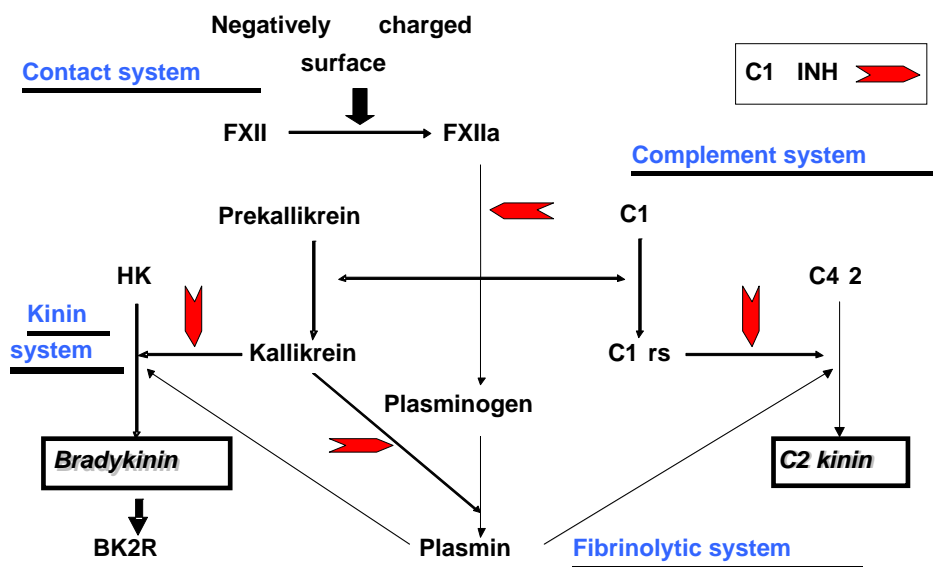
C1 inhibitor (C1INH), a serine proteinase inhibitor (serpin), is primarily synthesized in the liver and the normal range of C1INH activity in the general population is 0.7 to 1.3 U/mL (70 to 130%). The main function of C1INH is inhibition of several complement proteinases and contact-system proteinases.

Hereditary angioneurotic oedema (HAE) is characterized by recurrent, often unpredictable, acute attacks of soft tissue swelling (angioedema). Acute angioedema attacks in HAE patients impair the quality of life, and can be fatal if the angioedema swelling occurs in the throat. An untreated attack can persist for up to five days. Attacks of oedema of the gastrointestinal tract are associated with severe

pain similar to acute abdominal syndromes and may cause nausea, vomiting, diarrhoea, ascites and symptoms of hypovolemia.

Two types of congenital functional C1INH deficiency (phenotypic variants) can be distinguished (HAE Type I and HAE Type II). Both types are autosomal dominant disorders and the levels of functional C1INH in plasma are below 50% of normal levels. The median plasma level of C1INH activity in patients with HAE is about 0.2 U/mL, or 20% of the level found in healthy individuals

Key inflammatory mediators regulated by C1INH of concern for patients with HAE include activated proteases of the complement system such as C1r, C1s and Mannan Binding protein (MBP)-associated proteinases (MASPs), and factor XIIa, factor XIa and kallikrein of the contact system (Figure 1). Over activity of these inflammatory proteases is thought to lead to the generation of vasoactive peptides such as bradykinin that mediate angioedema attacks.



**Figure 1.** Schematic picture showing the C1INH mechanism of action.

The current available treatments of acute attacks of HAE include:

- Human C1INH preparations, which are purified and pasteurized concentrates from pooled human plasma (one approved in most EU member states via the Mutual Recognition Procedure, one is approved in the Netherlands);
- Icatibant (approved through the centralised procedure), which acts as a selective competitive antagonist at the bradykinin type 2 (B2) receptor.

Conestat alfa, the active substance of Ruconest, a recombinant human component 1 (C1) esterase inhibitor (rhC1INH), is the recombinant analogue of human C1 esterase inhibitor (C1INH), and is obtained from the milk of rabbits expressing the gene encoding for human C1INH. The transgenic rabbits, which are genetically modified organisms (GMO), are maintained in specific pathogen free enclosed housings. The product, however, is not a GMO. The availability of a non-blood product derived C1INH for treatment of acute attacks of HAE provides a further treatment option for patients.

The applicant Pharming Group N.V. submitted a complete and independent application for Marketing Authorisation to the European Medicines Agency for Ruconest (previously known as Rhucin) for treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

Ruconest was designated as an orphan medicinal product in the EU with the following orphan indication: treatment of angioedema caused by C1 inhibitor deficiency. HAE was considered as chronically debilitating conditions, characterised by acute and repetitive attacks, which might be life-threatening. The calculated prevalence of this condition at the time of orphan medicinal product designation was

2.1 per 10,000 EU population. The significant benefit at the time of designation was based on major contribution to patient care with regards to currently authorised medicinal products on the basis of a source of non-blood derived C1INH.

In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 September 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 9 September 2010.

The applicant received Protocol Assistance from the CHMP on the quality, preclinical and clinical development. There are no guidelines on the evaluation of medicinal products for the treatment of acute HAE attacks. The primary and secondary endpoints used in the two RDCT 1205 and 1304 are mainly in line with the Protocol Assistance given by the CHMP.

With regard to the paediatric development, the applicant has agreed to generate data in paediatric patients aged 2-18 years; these data are not yet available and will need to be provided post-authorisation. Studies in patients under 24 months are not requested.

This is the second marketing authorisation application (MAA) submitted for this medicinal product. The first MAA was submitted in July 2006 and received a negative opinion on the basis of the limited clinical database and concerns regarding severe allergic reactions and the potential for immunogenicity following repeated administrations. Additional clinical data for the present application for the present MAA was submitted with two finalised placebo-controlled studies and data from the ongoing extension phases of the two open-label studies. The current data also specifically addresses immunogenicity, efficacy in laryngeal attacks, and the possibility of thrombogenic potential. Furthermore, a new dose regimen was proposed.

The applicant initially applied for the following indication:

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

The finally approved indication is as follows:

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

The product is administered by intravenous injection. The posology is one single dose of 50 U/kg body weight for adults up to 84 kg body weight or 4200 U for adults of 84 kg body weight and above.

## ***2.2. Quality aspects***

### **2.2.1. Introduction**

C1 inhibitor (C1INH) is a serine protease inhibitor belonging to the serpin superfamily. The active substance of Ruconest is a recombinant analogue of human C1INH (rhC1INH, INN: conestat alfa) that is purified from the milk of rabbits expressing the gene encoding for human C1INH. It is a plasma single-chain glycoprotein containing 478 amino acids with six sites of N-glycosylation and at least seven sites of O-glycosylation. It has a molecular mass of approximately 67,000 Da of which approximately 22% is due to oligosaccharides. The amino acid sequence has been provided and includes two disulphide bonds (between cys101- cys406 and cys108 - cys183).

The drug product is presented as a powder for solution for injection. It is a sterile, non-pyrogenic, preservative-free, white to off-white lyophilized powder contained in a single-use type I, colourless sealed glass vial. The product is to be reconstituted with 14 mL sterile water for injections (WFI) before intravenous injection. Each vial contains 2100 U of rhC1INH (150 U/mL after reconstitution). The excipients used in the formulation are sodium citrate, sucrose and citric acid.

## 2.2.2. Active substance

### 2.2.2.1. Manufacture

#### *Generation of the transgenic herd*

The genomic DNA fragment containing the C1 inhibitor gene and flanking regions was isolated from a P1 phage clone. The promoter regions are derived from the casein sequences since the caseins are the predominant milk proteins.

Microinjection of DNA into a fertilized oocyte and transfer of the embryo into a foster mother led to the generation of a transgenic rabbit (Generation F0). This transgenic male animal was selected as the founder, establishing a transgenic line. The founder line was selected on the basis of expression level of C1INH in milk, gene copy number, site of integration and number of integration sites. The suitability of the selected line was determined by monitoring stability of expression throughout lactation, stability of transmission of the transgene, health and fertility of the rabbits. Following breeding with a non-transgenic female, an F1 male was selected for genetic characterization and sperm collection to establish the Master Transgenic Bank (MTB). From the MTB, transgenic bucks were generated and genetically characterized. The selected bucks were then used to establish a Manufacturing Working Transgenic sperm Bank (MWTB).

The development genetics has been fully discussed with relevant information provided about gene construction and identity, copy number, integration site and stability. Similarly, the information provided on the establishment, maintenance and pathogen safety of the transgenic line of rabbits is satisfactory. A two tier sperm bank has been established and production is limited to transgenic F4 female New Zealand White rabbits, therefore preventing the possibility of genetic drift.

#### *Manufacture of milk starting material*

The manufacture of the milk starting material includes breeding, maintenance and milking of transgenic rabbits.

A production rabbit colony is a group of rabbits of defined and tested genealogy housed in containment behind a biosecurity barrier.

After a general health check, the rabbits are milked using a milking machine. Following collection and storage, the milk is skimmed by centrifugation and frozen before transfer to storage facilities. Milk from individual rabbits may be pooled prior to skimming.

Besides maintenance of the rabbits as "closed" colonies behind a biosecurity barrier, a comprehensive health monitoring program for control of production and sentinel animals are used to control the safety of the raw material of the skimmed milk. The applied control procedures are considered acceptable. Pooling of thawed skimmed milk is adequately described and ensures a consistent starting material for the downstream purification. Control of the process is adequate, including in-process controls for the milking of the female rabbits as well as specifications for skimmed milk.

#### *Manufacture of formulated drug substance*

The formulated drug substance is manufactured and routinely controlled in compliance with GMP.

The downstream processing of the milk consists of thawing of milk, pooling of milk bags, fat removal by centrifugation and a succession of filtration and chromatography steps as well as viral inactivation/removal steps. The drug substance is formulated using ultra-/diafiltration and subsequently filtered and filled in a bag for storage.

#### *Validation*

Three consecutive process validation runs at commercial scale have been performed and extended in process control tests have been presented for these batches and compared to data collected from pilot scale batches. These data have adequately validated the process and demonstrates process comparability to pilot scale manufacturing runs. A summary of all batches which have been used in pre-clinical and clinical trials has also been presented and comparability of (pre)-clinical product to commercial product has been demonstrated by validation data from the process runs and extended characterisation of the product.

### *Characterisation*

The product has been extensively characterised, and 87% of the amino acid backbone has been sequenced. The sites of the 2 disulphide bridges have been identified and 9 of the reported 13 sites of glycosylation have been identified. A quantitative assay for isoform analysis has been developed and will be implemented as a batch release assay. A quantitative specification will be set after the assay is validated and sufficient batch release data has been obtained. Alongside the characterisation data presented in the dossier, this extent of sequence identification is considered to be adequate. Monosaccharide composition has been demonstrated to be very consistent. Of the sialic acids, only NANA has been identified, the potentially immunogenic NGNA has not been found. The N-linked profile has been adopted by the Applicant as a drug substance batch release assay, but the O-linked assay has not. Instead, the applicant has successfully argued that rates of sialylation and (O-glycosylation) site occupancy are the most important parameters to monitor instead of the O-glycosylation profile and a site occupancy assay is currently being validated. Sialylation is already a batch release parameter. The Applicant has successfully demonstrated that the product has a very low level of host related impurities (milk proteins) and that this parameter is well controlled. Clinical assessment has confirmed a very low level of patient antibody formation to HRIs.

#### **2.2.2.2. Specification**

Specifications for the skimmed milk intermediate and the formulated bulk drug substance are generally considered adequate to ensure a good level of control. The analytical methods used are considered to be state-of-the-art and have been adequately validated. Each batch of active substance is tested for appearance, identity, purity, potency, quantity, excipients, general physicochemical properties and contaminants.

The rhC1INH activity assay is based on the principle that C1s activity can be measured using a commercially available peptide. C1s cleaves the pNA part of the peptide, which absorbs at a wavelength of 405 nm. The amount of released pNA is directly proportional to the C1s activity.

Consistency of the protein composition of the skimmed milk starting material is monitored, and a qualitative specification for this assay has been set and will be updated with quantitative specifications. To ensure blood proteins have not leaked across the blood/mammary barrier, a specific test has also been introduced to monitor skimmed milk. A specification for this assay will be set after 20 batches have been analysed.

The applicant has committed to monitoring the O-glycan profile for all batches of drug substance, to complete validation of the O-glycan site occupancy assay and to introduce a specification for O-linked glycosylation.

A new primary reference standard, derived from a commercial scale batch has been characterised and introduced. The procedure to introduce new reference standards has been provided. This reference standard is also used for drug product. It should be noted that International Standards for C1INH (plasma and concentrate) are being developed. The Applicant has committed to providing traceability to an international standard once established.

Batch release data has been provided to demonstrate compliance of commercial product with the specifications.

#### **2.2.2.3. Stability**

Stability studies under real time, accelerated and stress conditions have been performed and the data provided support a drug substance shelf life of 3 years at -20°C.

In accordance with EU GMP guidelines<sup>1</sup>, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

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<sup>1</sup> 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union



### **2.2.3. Finished Product**

#### **2.2.3.1. *Pharmaceutical Development***

Ruconest 2100 U powder for solution for injection is a sterile, non-pyrogenic, preservative-free, white to off-white lyophilized powder contained in a single-use type I, colourless sealed glass vial. The product is to be reconstituted with 14 mL sterile water for injections (WFI) before intravenous injection. The solvent (sterile WFI) for reconstitution is not supplied with the drug product.

Each vial contains 2100 U of conestat alfa (150 U/mL after reconstitution). The excipients used in the formulation are sodium citrate, sucrose and citric acid.

A justification of the formulation components has been provided, along with a description of how the formulation was developed. A full description of manufacturing process development has been provided which details changes to the process, closure system and fill volume, and relates changes to batch numbers and clinical studies.

Initially, liquid formulations were investigated, however it was ultimately decided to have a lyophilised presentation as a liquid presentation was considered impractical.

The same composition of drug product has been used throughout clinical development and this is the formulation intended for commercial batches.

#### **2.2.3.2. *Adventitious agents***

The rabbit is not considered to be a TSE susceptible species and therefore TSE considerations for the rabbit milk are not deemed necessary. Adequate precautions to prevent contamination by TSE from alternative sources have been described.

The animals are kept in SPF (specified pathogen free) conditions and are routinely monitored for evidence of viral contamination. The manufacturing process has been validated for the inactivation or removal of a panel of relevant or model viruses. The two specific virus inactivation/removal steps demonstrate excellent capacity for virus depletion with the three chromatography steps also contributing to viral safety. A risk assessment has been performed based on the worst case possible viral contamination (calculated from the LOD of the in vitro assays and quantity of starting material per dose) and validated virus removal capacity of the process.

Overall, and taking all factors into consideration, it is considered that this product should not pose a risk to patients through adventitious agents.

#### **2.2.3.3. *Manufacture of the product***

Manufacture of the drug product, including labelling and packaging and batch release, is carried out at GMP-qualified sites. Batch release is performed by Pharming Technologies B.V., The Netherlands.

The manufacturing process for the drug product has been described in sufficient detail. Batches of drug substance are thawed, pooled, sterile filtered and filled aseptically into vials. The drug product is thereafter freeze-dried, capped, inspected, packaged and stored prior to shipment. No other components are added in the manufacturing process of the drug product.

The container closure system consists of a type I, colorless glass vial, a siliconized chlorobutyl rubber stopper, and a flip-off seal of aluminum and colored plastic.

Critical steps are identified and adequately controlled. The process has been appropriately validated.

#### **2.2.3.4. *Product specification***

The drug product specification is generally relevant and justified, although several limits will be updated when 20 batches have been manufactured.

Acceptable batch release data has been presented.

#### **2.2.3.5. Stability of the product**

Real-time and accelerated stability studies were performed on 4 batches of finished product. In addition, data from one batch stored under stress conditions was provided.

Based on the data presented, a shelf-life for the drug product of 36 months at 25°C is considered justified.

The applicant also performed studies on photostability and in-use stability of the reconstituted product.

In accordance with EU GMP guidelines<sup>2</sup>, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

#### **2.2.3.6. GMO**

The transgenic rabbits are considered to be genetically modified organisms (GMO). The manufacturer has been authorised by the authorities to handle transgenic rabbits in a contained environment and the rabbit housing areas are classified in accordance with GMO regulations. The product itself is not a GMO.

#### **2.2.3.7. Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

### **2.3. Non-clinical aspects**

#### **2.3.1. Introduction**

The non-clinical testing program was conducted to establish the safety of rhC1INH for short term use (< 7 days) in this chronically debilitating and potentially life-threatening disease. Studies presented covered *in vitro* pharmacology, *in vivo* safety pharmacology, pharmacokinetics, general toxicology with dosing of up to two weeks, teratology in rats and rabbits and local tolerance.

Two different pharmaceutical presentations were developed: a liquid formulation of 25 mg/mL and a freeze-dried presentation. Liquid presentations were used in early non-clinical studies. However, from formulation studies it became apparent that a lyophilized formulation was preferred for stability reasons. Later studies were performed with the lyophilized presentations.

Protocol Assistance from CHMP was obtained on the appropriateness of the proposed duration of 2 weeks for the repeated dose toxicity studies in rats, to support product safety with regard to the intended clinical use of recombinant human C1 inhibitor (acute treatment of angioedema caused by C1 inhibitor deficiency).

The pivotal safety studies were performed under GLP.

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<sup>2</sup> 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

## 2.3.2. Pharmacology

### 2.3.2.1. Primary pharmacodynamic studies

Four *in vitro* studies assessing kinetics of binding with enzymes that are presumed to be inhibited by the product (C1s, FXIa, FXIIa, kallikrein) were reported as the primary pharmacodynamic characterisation of rhC1INH. These studies report the second order rate constant of inhibition ( $k_{on}$ ) of rhC1INH, in comparison with that of human plasma-derived C1 INH, for batches used in preclinical and clinical studies. The results are presented in the table below.

**Table 5: Second order rate constants of rhC1INH and human plasma-derived C1INH at target enzymes**

	$k_{on} (M^{-1}.s^{-1})$			
	C1s	Factor XIa	Factor XIIa	Kallikrein
rhC1INH <sup>a</sup>	$6.1 \pm 0.3 \times 10^4$	$9.8 \pm 0.5 \times 10^2$	$6.9 \pm 0.5 \times 10^3$	$9.1 \pm 0.1 \times 10^3$
H-C1INH <sup>a</sup>	$5.1 \pm 0.3 \times 10^4$	$9.0 \pm 0.2 \times 10^2$	$5.7 \pm 0.4 \times 10^3$	$7.6 \pm 0.3 \times 10^3$
H-C1INH <sup>b</sup>	$6.3 \times 10^4$	-	$5.7 \times 10^3$	$8.2 \times 10^3$
H-C1INH <sup>c</sup>	$6.2 \pm 0.4 \times 10^4$	$3.9 \pm 0.3 \times 10^2$	$4.5 \pm 0.3 \times 10^3$	$7.8 \pm 0.4 \times 10^3$

(a) Data generated at Pharming Technologies B.V. The data are the mean  $\pm$  sd of three experiments. The values for  $k_{off}$  were virtually zero.

(b) Data reported in literature<sup>4</sup>

(c) Data reported in literature<sup>5</sup>

These findings demonstrated that the inhibitory activity of rhC1INH towards the target enzymes (C1s, FXIa, FXIIa and kallikrein) can be regarded to be comparable with plasma derived C1 inhibitor. Most importantly, rhC1INH is also able to inhibit the activity of C1s derived from human and cynomolgus monkey with equal efficacy.

### 2.3.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies are presented. This is acceptable for this biotechnology-derived product.

### 2.3.2.3. Safety pharmacology programme

Safety pharmacology was assessed in one *in vivo* study evaluating the effect of rhC1INH on cardiovascular and respiratory systems in anaesthetised dog. Vehicle or 625 U/kg (corresponding to 104 mg/kg) rhC1INH was administered intravenously in a crossover design. There were no marked changes in the QT<sub>CB</sub> interval following treatment with vehicle or rhC1INH. No treatment-related effects were observed for the remaining monitored parameters (arterial blood pressure, heart rate, PR and QT interval and QRS complex duration).

### 2.3.2.4. Pharmacodynamic drug interactions

C1INH has been shown to interact with clotting proteases. The treatment of an angioedema attack in HAE patients with rhC1INH will consist of a single dose of 50 U/kg, which will result in plasma levels of 0.7 to 2 U per mL, i.e. 70 to 200% of the level in normal healthy subjects (see study C1 1101-01). It is therefore unlikely that rhC1INH would contribute to an increased risk for thromboembolic side effects. In addition, steps have been taken to address the risk for thromboembolic events in the clinical part of development.

## 2.3.3. Pharmacokinetics

Pharmacokinetics was studied in rats, dogs and cynomolgus monkeys with detection methods applied that are suitable overall. The species used for analyses of pharmacokinetics were also used in the safety pharmacology and toxicology studies.

Single intravenous dose administration of several rhC1INH batches was studied in rats. Results of toxicokinetic blood sampling during toxicology studies in rats and dogs (single dose toxicity rats and escalating dose toxicity in dogs) were also presented.

### Methods

Two methods for quantification of rhC1INH in plasma were described. The first was a functional assay using the commercially available C1-inhibitor kit. This kit is used in clinical practice for the determination of the functional activity of C1-inhibitor in plasma to diagnose states of reduced C1 inhibitor concentration in plasma and for monitoring substitution therapy in patients. Validation of this method was shown for rat, dog and human plasma samples. Stability of plasma samples at room temperature was assured for at least 72 hours and at -18 ° C for at least 61 days, with stability over three freeze-thaw cycles.

The second method was an ELISA which was applied to rat and dog plasma samples. Validation reports for the assessment of antibodies to rhC1INH in rat plasma and their neutralising potential were provided and considered acceptable. The ELISA used in toxicity studies met the validation criteria for precision and specificity at low, medium and high concentrations of anti-rhC1INH IgG. It was noted that there is some crossreactivity between endogenous rat C1INH and human C1INH specific antibodies used in the ELISA. However, the applicant gave a quantitative consideration that pre-dose concentrations amounted to less than 0.01% of  $C_{max}$  values.

### Absorption

As the product is intended for intravenous administration only, no studies in animals were done by other routes and no studies were conducted to assess bioavailability.

### Distribution

No specific studies assessing distribution of rhC1INH were reported. However, from the single dose administration of rhC1INH in rats and escalating dose administration in dogs, the  $C_{max}$  values were considered to be in accordance with the measured concentration of the injected dose.

### Metabolism

The role of hepatic receptors in removing rhC1INH from the blood circulation was studied in a non-GLP single dose pharmacokinetic study. RhC1INH was administered in male Wistar rats treated with competitors for the asialoglycoprotein receptor on parenchymal liver cells and the mannose receptor on liver endothelial cells.

Results indicate that the exposure and half life were each greater and the elimination rate constant (ERC in table 6) was reduced when either, or both, inhibitors were injected just prior to injection of rhC1INH. These results suggest that rhC1INH is mainly cleared from the circulation by the liver via receptor-mediated endocytosis. Removal is dependent on clearance mechanisms that are saturable at higher doses. This is inferred to be mannose receptors and hepatic asialoglycoprotein receptors both located mainly in the liver. The product is presumed to be broken down in the liver. This is acknowledged in the SPC which includes a statement regarding use in patients with hepatic impairment.

**Table 6: Pharmacokinetic data (mean) showing delayed clearance of rhC1INH when blocking the asialoglycoprotein receptor, the mannose receptor, or both**

rhC1INH Competitor	04I00013 -	04I00013 GalNAc	04I00013 Mannan	04I00013 GalNAc & Mannan
ERC	0.056 ± 0.009	0.013 ± 0.003	0.021 ± 0.006	0.004 ± 0.002
T1/2	12.6 ± 2.1	54.2 ± 12.7	35.5 ± 11.2	196 ± 101
AUC0-t	7380 ± 1430	11655 ± 1035	10788 ± 749	15783 ± 2825
AUC0-inf	7649 ± 1257	24272 ± 5123	16119 ± 4381	91257 ± 57785

### Excretion

No specific excretion studies were reported as, according to the applicant, the pathway of amino acid degradation is generally understood. This was considered to be acceptable for this product.

### Other Pharmacokinetic Studies

The product is presented as a lyophilisate for reconstitution. Some of the studies in animals used a liquid formulation which was not adopted for commercialisation due to the lyophilisate being preferred for pharmaceutical reasons. Pharmacokinetic comparison of batches of liquid formulation with batches of lyophilized formulation failed to demonstrate comparability between both formulations.

Results shown in the table below indicate that the half life of rhC1INH was less than 20 minutes and the volume of distribution was close to the blood volume. No difference was seen between the batches.

**Table 7: Mean pharmacokinetic parameters of various rH-C1INH after a single intravenous dose in male Wistar rats**

Mean pharmacokinetic parameters of various rH-C1INH compounds after a single intravenous dose in male Wistar rats

Parameter	Unit	04I00011		04I00014	
		Mean	SD	Mean	SD
Body weight	Kg	248	± 7.1	249	± 11.0
Dose	U/kg	125	± 0.0	125	± 0.0
$t_{1/2}$ (median value)	Min	30.0 (15-60) <sup>#</sup>		30.5 (30-32) <sup>#</sup>	
AUC <sub>0-last</sub>	mU.min/ml	46066	± 12782	44556	± 4383
Dose normalized AUC <sub>0-last</sub>	mU.min/ml	368.5	± 102.3	356.4	± 35.06
AUC <sub>0-24h</sub>	mU.min/ml	46066	± 12782	44556	± 4383
Dose normalized AUC <sub>0-24h</sub>	mU.min/ml	368.5	± 102.3	356.4	± 35.06
AUC <sub>0-∞</sub>	mU.min/ml	74353*	± 19073*	62798*	± 6960*
Dose normalized AUC <sub>0-∞</sub>	mU.min/ml	594.8*	± 152.6*	502.4*	± 55.68*
% extrapolated		34.15	± 23.91	28.69	± 6.788
$\beta$	1/min	0.04401*	± 0.02086*	0.04253*	± 0.008891*
$t_{1/2}$	min	18.71*	± 7.701*	16.89*	± 3.476*
Corr. coeff.	$r^2$	0.9849	± 0.01941	0.9779	± 0.02465
Cl	ml/min/kg	1.789	± 0.5113	2.012	± 0.2330
Vd <sub>area</sub>	l/kg	0.04450	± 0.01075	0.04841	± 0.007221
Vd <sub>ss</sub>	l/kg	0.04836	± 0.005962	0.04973	± 0.006128
MRT	min	29.15	± 9.527	25.08	± 4.380

\* accurate determination not possible. When  $t_{1/2}$  and  $\beta$  are approximations also the derived parameters AUC<sub>0-∞</sub>, Cl, Vd<sub>area</sub>, Vd<sub>ss</sub> and MRT are approximations.

Dose normalisation to 1 U/kg

<sup>#</sup> median and range

An additional study comparing 2 pilot scale and 3 commercial scale batches of rhC1INH revealed differences for  $C_{max}$  and AUC between the groups, however this was considered as not significant. Overall, bioanalytical comparability was considered to be demonstrated.

## 2.3.4. Toxicology

The toxicology program was designed to reflect the anticipated short-term use of rhC1INH in humans, and included single-dose studies in rat, dog, cynomolgus monkeys, repeat-dose studies in rats (up to 2 weeks), dogs (up to 5 days), cynomolgus monkeys and marmosets. Embryofetal development studies were performed in rat and rabbit, and local tolerance was studied in the rabbit. Immunogenicity was evaluated in rats, rabbits and monkeys.

### 2.3.4.1. Single dose toxicity

The single dose toxicity study conducted in rats using intravenous administration showed tolerability at doses achieving about 7 to 9 fold excess the human plasma concentration. rhC1INH was administered once at doses of 0, 25, 125, 625 and 1250 U/kg.

Treatment-related clinical signs were mainly piloerection at the highest dose.

In addition, the enlargement of spleen in 2/3 male rats may be evidence for immunological reactions. The maximal exposure to functional rhC1INH in this study was achieved in rats given the highest dose, 1250 U/kg. The mean maximal concentration was 18,562 mU/mL (3094 mcg/mL). In comparison, plasma concentration in patients after the proposed dose of 100 U/kg (approximating to the recommended dose of 15 mg/kg) was typically between 2,000 and 3,000 mU/mL. This concentration was achieved in some rats given 125 U/kg.

Overall, the rat study demonstrated tolerability at doses achieving about 7 to 9 fold excess the human plasma concentration.

There was no effect on coagulation and fibrinolytic parameters in this study.

There were no deaths in the tested species.

#### **2.3.4.2. Repeat dose toxicity (with toxicokinetics)**

Toxicity after repeated dose was assessed in two studies in rats, two in monkeys (cynomolgus and marmoset), and one in the dog.

##### Rats

In the rat, 2 studies were conducted, one using repeated daily administration for 4 days and one with continuous infusion over 14 days.

In the 4-day study rats were treated with rhC1INH, from two batches, by slow intravenous infusion at doses of 0, 625 and 1250 U/kg once per day and with 1250 U/kg twice per day, with a 7 hour interval between doses, for 4 consecutive days with toxicokinetic evaluation. In addition, 5 rats/sex were kept for a recovery period of 10 days. Anti-rhC1INH antibody determination was undertaken on all rats, using samples taken just prior to termination on Days 4 and 14. Almost all rhC1INH-treated rats had a swollen muzzle and/or limbs after treatment. Swelling persisted beyond 7 hours for several animals but regressed within 24 hours. The incidence of swelling generally decreased as the study progressed. There were no other signs of overt toxicity, no significant findings in laboratory investigations and no identified target organ of toxicity after histopathological examination.

Among 90 rats given rhC1INH, 34 tested positive for IgG antibodies (38%). There was no correlation of antibody titre with dose, sex or whether rats were killed on Day 4 or 14. After two week recovery period product-specific antibody (IgG) titres were determined by ELISA. None or only relatively low rhC1INH-specific antibody titres were measured in all groups.

In the second repeated dose toxicity study, rats received a continuous intravenous infusion at doses of 25, 125 or 625 U/kg/day rhC1INH and 625 U/kg/day plasma derived C1INH (pdC1INH) for 14 consecutive days, followed by a 14-day observation period, and including toxicokinetics. This dosing route design (i.e. continuous infusion) was chosen to try to avoid immunogenicity associated with repeated bolus administration.

There were no effects of rhC1INH detected on any parameters measured in the study. The NOEL was therefore determined to be 625 U/kg. In the comparator product (plasma derived C1INH) group, minimal changes in haematological and clinical biochemical parameters and in organ weights (increases to liver, kidney and spleen) were observed.

The exposure to rhC1INH achieved in this was significantly less than that achieved in other studies and was less with rhC1INH than with the comparator pdC1INH. However, it was noted that the maximum reported plasma concentration was much lower, compared to rats treated with the same intravenous dose of 625 U/kg rhC1INH once, where a plasma concentration in the range of 2351 - 3635 mU/mL was reported 2 hours after dosing. The active comparator group had substantially greater exposure (concentrations range from 3179 to 6206 mU/mL in accordance with previous studies. The low exposure was explained by faster clearance of rhC1INH compared to plasma derived C1INH through receptor-mediated endocytosis by the liver. Based on this limited exposure, the study was considered to be of limited toxicological relevance.

Investigation of antibody titres was performed for three groups (625 U/kg rhC1INH, 625 U/kg pdC1INH and vehicle) in order to determine the immunogenicity of the test substance in rats after prolonged exposure. After five days no significant differences was found between groups. However, after day 16 and day 29, differences in antibody titres between rhC1INH and vehicle became highly significant. In addition, the titres of the rats dosed with plasma-derived C1INH were not significantly increased as compared to the control group (vehicle). Although these findings are not considered to be predictive of immunogenicity in humans, they might suggest differences in immunogenic properties of rhC1INH and pdC1INH. The immunogenic potency of plasma derived C1INH was not assessed in this study as immunogenicity was assessed using a validated test for rhC1INH.

##### Dogs

In the dog, toxicity was investigated in a dose escalation study for 5 consecutive days administering doses of 25, 125, 625, or 1250 U/kg rhC1INH intravenously to 2 males and 2 females, including toxicokinetic sampling.



There was no mortality or clinical signs of overt toxicity in either stage of this study. Total white blood cell and platelet counts were decreased with reductions in the relative proportion of segmented neutrophils and increases in lymphocytes in both sexes. Neither APTT nor PT were altered by treatment with rhC1INH. Histopathological examination of all tissues did not reveal treatment-related findings.

It was concluded that 5 daily treatments of 625 U/kg (104 mg/kg) did not result in toxic effects and that daily escalating doses that reached 1250 U/kg (208 mg/kg) were not associated with overt toxicity. Toxicokinetic measurements demonstrated tolerability at doses achieving about 7 fold excess the human plasma concentration.

Overall, the dose escalating study in dogs did not reveal treatment related adverse effects.

#### Cynomolgus monkey

In cynomolgus monkeys, toxicity was investigated in a dose escalation study for two weeks administering doses of 250, 500, 1000, or 2000 U/kg rhC1INH intravenously into 21 males and 21 females twice daily. Dose-related histopathological changes (microvacuoles in epithelial cells lining the renal tubules) were noted in the kidneys at 500 U/kg/administration and higher. The NOAEL was estimated to be 1000 U/kg/administration.

#### **2.3.4.3. Genotoxicity**

No genotoxicity studies were performed on the basis that the drug is unlikely to interact directly with DNA or other chromosomal material, in accordance with current guidelines (ICH S6R1).

#### **2.3.4.4. Carcinogenicity**

No carcinogenicity studies were performed, on the basis that such studies are generally inappropriate for biotechnology-derived pharmaceuticals. This is in agreement with current guidelines (ICH S6R1).

#### **2.3.4.5. Reproduction Toxicity**

An embryofoetal development study in pregnant rats to assess the potential for teratogenicity was performed by intravenous injection at one dose level of 625 U/kg with a parallel control group. During dosing, all drug-treated dams were observed to have swollen muzzles and limbs for up to 4 hours after dosing. However, there were no other abnormalities noted in the dams, including at necropsy. No adverse effects on the different parameters of pregnancy were observed. No external, visceral or skeletal abnormalities were noted in foetuses and there was no difference in the number or type of skeletal anomalies or variations. Toxicokinetic measurements were of limited value as the sampling was performed 24h after dosing leading to values of endogenous concentration of C1INH. There was no evidence of development of IgG antibodies to rhC1INH.

In rabbits rhC1INH caused a slight delay in foetal skeletal ossification but not otherwise to have any adverse effects on the course or outcome of pregnancy. Delayed ossification was observed, an effect that is sometimes indicative of a nonspecific maternal effect and there was body weight loss in rabbits suggesting maternal toxicity. However, the formation of high titers of antibodies against rhC1INH has not been considered by the applicant as a possible cause of the detected embryotoxicity. The possibility of an effect on reproduction in rabbits was not excluded; information was requested to be included in the SmPC, section 4.6 and section 5.3.

Studies on fertility, early embryonic and postnatal development as well as studies in which the offspring (juvenile animals) are dosed have not been performed. It could not be excluded that rhC1INH will cross the placenta; foetal exposure and transfer in milk in lactating patients could not be excluded as there were no data to support this view. However, rhC1INH was rapidly eliminated by receptor-mediated endocytosis.

#### 2.3.4.6. Toxicokinetic data

**Table 8: Toxicokinetic data from treated rats (4-day study)**

– Toxicokinetic parameters from treated groups were as follows:

Occasion	Dose (U/kg/day)	Sex	C <sub>max</sub> (mU/mL)	AUC <sub>0-2h</sub> (mU.h/mL)
day 0	625	Male	15051	18870
		Female	15342	16523
	1250	Male	28679	33632
		Female	33855	35439
	2500*	Male	32026	41389
		Female	31464	40194
day 2	625	Male	16652	20272
		Female	15091	16424
	1250	Male	33161	41768
		Female	33108	35004
	2500*	Male	32312	42907
		Female	29390	37536

\* given as 2 doses of 1250 U/kg with a 7 hour interval

The systemic exposure was similar after the first or the second daily administration and no accumulation was observed between days 0 and 2. AUC values increased proportionally between 625 and 1250 U/kg/day for both sexes. There were no sex differences in C<sub>max</sub> and AUC. The C<sub>max</sub> data were approximately 10 fold the highest C<sub>max</sub> in human subjects at the recommended dose.

**Table 9: Toxicokinetic results in the dog (escalating dose study)**

Parameters	25 U/kg		100 U/kg		250 U/kg		625 U/kg		1250 U/kg	
	M	F	M	F	M	F	M	F	M	F
Half-life (min)	7.3	6.5	14.1	18.4	36.8	44.4	59.5	56.0	219	174
Clearance (mL/min/kg)	6.2	5.8	8.0	1.9	1.2	0.9	0.7	1.7	0.3	0.4
AUC <sub>0-inf</sub> (U.min/mL)	4.1	4.3	26.9	52.7	211	292	910	700	4437	3205
Dose norm. AUC <sub>0-inf</sub> (U.min/mL)*	0.2	0.2	0.3	0.5	0.8	1.2	1.5	1.1	3.6	2.6

\* Dose normalization to 1 U/kg

Toxicokinetic data from cynomolgus monkeys in study R-03-040 from one female and male cynomolgus monkey were reported and suggests that C<sub>max</sub> and AUC increased in proportion with dose over the range 500-3000 U/kg/administration with no gender difference noted. The study design was to give two infusions on one day, 6 hours apart, and this has the consequence that at the time of the second dose, not all drug from the first dose had been eliminated.

#### 2.3.4.7. Local Tolerance

Local tolerance was evaluated following administration of the liquid formulation in New Zealand White rabbits and in the 4-day rat toxicity study using the lyophilised formulation. The data support the conclusion that the product does not pose a risk of local intolerance.



#### **2.3.4.8. Other toxicity studies**

##### *Immunogenicity*

Investigation of antibody titres was performed in repeat-dose studies. In the rat, differences in antibody titres between rhC1INH and vehicle became highly significant at the end of the investigation period whereas titres of the rats dosed with plasma-derived C1INH were not significantly increased as compared to the control group.

The results from an additional repeat-dose study in rabbits confirmed that a high aggregate-containing presentation should not elicit immunogenic reactions in humans where there is some normal rhC1INH in their plasma. In cynomolgus the titers of antibodies increased with repeated dosing. However, titers showed no correlation with administered dose.

#### **2.3.5. Ecotoxicity/environmental risk assessment**

The applicant justified the lack of an environmental risk assessment as proteins are exempt from this requirement in accordance with CHMP/SWP/447/00 guidance on the Environmental Risk Assessment of Medicinal products for Human Use. This position is deemed acceptable.

#### **2.3.6. Discussion on non-clinical aspects**

rhC1INH was shown to have a pharmacological action similar to that of plasma-derived C1INH which is in use for the treatment of the same disease for which approval is sought. Although the applicant presented no data from *in vivo* studies in animals supporting the claim for activity in the indication, this is acceptable because C1INH is already well established as effective in this disease. The applicant's task in the pharmacology section of the dossier was to establish that its rhC1INH protein derived from transgenic rabbits inhibits proteins of the complement, coagulation and fibrinolytic systems in a similar manner to plasma-derived C1INH and secondly to establish that the drug is active in the species used in toxicity studies, rats, rabbits, dogs and cynomolgus monkeys. On both these considerations, the applicant's information is acceptable. As regards whether the drug acts in a quantitatively similar manner in animals as it does in humans, this has not been shown. Thus, the safety pharmacology study quantifies the plasma concentration at about 10 times that reached in humans given a therapeutic dose, but as it is not known whether the drug is equally active in dogs and humans, it cannot be concluded that the degree of pharmacological action in dogs is, in fact, 10 times that achieved in humans. As the product is used as replacement therapy in humans and quantitative comparison has been shown in humans, this weakness is not considered significant, as regards the pharmacology section of the dossier.

Pharmacokinetic parameters have been characterised in the species used and bioanalytical comparability between batches was considered to be demonstrated. Clearance of the product is occurring through receptor-mediated endocytosis by the liver.

The studies to assess general and reproductive toxicity are considered adequate in respect of the choice of species, the duration of dosing, the route of dosing and the doses actually given to support the nature of the intended therapeutic use of rhC1INH in patients. The studies presented are adequate to meet expectations of ICHS6 guidance, relating to development of biotechnology-derived pharmaceuticals (CHMP/ICH/286/1995). The single dose study in rats achieved 7-9 fold higher plasma concentrations than that shown in humans at the therapeutic dose with no toxicity identified. Methodological problems were encountered in the 14 day continuous dosing study in rats and these limit the interpretation of this study as the relative exposures quoted for rhC1INH and the comparator plasma-derived C1INH are inconsistent: the reported plasma concentrations of rhC1INH were much lower than those of plasma-derived C1INH. The applicant suggests this difference might be due to slower clearance of plasma-derived C1INH arising from glycosylation differences. Studies in rats, dogs and cynomolgus monkeys are sufficient to support registration of the product and in this 14 day rat study, no significant toxicity was identified. Repeated dose toxicity studies in dogs and cynomolgus monkeys indicated good tolerability of doses well in excess of that to be given to humans. Given the pharmacodynamic activity of rhC1INH to influence the coagulation and fibrinolytic systems, particular attention was given to thrombogenic risk in this assessment. The applicant clearly presented findings from toxicity studies in rats, dogs and monkeys that prothrombin and partial thromboplastin times were unaffected, even at doses substantially in excess of that to be given therapeutically were given to animals and concluded that risks of thromboembolic effects are very low. Nothing was noted in

necropsied animals that indicated thrombogenicity. It is concluded that adequate risk assessment for thrombogenicity has been presented in the dossier. Assessment of local tolerance was satisfactory.

In the rat, differences in antibody titres between rhC1INH and vehicle became highly significant at the end of the investigation period whereas titres of the rats dosed with plasma-derived C1INH were not significantly increased as compared to the control group. These findings might suggest differences in immunogenic properties of rhC1INH and pdC1INH. The immunogenic potency of plasma derived C1INH was not assessed in this study as immunogenicity was assessed using a validated test for rhC1INH.

From the discussed rat study it can be concluded that the presence of neutralising antibodies directed against endogenous C1INH is unlikely. In addition, treated animals show no signs of angioedema which would be expected in animals with low levels of functional endogenous C1INH.

No genotoxic or carcinogenic potential is expected from this biotechnology-derived product, justifying the absence of such studies.

In pregnant animals, no toxicity to the fetus was identified at doses tolerated by maternal rats. rhC1INH in rabbits did cause maternal bodyweight loss which may have given rise to a slight delay in development. The degree to which pharmacodynamic activity of rhC1INH in rabbits had been established was initially judged less than for other species, and the applicant was asked to provide further evidence of the suitability of rabbits from a pharmacodynamic perspective. This was satisfactorily demonstrated using SDS-PAGE analyses of rabbit sera. When pregnant rabbits were given rhC1INH, a small number of malformations were recorded (eg of cardiac vessel defects) which were difficult to assess as either product related or unrelated. The applicant was asked to compare the frequency of these findings with historical controls and although the absolute number was low, the frequency was notably higher than background (eg 1.12 v 0.03%). The possibility of an effect on reproduction in rabbits was not excluded hence this was to be reflected in the wording in the SmPC, section 4.6 and section 5.3.

No risk for the environment is expected.

### **2.3.7. Conclusion on the non-clinical aspects**

A nonclinical testing programme has been performed which was overall considered appropriate and to meet regulatory guidances. All nonclinical issues have been addressed satisfactorily during the assessment, and there are no outstanding nonclinical concerns. Relevant information has been introduced into the SmPC.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

The clinical data in support of this application were derived from the following clinical trials:

- Study C1 1101-01: A Phase I study in patients with asymptomatic HAE;
- Study C1 1202-01: A Phase II exploratory open-label study;
- Study C1 1203-01: A Phase II/III open-label study;
- Study C1 1106-02: A Phase I study investigating repeated intravenous doses of rhC1INH in healthy volunteers.
- Study C1 1205-01: A Phase II study in patients with HAE with attacks of angioedema;
- Study C1 1304-01: A Phase III study in patients with HAE with attacks of angioedema.

For details of these studies please refer to table 10. Studies C1 1205-01 and C1 1304-01 were the main efficacy studies for the present assessment.

Protocol Assistance has been received for the following areas of the clinical development: the primary and secondary endpoints used in the two RDCT 1205 and 1304 and the use of VAS score in the evaluation of treatment of HAE attacks. The main studies submitted with this application are in all major parts in compliance with this advice given by the CHMP.

**Table 10 Tabular Listing of All Clinical Studies**

<b>Study Identifier</b>	<b>Objectives of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>Number of Treated Patients</b>	<b>Healthy Subjects or Diagnosis of Patients</b>	<b>Duration of Treatment</b>
1101 (Phase 1)	Safety, Tolerability & PK/PD	Open label	rhC1INH 6.25, 12.5, 25, 50, 100 U/kg 15 min. iv infusion 2 doses, at least 5-week intervals	12 (24 administrations)	Asymptomatic HAE patients	Single dose
1106 (Phase 1)	Safety, Tolerability & PK/PD	Open label	rhC1INH 100 U/kg iv infusion (6 mL/min) 5 doses at 3-week intervals	14 (59 administrations)	Healthy Volunteers	Single dose
1202 (Phase 2)	Efficacy, Safety, Tolerability & PK/PD	Open label	rhC1INH 100 U/kg One dose per acute attack 15 min. iv infusion	4 (6 administrations)	Symptomatic HAE patients	Single dose
1203 (Phase 2/3)	Efficacy, Safety, Tolerability & PK/PD	Open label	rhC1INH 100 U/kg One dose per acute attack 15 min. iv infusion	10 (15 administrations)	Symptomatic HAE patients	Single dose
1304 RCT (Phase 3)	Efficacy, Safety & Tolerability	Randomized, saline-controlled, double-blind	rhC1INH 100 U/kg Saline (vehicle) single dose iv infusion at a flow rate of 6 mL/ per minute	32 (16 rhC1INH and 16 Saline administrations)	Symptomatic HAE patients	Single dose
1205 RCT (Phase 2)	Safety, Tolerability, Efficacy & PK/PD	Randomized, saline-controlled, double-blind	rhC1INH 50 or 100 U/kg Saline (vehicle) single dose 15 min. iv infusion	38 (25 rhC1INH and 13 Saline administrations)	Symptomatic HAE patients	Single dose
1304 OLE (Phase 3)	Efficacy, Safety, Tolerability & PK/PD	Open label extension	rhC1INH 2,100 units initial dose with the provision for a second dose of 2,100 units mg or 4,200 units	41 (76 administrations)*	Symptomatic HAE patients	Single dose with the option of second dose for the same attack
1205 OLE (Phase 2)	Safety, Tolerability & Efficacy	Open label extension	rhC1INH 50 U/kg initial dose, upon clinical response a repeat dose of 50 U/kg may be given	38 (79 administrations)*	Symptomatic HAE patients	Single dose with the option of second dose for the same attack

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

\* = 1304 OLE and 1205 OLE continue to treat patients. The number of patients and administrations given was at the time of the interim analysis cut-off of 03 September 2008

## 2.4.2. GCP

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

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

## 2.4.3. Pharmacokinetics

Pharmacokinetic properties of rhC1INH were investigated in four phase I/II studies in healthy volunteers, asymptomatic HAE patients and symptomatic HAE patients, respectively, at doses from 6.25 U/kg to 100 U/kg (studies 1101-01, 1202-01, 1203-01, 1106-02). In addition, pharmacokinetic sampling for a population pharmacokinetic analysis was made in the pivotal placebo-controlled and open studies (1205-01, 1305-01). For details of these studies see tabular listing (Table 10).

### METHODS

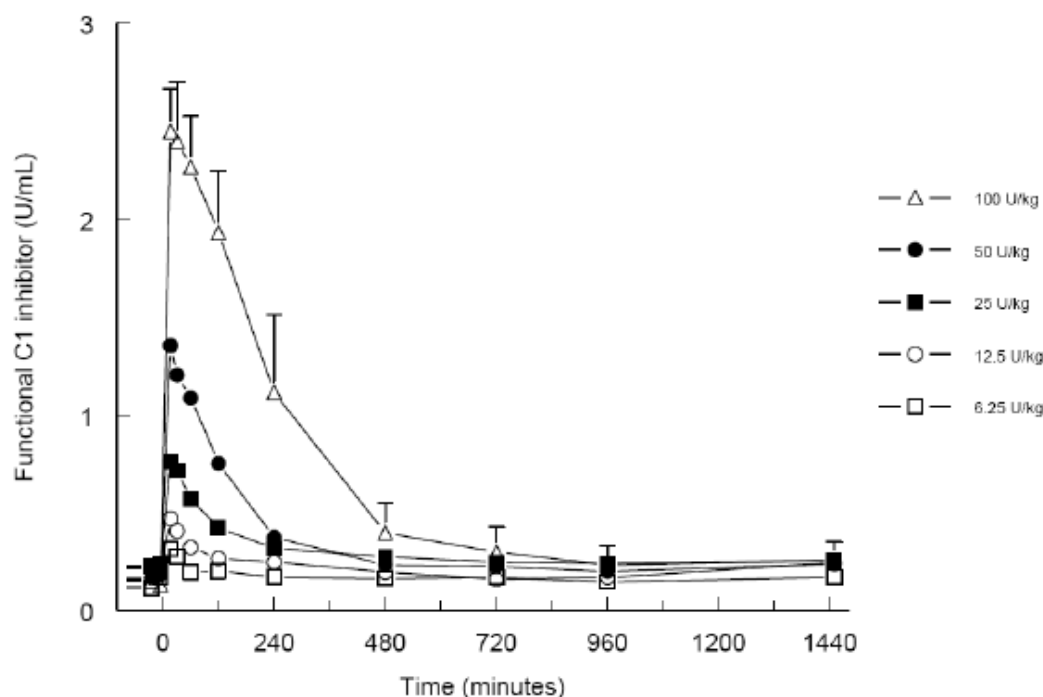
Analytical methods for determination of C1INH in plasma were adequately validated. Different methods were also developed for monitoring an immunogenic response in patients. Functional C1INH was determined by chromogenic assay. Antigen levels of C1INH were determined by a nephelometric immunoassay. The sensitivity of these methods has been validated using mainly human citrate plasma samples spiked with known concentrations of anti-rabbit antibodies directed against C1INH or HRI, and the detection/quantification limits of the analyses are defined in ng/mL.

The use of plasma was required for complement component measurements and evidence for the suitability of plasma as a matrix for antibody detection was provided by the applicant.

### RESULTS

Based on the dose-finding study in asymptomatic HAE patients, doses of rhC1INH of 50 U/kg and 100 U/kg were both found to restore C1INH activity to normal levels (0.7 U/mL to 1.3 U/mL), while doses of 25 U/kg and lower did not (Figure 1).

**Figure 2: Concentration-time profiles of mean C1INH /U/mL after administration of five different doses to asymptomatic HAE patients in study 1101**



The standard deviation (SD) in the highest dosage group (100 U/kg) is indicated by a bar.

#### **2.4.3.1. Absorption**

rhC1INH is intended for intravenous administration.

#### **2.4.3.2. Distribution**

After intravenous administration, the volume of distribution for rhC1INH was around 3 L, indicating distribution mainly to the plasma compartment.

#### **2.4.3.3. Elimination**

The pharmacokinetic data derived from the phase 1 trials demonstrated that the half-life of rhC1INH is shorter than pdC1INH which is due to the different glycosylation of rhC1INH (leading to more rapid hepatic clearance compared with pdC1INH). Therefore more rhC1INH needs to be given compared with pdC1INH on a U/kg basis to achieve a comparable PD effect.

The results of the dose-finding study indicated that elimination of rhC1INH is saturable. This is in agreement with the suggestion that rhC1INH is cleared via mannose/asialoglycoprotein receptors on hepatic cells and macrophages with carbohydrate recognition. These receptors become saturated at sufficiently high plasma levels.

With a molecular weight of 67 kDa, rhC1INH is not expected to be excreted, but to be fully eliminated by degradation.

#### **2.4.3.4. Dose proportionality and time dependencies**

There was no difference in the PK profiles of rhC1INH after the 1<sup>st</sup>, 3<sup>rd</sup>, and 5<sup>th</sup> administration of 100 U/kg rhC1INH at 3-week intervals in healthy volunteers. No neutralising antibodies against rhC1INH have been detected, which is in line with the finding of similar pharmacokinetics after late, repeated doses.

The applicant has performed a Population pharmacokinetic analysis (with NONMEM) including data from healthy volunteers (N=14) and patients with (N=94) and without (N=12) clinical symptoms. The subjects weighed between 45 and 119 kg and were between 16 and 66 years of age. A one-compartment model with nonlinear elimination was used to describe the time course of C1INH.

No formal covariate analysis was performed, but volume of distribution was set as a function of weight with an estimated allometric coefficient of <1 (0.56). Hence, with dosing directly by body weight 1:1 the model predicts increased  $C_{max}$  in subjects with larger body weight. For rhC1INH, the initial concentrations/ $C_{max}$  might be determinant of effect.  $C_{max}$  is dependent on dose and volume of distribution. The volume of distribution for rhC1INH more or less equals the plasma volume, which is related to body size. In normal weight subjects, plasma volume is usually directly related to body size, i.e. the coefficient used for allometric scaling is 1. In the response to the day 120 LoQ the applicant discussed whether the proposed dosing by body weight is appropriate over the entire Body Weight or Body Mass Index range. A fixed dose of 4200U for subject  $\geq 84$ kg was proposed by the applicant based on clinical efficacy and PK data in subjects in this weight range, simulations based on PK modelling as well as by calculation based on the literature about the relationship between plasma volume, body weight and height. The applicant's data in support of a fixed dose in adults  $\geq 84$ kg was accepted.

The simulation suggested that the administration of a single dose of 50 U per kg body weight of rhC1INH would result in almost all HAE patients achieving C1INH activity levels of at least 0.7 U/mL, while a fixed dose of 2100 U would fail to achieve C1INH activity levels of at least 0.7 U/mL, in one quarter of the patients which is in line with efficacy data. The simulation further indicated that administration of a second dose of 50 U/kg would not result in peak C1INH activity levels any higher than those following a single administration of 100 U/kg. For assessment of whether the model was adequate for its intended use, a comparison of observed and simulated  $C_{max}$  values stratified by dose levels would have been valuable. However, although not formally discussed by the applicant, if volume of distribution can be assumed to be dose independent it can be theoretically deduced that two repeated doses of 50 U/kg would not result in higher maximum concentration than a 100 U/kg unit dose. Therefore, further discussion on the potential problems identified in the modelling and simulation exercise are not considered needed for the specific purpose of estimating  $C_{max}$  at repeated doses.

#### 2.4.3.5. Special populations

There are no studies in special populations.

#### 2.4.3.6. Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been performed which is acceptable for a therapeutic protein.

#### 2.4.3.7. Pharmacokinetics using human biomaterials

No pharmacokinetic interaction studies have been performed, which is acceptable for a therapeutic protein.

### 2.4.4. Pharmacodynamics

#### 2.4.4.1. Mechanism of action

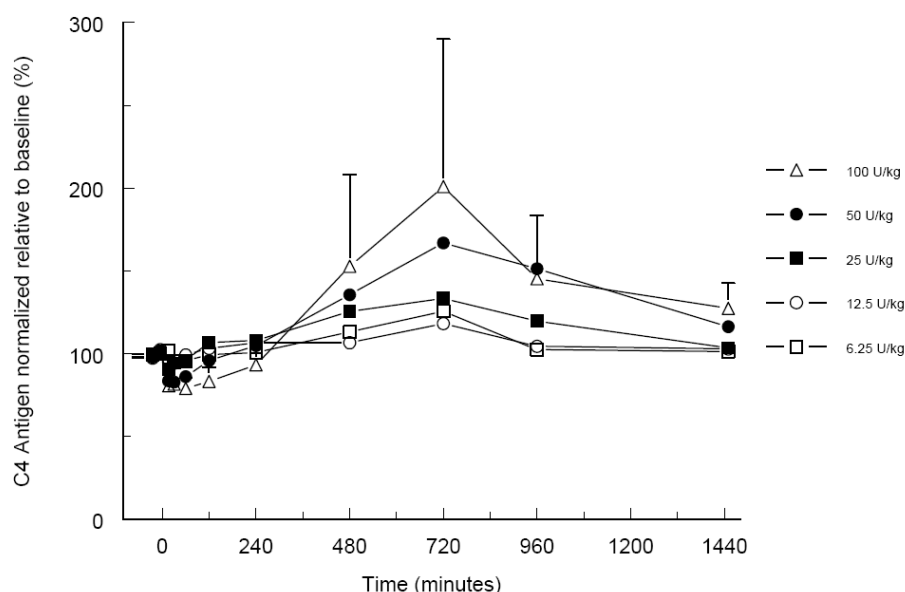
C1INH inhibits targets in the complement cascade (C1r, C1s and MASPs) and clotting pathway (factor XI, factor XII and kallikrein). C1INH deficiency results in an inappropriate activation of these systems, in the release of vasoactive peptides (C2-kinin and bradykinin) and also in increased vascular permeability which causes uncontrolled, local oedema. Insufficient control of C1INH on the (auto) activation of the complement component 1 (C1) results in activation and consumption of complement component 4 (C4) through cleavage of native C4 by activated C1.

#### 2.4.4.2. Primary and Secondary pharmacology

##### Primary pharmacology

Due to C1 inhibitor deficiency, HAE patients typically have low levels of complement component 4 (C4) because it is cleaved by activated C1. In Study 1101, which was the first study in man in the rhC1INH clinical development program (see Table 10 for description), rhC1INH was shown to be pharmacodynamically active in HAE patients through a dose-dependent decrease in the formation of C4b/c, the activation cleavage product of plasma complement component 4 (C4). Doses of 100 U/kg and 50 U/kg increased mean normalized levels of C4 relative to baseline, and cleavage of C4 resumed once functional C1INH levels fell below 0.7 U/mL. Doses of rhC1INH of 25 U/kg or lower only resulted in a temporary, minimal elevation of C4 levels relative to baseline.

**Figure 3: Study 1101 - Time profiles of mean normalized C4 antigen (in percentages) in the five dose groups**



The SD in the highest dosage group (100 U/kg) is indicated by a bar.

In Studies 1202 and 1203 (see Table 10 for description), the biological activity of rhC1INH was confirmed in HAE patients who were treated for an acute angioedema attack. Treatment with rhC1INH at a dose of 100 U/kg body weight, was followed by a rapid and substantial increase in plasma C1INH activity and a sustained elevation of C4 antigen. The mean normalized C4 antigen increased about two-fold between 4 and 12 h post-treatment.

### Secondary pharmacology

#### *Immunogenicity*

The active substance rhC1INH is purified from the milk of rabbits expressing the gene encoding for human C1 inhibitor (C1INH). The amino acid sequence of the recombinant form is identical to that of human C1INH. The purification process has been designed to eliminate to the maximum extent possible host related protein impurities (HRIs) originating from the rabbit milk. HRI levels in batches of the drug substance and the drug product range from 5-15 ppm.

Recombinant protein products such as rhC1INH administered to human subjects may elicit antibodies against the recombinant protein, its endogenous counterpart, and host-related impurities (HRI) in the drug product.

#### *Thrombogenicity*

Asymptomatic HAE patients have mild activation of coagulation and fibrinolysis as reflected by increased circulating levels of parameters such as F1+2 fragment, thrombin-antithrombin III (TAT) complexes and plasmin- $\alpha$ 2-antiplasmin (PAP) complexes. These activation processes further enhance during acute angioedema attacks. There are data indicating that infusion of pdC1INH can diminish platelet aggregation and decrease factor XIIa and F1+2 fragment levels in patients with HAE.

A possible risk for thromboembolic complications has been described in published reports with off-label administration of high dose pdC1INH (500-1050 U/kg, which is 25 to 50 times higher than the recommended dose for an angioedema attack) in neonates at risk for capillary leak syndrome who underwent cardiosurgery with extracorporeal circulation for major cardiovascular malformations.

### Pharmacodynamic interactions with other medicinal products or substances

No studies were performed. RhC1INH is the recombinant analogue of endogenous C1INH. Literature data indicate an interaction of tissue type plasminogen activator (tPA) and C1INH product. Interactions with other drugs are not anticipated due to the nature and metabolism of the product.

### Genetic differences in pharmacodynamic response

No studies were performed. Due to the existence of circulating C1INH levels the risk for immunogenic response to exogenous C1INH is expected to be low. Other aspects of genetic differences were not discussed in the application and the number on non-Caucasians included in the studies was very low.

## **2.4.5. Discussion on clinical pharmacology**

The mechanism of action of C1INH is rather well known. Previous experience with pdC1INH indicates that the administration of C1INH alleviates the symptoms of acute attacks in HAE patients.

Evaluation of pharmacodynamics was performed in asymptomatic HAE patients since healthy volunteer subjects, due to the absence of any genetic defect with respect to C1INH, have normal baseline functional C1 inhibitor activity and normal C4 levels. Since C4 levels are affected by the C1INH activity, C4 was chosen as a biomarker for pharmacodynamic effect of rhC1INH which is acceptable. A dose-related response in C4 levels could be demonstrated for rhC1INH.

Based on the now available efficacy data from the placebo-controlled study 1205 with the lower dose 50 U/kg, the applicant proposes the following dose regimen: For subjects less than 84 kg the dose is 50 U/kg, and for subjects  $\geq 84$  kg the dose is 4200U with the possibility to give a second dose within the same attack if the response is not sufficient.

It is well known that recombinant protein products such as rhC1INH administered to human subjects may elicit antibodies against the recombinant protein, its endogenous counterpart, and host-related impurities (HRI) in the drug product. The issues of immunogenicity have been further investigated by the applicant and a range of validated assays was developed to assess immunogenicity



## 2.4.6. Conclusions on clinical pharmacology

The overall clinical pharmacology data was satisfactory, with sufficient data provided to demonstrate the PK and PD activities of rhC1INH. Of particular importance is that the applicant during the assessment identified and reviewed the relevant factors to support the proposal for a fixed dose of 4200U (2 vials) in patients with body weight 84 kg or greater. This was supported by the PK model, efficacy in subject  $\geq 84$ kg as well as by calculation based on the literature about relationship between plasma volume, bodyweight and height. The proposed weight cut-off of 84kg for the fixed dose of 4200U is accepted.

## 2.4.7. Clinical efficacy

The studies included in the clinical development programme are shown in Table 10.

The main efficacy studies were two randomised controlled clinical studies (study C1 1205-01 and study C1 1304-01) and their open label extension studies.

### 2.4.7.1. Dose response study

#### **Study 1101**

This was an open-label study in twelve asymptomatic HAE (type I and II) patients of both genders. Patients had a plasma level of functional C1INH of less than 40 % of normal. The patients were divided in four groups and each patient was infused i.v. with rhC1INH on two occasions with an interval of at least five weeks. The doses tested were in the range of 6.25 U/kg up to 100 U/kg. Kinetics of functional C1INH was determined as well as changes in C4 antigen concentration as a biomarker for PD (results shown in Figure 3).

Based on the PK/PD results of study 1101, the doses of rhC1INH of 50 and 100 U/kg were selected for clinical evaluation with the following considerations.

- The normal physiological state in healthy patients supports the pharmacodynamic assumption that acute angioedema attacks cannot occur if endogenous C1INH activity is maintained above the lower limit of the normal range (0.7-1.3 U/mL plasma). It is therefore extrapolated that treatment of an angioedema attacks requires restoration of functional C1INH levels into the normal range.
- Experience with pdC1INH products indicates onset of relief of symptoms of an angioedema attack may not occur until 4 hours after administration.

Hence, a dose of rhC1INH that leads to restoration of circulating functional C1INH levels above the lower limit of normal for 4 hours was selected for initial evaluation in symptomatic HAE patients. The results of the Phase 1 Study 1101 suggested that dosing at 100 U/kg, and to a lesser extent 50 U/kg, was able to correct C1INH activity in blood for a sufficiently long period and to restore the disturbed biochemical homeostasis due to the C1INH deficiency state, and to halt progression of a swelling episode and to allow the resolution of oedema.

The selection of doses is considered adequate and supported by the available pharmacodynamic data.

### 2.4.7.2. Main studies

The efficacy of rhC1INH in symptomatic HAE was evaluated and established in two independent randomized double-blind placebo-controlled (RCT) studies (C1 1205-01 and C1 1304-01). As a result of their interim analysis the double-blind phase was terminated and only the open-label extension (OLE) phases were continued.

**Study C1 1205-01;** was a randomised, placebo-controlled, double-blind Phase II study on the safety and efficacy of rhC1INH at doses of 50 and 100U/kg in relieving eligible attacks of angioedema with involvement of sub-mucosal tissues in patients with HAE.

**Study C1 1304-01;** was a randomised, placebo-controlled, double-blind, multi-centre study performed in order to demonstrate the efficacy of rhC1INH at 100 U/kg in patients with HAE with attacks of angioedema.



#### **2.4.7.2.1. Methods for Study 1205-01**

##### **2.4.7.2.1.1. Study Participants**

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

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

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

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

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

##### **2.4.7.2.1.2. Treatments**

Study drug was scheduled to be administered within 6 hours after the onset of symptoms of the eligible angioedema attack. The solutions were dispensed in opaque syringes.

Double-blind treatment was an iv infusion 6 mL per minute of either:

- rhC1INH at 100 U/kg body weight
- rhC1INH at 50 U/kg body weight
- 0.9% sodium chloride (NaCl) in water for injection (Saline solution).

The solution was infused through an iv cannula using a calibrated infusion pump. For patients who received Saline, the volume of NaCl 0.9% solution was adjusted according to each patient's body weight.

Patients were followed until day 90 after treatment of an acute attack unless they experienced a new attack and were enrolled in the open-label study.

##### *Prior and Concomitant Therapy*

The use of any concomitant medication was documented in the CRF. After recruitment, patients continued with any medication prescribed for HAE that they were using at study start. In addition, acetaminophen could be used to treat pain. Prohibited medication included narcotics or other treatment anticoagulants (e.g., heparin or warfarin) in the 14 days preceding treatment with rhC1INH as well as pdC1INH concentrates or any blood or plasma-derived therapeutics (e.g., fresh or frozen plasma) within 7 days before treatment with rhC1INH.

##### **2.4.7.2.1.3. Objectives**

The study was designed to show superiority for rhC1INH when comparing with placebo. Objectives of the double-blind, saline-controlled, randomized phase were:

- To assess the safety and tolerability of rhC1INH in symptomatic patients with HAE,
- To demonstrate the efficacy of rhC1INH in the treatment of acute attacks in patients with HAE,
- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of rhC1INH in symptomatic patients.

#### **2.4.7.2.1.4. Outcomes/endpoints**

A patient reported visual analogue scale (VAS) was chosen to assess efficacy. VAS scores were recorded repeatedly throughout the study at defined timepoints and were measured at up to 4 different locations (abdominal, genitourinary, orofacial-pharyngeal-laryngeal or peripheral), depending on the affected locations. A series of VAS assessments were taken that varied for each location. To allow consistent evaluation of attacks at different anatomical locations, an overall severity VAS for each location was used. The last VAS question for each location indicated the overall severity of angioedema symptoms as felt by the patient for that location. All VAS scores were measured as a continuous scale from 0 to 100 mm. For most of the VAS questions, including the overall severity VAS, 0 mm corresponded to 'No symptoms at all' and 100 mm corresponded to 'Extremely disabling'.

*Primary Efficacy Endpoint - Time to Beginning of Relief of Symptoms (VAS Score Decrease of  $\geq 20$  mm with Persistence)*

The primary efficacy variable was time to beginning of relief of symptoms assessed using the overall severity VAS score. For the primary endpoint, the time of beginning of relief of symptoms was the first timepoint at which the overall severity VAS score decreased by at least 20 mm with respect to Baseline, at any eligible location, with persistence of the decrease at the next assessment time so that for the next value at the location a decrease of at least 20 mm with respect to Baseline was also observed.

*Secondary Efficacy Endpoint*

The secondary efficacy variable was time to minimal symptoms for an attack assessed using the overall severity VAS score. Time to minimal symptoms for an attack (assessed using VAS score) was defined as the time at which all overall severity VAS scores fell below 20 mm for all locations for which the VAS scores were collected at Baseline.

*Exploratory Endpoints*

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

#### **2.4.7.2.1.5. Sample size**

The sample size was estimated based on the results with time to relief from placebo-controlled studies of human pdC1INH. It was assumed that the mean times to the beginning of relief and their standard deviation would be the same for both active treatment groups as those observed by Kunschak et al (mean = 15.35 h SD = 10.83 h for the saline arm and mean = 2.7 hours and SD = 4.09 hours for the C1INH treatment arm). With 39 patients (13 in each treatment group), the study would have a power of 78% to detect a difference between the saline group and an active treatment group, using a two-sided 1% level of significance.

#### **2.4.7.2.1.6. Randomisation**

The central randomization was carried out when the patient presented with an acute angioedema attack. The block size used was 3 with an allocation ratio of 1:1:1. There was no stratification factor used in the randomization.

#### **2.4.7.2.1.7. Blinding (masking)**

The blinding procedure appears acceptable. Diagnostic laboratory results were not disclosed to any study personnel until the study had been unblinded, and functional C1INH level results were not disclosed to the investigators to ensure the blind was maintained.

#### **2.4.7.2.1.8. Statistical methods**

Two key analysis sets were defined for efficacy:

- The FAS or mITT Set was defined as the set of patients who provided informed consent, were randomized to one of the treatment groups and who took at least one dose of the study drug.
- The PP analysis set was defined as the subset of patients in the FAS without any major protocol deviation.

The FAS (mITT) was the primary analysis set of interest in all efficacy analyses, with the exception of the confirmatory analysis of the primary and secondary endpoint, which was performed on the PP analysis set.

The overall alpha level for the testing at the interim and final analysis was set as equal to 0.05 (two-sided). This value was split up into 0.01 in the interim analysis and 0.045 for the final analysis. The results of the interim analysis indicated that no further patients were needed to show significance of the primary endpoint, and recruitment into the double-blind phase of the study was discontinued. No further patients were randomized subsequent to the interim analysis. The efficacy endpoints were assessed using a two-sided, 1% significance level.

For each analysis a hierarchical test procedure was applied. At first, the rhC1INH treatment arm with the higher dose (100 U/kg) was compared with the saline solution arm, and only if it was shown to be statistically significantly superior was the rhC1INH treatment arm with the lower dose (50 U/kg) then compared with the saline solution arm. This hierarchical closed test principle was applied separately for all endpoints, without any adjustment for multiplicity.

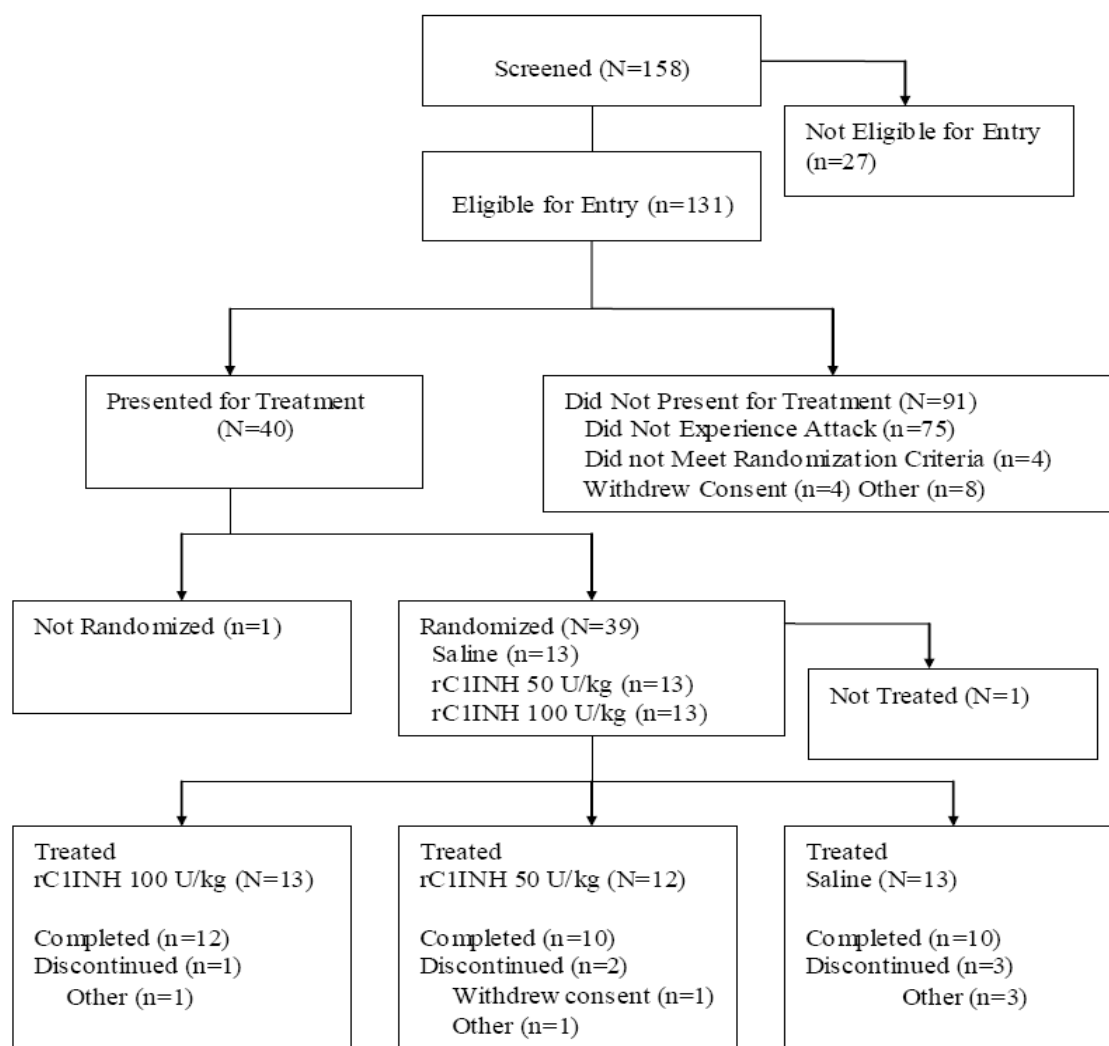
The study was only to be deemed a success if the p-value for the primary endpoint was significant at the two-sided significance level of 1%, the p-value for the secondary endpoint was significant at the two-sided significance level of 10% and the examination of therapeutic failures supported the efficacy of rhC1INH.

#### **2.4.7.2.2. Results for Study 1205-01**

##### **Participant flow**

Patient disposition is presented in Figure 4.

##### **Figure 4: Patient Disposition**



Source: [Tables 14.1.1, 14.1.2, 14.1.3.1, 14.1.3.2 and Appendix 16.2.1.2](#)

<sup>a</sup>Patient 33003: had a HAE attack and was treated in the OLE phase of the study.

<sup>b</sup>Patient 11005: retreated and did not complete Day 90

<sup>c</sup>Patient 28011: PI discretion, Patient 28026: approved by sponsor for open-label dosing, Patient 43001: Treatment 1

#### 2.4.7.2.2.1. Recruitment

First patient was enrolled 10<sup>th</sup> June 2005 and last patient completed 24<sup>th</sup> Jan 2008.

#### 2.4.7.2.2.2. Conduct of the study

The study was conducted at 26 sites in United States and 4 sites in Canada.

Six amendments relevant to the double-blind phase of the study were made. The major amendment was the change of the inclusion criteria to allow patients with peripheral attacks, which was in line with the recommendation given by the CPMP.

#### 2.4.7.2.2.3. Baseline data

**Table 11: Demographics of the Randomised Control Trial Study Population**

	rhC1INH 100 U/kg (N=13)	rhC1INH 50 U/kg (N=12)	Saline Solution (N=13)
Age on date of Attack (years)			
Mean	34.2	40.7	32.4
SD	15.68	12.18	11.30
Range	17-66	20-59	17-55
Categorized Age			
<18 years	1 (8%)	0	2 (15%)
18-64 years	11 (85%)	12 (100%)	11 (85%)
>=65 years	1 (8%)	0	0
Sex			
Male, n (%)	5 (38%)	4 (33%)	1 (8%)
Female, n (%)	8 (62%)	8 (67%)	12 (92%)
Race			
Caucasian, n (%)	12 (92%)	12 (100%)	11 (85%)
Black, n (%)	0	0	1 (8%)
Asian, n (%)	1 (8%)	0	1 (8%)
Other, n (%)	0	0	0
Mean (SD) Height (cm)	168.78 (7.22)	170.17 (8.09)	164.82 (6.82)
Mean (SD) Body Weight on date of admission (kg)	75.05 (19.23)	86.59 (22.69)	69.95 (15.65)
Mean (SD) BMI (kg/m <sup>2</sup> ) on date of admission	26.13 (5.29)	29.78 (7.10)	25.63 (4.76)

SD = Standard Deviation, BMI = Body Mass Index, RCT = Randomized Controlled Trial

**Table 12: Baseline Characteristics of the Randomized Control Trial Study Population (Study 1205 RCT and 1304 RCT)**

	rhC1INH 100 U/kg (N=13)	rhC1INH 50 U/kg (N=12)	Saline Solution (N=13)
Total Number of HAE Attacks per year (FAS [mITT])			
Mean	27.7	31.5	34.5
SD	15.89	24.00	28.27
Median	24.0	24.5	27.0
Range	8-62	4-87	8-101
Eligible anatomical location <sup>a</sup>			
Abdominal	5	5	3
Orofacial-pharyngeal and/or laryngeal	2	0	6
Laryngeal	0	0	3
Orofacial	2	0	3
Pharyngeal	0	0	0
Genitourinary	0	1	1
Other (peripheral)	6	6	5

SD = Standard Deviation, FAS = Full Analysis Set, mITT = Modified Intent-To-Treat, HAE = Hereditary Angioedema, RCT = Randomized Controlled Trial,

<sup>a</sup>This includes patients with more than 1 eligible anatomical location

#### 2.4.7.2.2.4. Numbers analysed

There were 39 patients randomized to treatment. One patient was randomized, but not treated (one patient in the rhC1INH 50 U/kg treatment group presented for treatment but was mistakenly randomized as eligibility criteria for attack severity were not met). The FAS (mITT) and safety analysis set, therefore, comprised of 13, 12 and 13 patients in the rhC1INH 100 U/kg, rhC1INH 50 U/kg and Saline solution treatment groups, respectively.

The PP analysis set comprised of 11, 8 and 11 patients in the rhC1INH 100 U/kg, rhC1INH 50 U/kg and Saline solution treatment groups, respectively.

#### 2.4.7.2.2.5. Outcomes and estimation

##### Primary endpoint

The median time to beginning of relief of symptoms (in minutes) along with the p-values calculated from a log-rank test are presented for the FAS (mITT) population and the PP Analysis Set in Table 13.

**Table 13 Median Time (Minutes) to beginning of Relief of Symptoms: Overall VAS Score Decrease  $\geq$  20 mm with Persistence**

Minutes	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	Saline Solution
FAS (mITT): median (95% CI)	68.0 (62.0, 132.0)	122.0 (72.0, 136.0)	258.0 (240.0, 495.0)
	[n=13]	[n=12]	[n=13]
Log rank test p-value <sup>a</sup>	<b>0.001</b>	<b>&lt;0.001</b>	
PP Set: median (95% CI)	68.0 (62.0, 143.0)	122.0 (70.0, 136.0)	258.0 (240.0, 495.0)
	[n=11]	[n=8]	[n=11]
Log rank test p-value <sup>a</sup>	<b>0.005</b>	<b>0.004</b>	

CI=confidence interval, FAS=full analysis set, mITT=modified intention-to-treat, PP=Per Protocol, SD=Standard deviation, VAS=visual analog scale

95% CI's are displayed as conventional estimates of CI, statistical tests are performed at 1% level.

<sup>a</sup>Comparing against Saline Solution.

### Secondary endpoint

Treatment with 100 U/kg body weight rhC1INH was not statistically significant in reducing the time to minimal symptoms compared to Saline Solution at the 1% level ( $p=0.040$ ) Table 14.

Although  $p=0.04$  for the 100 U/kg body weight dose statistical test, the FAS (mITT) log rank test for the comparison of 50 U/kg body weight versus Saline Solution for the time to minimal symptoms was explored and found to have a  $p<0.001$ .

**Table 14 Time to Minimal Symptoms: Overall VAS score**

Minutes	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	Saline Solution
FAS (mITT): median (95% CI)	245.0 (125.0, 270.0)	246.5 (243.0, 484.0)	1101.0 (970.0, 1494.0)
	[n=13]	[n=12]	[n=13]
Log rank test p-value <sup>a</sup>	<b>0.040</b>		
PP Set median (95% CI)	242.0 (124.0, 270.0)	246.5 (237.0, 484.0)	1210.0 (970.0, 1650.0)
	[n=11]	[n=8]	[n=11]
Log rank test p-value <sup>a</sup>	<b>0.006</b>	<b>&lt;0.001</b>	

<sup>a</sup>Comparing against Saline Solution. If rhC1INH (100 U/kg) versus Saline Solution is not significant at 1% then following closed test procedure no hypothesis test is carried out for the comparison of 50 U/kg rhC1INH and Saline solution.

### Exploratory endpoints

#### Therapeutic failure

No patients experienced therapeutic failure in either of the rhC1INH treatment groups and 5 patients experienced therapeutic failure in the Saline Solution treatment group. Although the difference was not statistically significant at the 1% level (for the comparison of rhC1INH [100 U/kg body weight] and Saline Solution), the number of therapeutic failures support the efficacy of rhC1INH (Table 15).

**Table 15 Therapeutic failure (FAS[mITT])**

	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	Saline Solution
Patients with therapeutic failure	0/13	0/12	5/13
p-value (Fisher's exact test)	<b>0.039</b>		

#### Other exploratory endpoints

The median time to beginning of relief based on IS was shorter for both the rhC1INH groups compared to the Saline solution group, however, this was not statistically significant at the 1% significance level (for the comparison of rhC1INH [100 U/kg] and Saline solution).

All patients in both the rhC1INH groups achieved beginning of relief of symptoms by 4 hours according to VAS scores and none had relapse of symptoms. Eight of 13 patients in the Saline solution group had a response at 4 hours and none had a relapse of symptoms.

The 13 patients in the rhC1INH (100 U/kg) group achieved beginning of relief of symptoms by 4 hours according to IS assessment, and 1 patient had an early relapse at a peripheral location at the scheduled timepoint 2 hours after treatment. Eleven of 12 patients in the rhC1INH (50 U/kg) group had a response by 4 hours according to IS assessment, and none had a relapse of symptoms. In the saline solution group, 10 of the 13 patients had a response by 4 hours. Of the patients who responded, 3 patients had an early relapse and 1 patient had a late relapse at a peripheral location at the 8 hours scheduled timepoint.

### 2.4.7.2.2.6. Ancillary analyses

A subgroup analysis was performed for the following subgroups for the FAS (mITT) Population: eligible anatomical location, sex, race, and age category. Numbers were so small in the subgroup analysis, that no firm conclusions can be drawn.

#### **2.4.7.2.3. Methods for Study 1304-01**

##### **2.4.7.2.3.1. Study Participants**

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

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

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

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

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

##### **2.4.7.2.3.2. Treatments**

Study drug was scheduled to be administered within 6 hours after the onset of symptoms of the eligible angioedema attack. Only one-dose level was studied in this study. The solutions were dispensed in opaque syringes.

Double-blind treatment was an intravenous infusion at a rate of 6 mL per minute of either:

- rhC1INH at 100 U/kg of body weight
- 0.9% sodium chloride (NaCl) in water for injection (placebo).

The solution was infused through an intravenous cannula using a calibrated infusion pump. For patients who received Saline, the volume of NaCl 0.9% solution was adjusted according to the patient's body weight.

Patients were followed until day 90 after treatment of an attack unless they experienced a new attack and were enrolled in the open-label study.

##### *Prior and Concomitant Therapy*

The use of any concomitant medication was documented in the CRF. After recruitment, patients continued with any medication prescribed for HAE that they were using at study start. In addition, acetaminophen could be used to treat pain. Prohibited medication included narcotics or other treatment anticoagulants (e.g., heparin or warfarin) in the 14 days preceding treatment with rhC1INH as well as pdC1INH concentrates or any blood or plasma-derived therapeutics (e.g., fresh or frozen plasma) within 7 days before treatment with rhC1INH.

##### **2.4.7.2.3.3. Objectives**

The study was designed to show superiority when comparing rhC1INH to placebo. Objectives of the double-blind, placebo controlled, randomized phase of clinical Study 1304 RCT were:

- To demonstrate the efficacy of rhC1INH in the treatment of acute angioedema attacks in patients with HAE,
- To assess the safety and tolerability of rhC1INH in symptomatic patients with HAE.



#### **2.4.7.2.3.4. Outcomes/endpoints**

A patient reported visual analogue scale (VAS) was chosen to assess efficacy (see methods for study 1205-01).

*Primary Efficacy Endpoint - Time to Beginning of Relief of Symptoms (VAS Score Decrease of  $\geq 20$  mm)*

The primary efficacy variable was time to beginning of relief of symptoms assessed using the overall severity VAS score. For the primary endpoint, the time of beginning of relief of symptoms was the first timepoint at which the overall severity VAS score decreased by at least 20 mm with respect to Baseline.

*Secondary Efficacy Endpoint*

The secondary efficacy variable was time to minimal symptoms for an attack assessed using the overall severity VAS score. Time to minimal symptoms for an attack (assessed using VAS score) was defined as the time at which all overall severity VAS scores fell below 20 mm for all locations for which the VAS scores were collected at Baseline.

*Exploratory Endpoints*

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

#### **2.4.7.2.3.5. Sample size**

The original assumption for sample size calculation was based on the data from Kunschak et al (Transfusion, 1998). This study was powered to show the same difference between the saline control and active treatment groups as was observed in the Kunschak study.

The primary efficacy variable is the time to the beginning of relief. For the study to have 90% power to show a difference of 12.65 hours between the two treatment groups at the 5% level of significance, with an estimation of the standard deviation of 7.66 hours, data must be available for 11 evaluable patients in each treatment group.

The secondary efficacy variable is the time to minimal symptoms. For the study to have 90% power to show a difference of 17.35 hours between the 2 treatment groups at the 5% level of significance, with an estimation of the standard deviation of 16.69 hours, data must be available for 25 evaluable patients in each treatment group.

In order for the study also to have sufficient power to show statistical significance for the secondary efficacy variable and to collect safety information on a more substantial population, it was decided to collect data on 50 evaluable patients.

#### **2.4.7.2.3.6. Randomisation**

The central randomization was carried out when the patient presented with an acute angioedema attack. Treatment allocation was stratified by attack type ('submucosal' and 'peripheral') at the discretion of the Investigator. The block size was 2 with an allocation ratio of 1:1.

#### **2.4.7.2.3.7. Blinding (masking)**

The blinding procedure appears acceptable. Diagnostic laboratory results were not disclosed to any study personnel until the study had been unblinded, and functional C1INH level results were not disclosed to the investigators to ensure the blind was maintained..

#### **2.4.7.2.3.8. Statistical methods**

Two key analysis sets were defined for efficacy:

- The Full Analysis Set (FAS or Modified Intention-To-Treat [mITT] Set) was defined as the set of patients who provided informed consent, were randomized to one of the treatment groups and who took at least one dose of the study drug.
- The Per Protocol (PP) analysis set was defined as the subset of patients in the FAS without any major protocol deviation.

The FAS (mITT) was the primary analysis set of interest in all efficacy analyses, with the exception of the confirmatory analysis of the primary and secondary endpoint, which was performed on the PP analysis set.

For all statistical tests, a significance level of 0.029 was considered. This level was chosen, based upon Pocock's group sequential procedure, in order to correct for multiple testing because of a previous interim analysis.

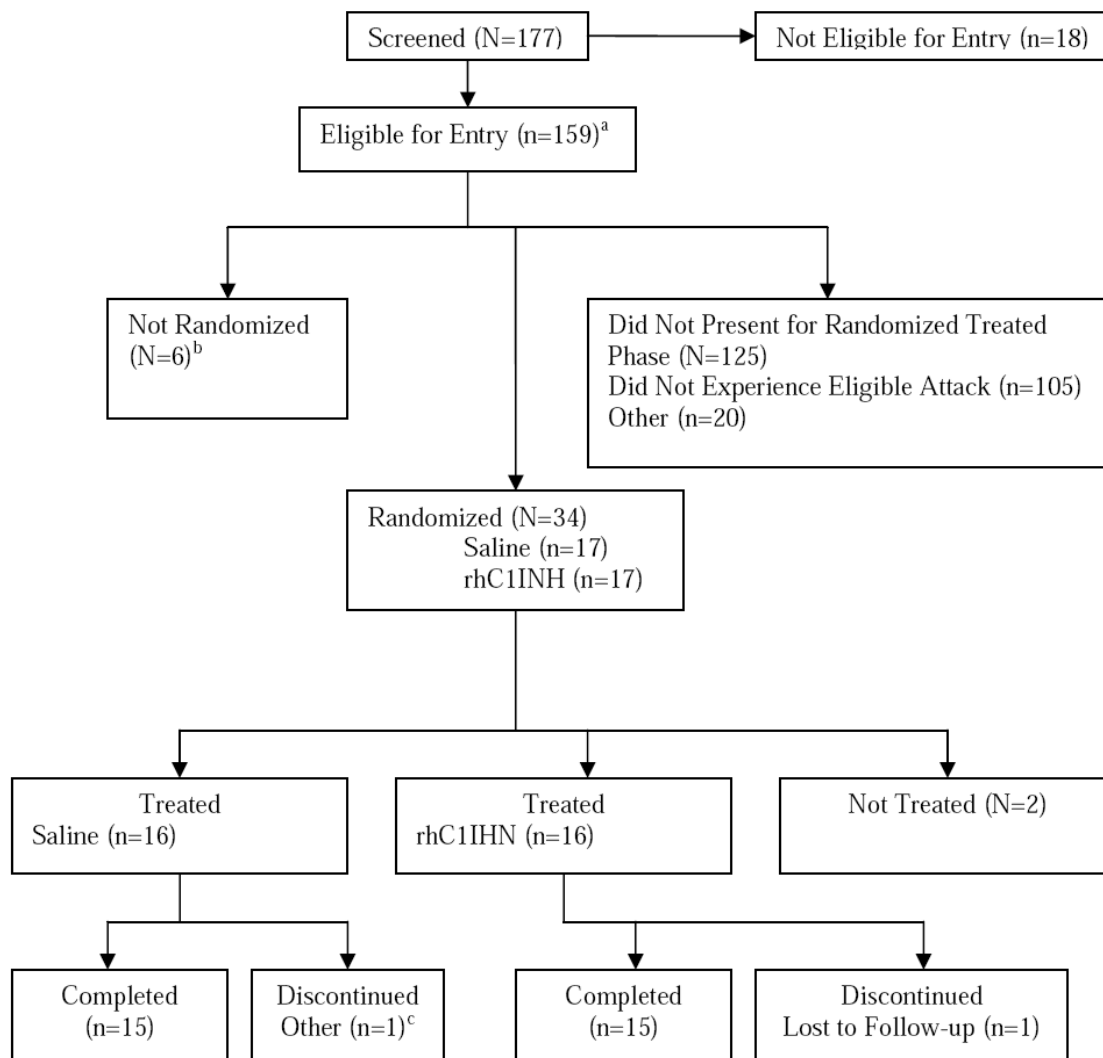
The study was only to be deemed a success if the p-value for the primary endpoint was significant at the two-sided significance level of 2.94%, the p-value for the secondary endpoint was significant at the two-sided significance level of 10% and the examination of therapeutic failures supported the efficacy of rhC1INH.

#### 2.4.7.2.4. Results for Study 1304-01

##### Participant flow

Patient disposition is presented in Figure 5.

**Figure 5: Patient Disposition**



<sup>a</sup> Includes 77 patients who did not have the final screening CRF page completed but were eligible for entry into the randomized treatment phase

<sup>b</sup> Six of the patients who were screened during the randomized phase did not present for treatment until the open label phase.

<sup>c</sup> Patient 309 had worsening of HAE symptoms

Two patients were randomized but not treated and, therefore, were not included in the FAS (mITT). One patient was not treated because she was in spontaneous regression of the attack. The other patient developed a potentially life-threatening attack location in the laryngo-pharynx with voice changes and a swelling in the uvula. The protocol had provision to withdraw such patients from the study.

The only discontinuation due to lack of effect occurred in the placebo group. One patient lost to follow-up. Two patients were randomised but not treated.

#### **2.4.7.2.4.1. Recruitment**

First patient was enrolled 27<sup>th</sup> June 2005 and last patient completed 13<sup>th</sup> Nov 2007.

#### **2.4.7.2.4.2. Conduct of the study**

The study was conducted at eleven active centers specialized in the treatment of hereditary angioedema in Italy (7), Spain (1), UK (1), Israel (1), Romania (1).

Six amendments were made to the protocol.

#### **2.4.7.2.4.3. Baseline data**

**Table 16 Demographics of the Randomised Control Trial Study Population (Study 1205 RCT and 1304 RCT)**

	rhC1INH 100 U/kg	Saline Solution
	(N=16)	(N=16)
Age on date of Attack (years)		
Mean	46.1	44.5
SD	14.51	16.77
Range	19-67	17-71
Categorized Age		
<18 years	0	1 (6%)
18-64 years	14 (88%)	13 (81%)
>=65 years	2 (13%)	2 (13%)
Sex		
Male, n (%)	8 (50%)	7 (44%)
Female, n (%)	8 (50%)	9 (56%)
Race		
Caucasian, n (%)	16 (100%)	16 (100%)
Black, n (%)	0	0
Asian, n (%)	0	0
Other, n (%)	0	0
Mean (SD) Height (cm)	171.2 (11.16)	170.6 (9.67)
Mean (SD) Body Weight on date of admission (kg)	84.16 (17.99)	77.25 (20.44)
Mean (SD) BMI (kg/m <sup>2</sup> ) on date of admission	28.86 (6.36)	26.17 (4.74)

SD = Standard Deviation, BMI = Body Mass Index, RCT = Randomized Controlled Trial

**Table 17: Baseline Characteristics of the Randomized Control Trial Study Population (Study 1205 RCT and 1304 RCT)**

	rhC1INH 100 U/kg	Saline Solution
	(N=16)	(N=16)
Total Number of HAE Attacks per year (FAS [mITT])		
Mean	25.7	26.5
SD	28.25	31.36
Median	14.0	15.5
Range	0 - 100	1-100
Eligible anatomical location <sup>a</sup>		
Abdominal	7	6
Orofacial-pharyngeal and/or laryngeal	2	4
Laryngeal	0	2
Orofacial	1	2
Pharyngeal	1	0
Genitourinary	0	0
Other (peripheral)	9	8

SD = Standard Deviation, FAS = Full Analysis Set, mITT = Modified Intent-To-Treat, HAE = Hereditary Angioedema, RCT = Randomized Controlled Trial,

<sup>a</sup>This includes patients with more than 1 eligible anatomical location

#### 2.4.7.2.4.4. Numbers analysed

There were 34 patients randomized to treatment. The FAS (mITT) and Safety Analysis set comprised of 16 patients in each treatment group. Two patients were randomized but not treated, one patient due to spontaneous regression of the attack and the other due to a potentially life-threatening attack location in the laryngo-pharynx with voice changes and a swelling in the uvula.

The PP analysis set comprised of 11 and 15 patients in the rhC1INH and Saline treatment groups, respectively.

#### 2.4.7.2.4.5. Outcomes and estimation

A patient reported visual analogue scale (VAS) was chosen to assess efficacy (see methods for study 1304-01).

*Primary Efficacy Endpoint - Time to Beginning of Relief of Symptoms (VAS Score Decrease of  $\geq 20$  mm)*

The primary efficacy variable was time to beginning of relief of symptoms assessed using the overall severity VAS score. For the primary endpoint, the time of beginning of relief of symptoms was the first timepoint at which the overall severity VAS score decreased by at least 20 mm with respect to Baseline.

*Secondary Efficacy Endpoint*

The secondary efficacy variable was time to minimal symptoms for an attack assessed using the overall severity VAS score. Time to minimal symptoms for an attack (assessed using VAS score) was defined as the time at which all overall severity VAS scores fell below 20 mm for all locations for which the VAS scores were collected at Baseline.

*Exploratory Endpoints*

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

#### 2.4.7.2.4.6. Ancillary analyses

The numbers for the subgroup analyses were so low that no firm conclusion can be drawn from the primary endpoint.

### 2.4.7.3. Analysis performed across trials (pooled analyses and meta-analysis)

The following analysis across trials also include data from the open label extension (OLE) phases of the main randomised-controlled trials (RCT), i.e. studies 1205-01 and 1304-01. Further information about these OLE phases is provided in section 3.4.7.5.

Table 17 shows the number of treatments and patients included in the efficacy data set up to September 2008.

**Table 17. Combined Population Number of Patients and Number of Attacks Treated: FAS (mITT)**

	03 September 2008
HAE Patients treated with rhC1INH	105
Total rhC1INH Treatments	196
Repeat rhC1INH Treatments	91
Number of Attack	Patients Treated with rhC1INH for Each Number of Attack
1	90
2	49
3	25
4	11
5	6
6	5
7	3
8	2
9	1
10 or more	1 <sup>a</sup>

<sup>a</sup> Includes 1 patient with 13 attacks and 12 rhC1INH treatments

The table shows the number of patients treated with rhC1INH for each attack number

15 patients received Saline Solution for their first attack, followed by rhC1INH for their second, their first rhC1INH attack therefore goes straight into Attack 2

During the assessment the applicant provided data on the 57 HAE patients that received a total of 194 open-label treatments in Study 1304 OLE and on 57 HAE patients that received a total of 144 OLE rhC1INH treatments in study 1205 OLE. No pattern suggestive of waning efficacy over repeated administrations was seen.

### **Additional dose**

The use of an additional dose and the rate of therapeutic failures with different dosing regimens is summarised in Table 18.

**Table 18. Number of Attacks with Additional Doses and Therapeutic Failure: FAS (mITT)**

	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	rhC1INH (18-40 U/kg)
Attacks treated with additional doses, n (%) <sup>a</sup>	n/a	7/79 (9%)	26/76 (34%)
Attacks with therapeutic failure, n (%)	3/29 (10%)	10/90 (11%)	13/75 (17%)

FAS = Full Analysis Set, mITT = Modified Intent-To-Treat.

<sup>a</sup> Only attacks treated in the OLE had the potential for more than one dose, therefore only OLE attacks are included in the summary

The proportion of patients experiencing treatment failure was similar between the two higher doses and somewhat higher in the group that received the lowest dose. The patients treated with the lowest dose also more often needed a second dose. These findings further support the posology of 50 U/kg with an option of a second dose since similar success rates are achieved using this strategy as in the group receiving 100 U/kg in spite of the fact that the majority of patients only received a single 50 U/kg dose.

Although median time to beginning of relief appears to be similar for all three doses in the open-label setting, the rate of patients who needed additional doses or were considered to be therapeutic failures

was highest in the treatment groups receiving the lowest dose. The simplified dosing regimen of one vial (2100 U) thus appears to be less efficient than the 50 U/kg dose.

In the open-label studies the initial treatment dose was to be administered within 1 hour after eligibility of the angioedema attack was confirmed. At the discretion of the investigator and depending upon the patient's clinical response, an additional iv dose could be administered within 4 hours from the initial dose. The applicant was asked to discuss whether this strategy should be reflected in the posology section of the SPC and whether there are any characteristics in the patient's response that could identify those who either need a second dose or are non-responders. The response demonstrated that there is no need to recommend a 1hr interval between presentation and treatment of an acute attack and that this time interval was to allow time for the various study procedures. The majority of cases improved within 4hrs and only 10% required an additional 50U/kg dose. Section 5.1 of the SPC includes relevant information on the observed time to beginning of relief and information on how many patients were treated with an additional dose.

### **Multiple treatments**

The maintenance of patients' response to rhC1INH for repeat treated attacks was assessed using a subset of patients from the FAS (mITT) Analysis Set. The patients included in the analysis were patients administered rhC1INH in the open label phase of Studies 1205 or 1304, and who were not treated in the RCT phase of either study.

The median time to beginning of relief of symptoms (minutes), and p-values from the paired t-test and Prentice-Wilcoxon test, are presented for the FAS (mITT) Analysis Set in Table 19.

**Table 19. Consistency of Findings of Repeat Attacks – Time (Minutes) to Beginning of Relief of Symptoms (VAS Decrease  $\geq 20$  mm with Persistence): Subset of FAS (mITT)**

	First Attack in OLE (N=19)	Last Attack in OLE (N=19)
Median Time (95% CI)	62.0 (35.0, 120.0)	65.0 (41.0, 120.0)
Prentice-Wilcoxon p-value		0.295

FAS = Full Analysis Set, mITT = Modified Intent-To-Treat, OLE = Open label extension, VAS = Visual Analog Scale, CI = Confidence Interval.

The median time to beginning of relief of symptoms, and confidence intervals, were very similar for first and last attacks. There was no evidence of a difference in the time to beginning of relief of symptoms at the 5% level with p-values of 0.295 (Prentice-Wilcoxon test).

There were 3 patients who had a significantly increased time to beginning of relief of symptoms for their last attack compared to their first attack. All 3 patients were administered a dose of 2100 U in 1304 OLE.

Similar findings were obtained when the same analysis was performed for the data on time to minimal symptoms.

### **Potentially Life-threatening Laryngeal attacks**

Within the randomized studies 1304 and 1205 and from their respective open-label extension phases, 196 sub-mucosal and peripheral acute angioedema attacks (105 patients) have been treated with rhC1INH.

Attacks, where a patient had completed the VAS scores for oro-facial-pharyngeal-laryngeal location symptoms at baseline, were selected for further analysis. Out of 62 attacks fulfilling the primary selection criteria, 53 had an overall severity VAS at the oro-facial-pharyngeal-laryngeal location  $\geq 50$  mm and were further analysed. Among these 53 attacks, 33 attacks met the criteria for PLA attacks.

**Table 20. Time to beginning of relief and time to minimal symptoms based on the VAS for PLA attacks**

Analysis Set	Attacks (N)	HAE Patients (N)	Time to beginning of relief Median [95% CI] (Minutes)	Time to minimal symptoms Median [95% CI] (Minutes)
All	33	25	115.0 [63 ; 120]	265.0 [241 ; 900]
All first OL	24	24	95.5 [62 ; 128]	253.0 [240 ; 1165]
All subsequent OL	8	5	93.5 [60 ; 242]	571.0 [120 ; 1128]

The pooled analysis of all laryngeal attacks show a somewhat longer time to relief than what was observed in the overall analysis of all attacks (95 minutes vs. 60 minutes). Three of the attacks did not achieve time to beginning of relief within four hours. However, none of the patients needed rescue medication or other therapeutic interventions and none experienced a relapse of symptoms.

Although the use of rhC1INH appears efficient in the treatment of severe laryngeal HAE attacks the applicant was asked to discuss the potential reasons for this difference in time to beginning of relief and whether this should be reflected in the SPC. Another concern was whether these attacks should be treated with 100U/kg at the onset.

The frequency of the use of an additional dose for PLA attacks compared with all other attacks treated in the open-label extension studies is shown in Table 21.

**Table 21. Additional dose use in the OLE phases of studies 1205 and 1304**

Study	PLA attacks treated with additional dose	All other attacks treated with additional dose
C1 1205-01-OLE	4/20 (20%)	3/59 (5%)
C1 1304-01-OLE	10/12 (83%)	16/64 (25%)

Eighty-three percent of PLA attacks in Study C1 1304-01 OLE were treated with an additional dose; whereas, only 20% of the 50 U/kg body weight dose PLA attack treatments in Study C1 1205-01 OLE were treated with an additional dose. The proportion of additional doses in PLA attacks was higher than for attacks at non-PLA anatomical locations in the 1205 OLE and 1304 OLE studies. Although 50U/kg is effective, the higher incidence of repeat dosing in PLA attacks raised the possibility that these cases should receive a 100U/kg dose.

The applicant provided additional efficacy data through to October 2009 during the assessment and addressed these questions for cases with PLA attacks.

The data provided support the proposed dose of 50U/kg demonstrating that the median time to beginning of relief of symptoms was the similar for PLA as for all attacks. No clinically relevant "treatment failure" occurred – such as requirement for intubation.

#### **2.4.7.4. Clinical studies in special populations**

Nine adolescent HAE patients (aged 13 to 17 years) were treated with 50 U/kg for 26 acute angioedema attacks, and seven (aged 16 to 17 years) with 2100 U for 24 acute angioedema attacks.

#### **2.4.7.5. Supportive studies**

##### **Studies 1202 and 1203**

Studies 1202 and 1203, undertaken in symptomatic HAE patients with a single dose of rhC1INH at 100 U/kg body weight, explored the safety, tolerability, pharmacokinetics and pharmacodynamics as well as the efficacy of rhC1INH in HAE patients who suffered from severe acute angioedema attacks. In these studies patients could be treated multiple times for subsequent new acute angioedema attacks. The two open-label, single arm studies were identical for key elements of study design.

The main differences in design between the studies were as follows:

- HAE patients presenting with acute laryngeal angioedema attacks could be included in study 1203.
- The sample size in study 1203 was larger and allowed for the evaluation of 30 severe acute attacks occurring in at least 10 different HAE patients. The sample size for 1202 allowed for the evaluation of 15 severe acute attacks occurring in at least 5 different HAE patients.

For these exploratory studies, a severe attack was defined as an acute attack of angioedema that resulted in the inability to work or perform daily activity.

In total in the two studies, fourteen HAE patients were treated with rhC1INH for 21 acute angioedema attacks. Seven out of 14 patients were treated for one acute angioedema attack and 7/14 patients were treated for 2 acute angioedema attacks. Seventeen of the 21 treated attacks occurred with



manifestations of angioedema at a single anatomical location, 4 attacks occurred with manifestations at 2 or 3 anatomical locations.

The median time to the beginning of relief of an attack was <60 minutes for all 3 symptom assessment methods (based on treatment benefit VAS [30 minutes], IS [30 minutes] and combination of pain and swelling VAS [60 minutes]).

Response rate (beginning of relief <4.0 hours) at all anatomical locations was 26/27 (96%), 25/27 (93%) and 22/25 (88%) based on the IS score, the VAS for treatment benefit, and the VAS for pain/swelling, respectively. None of the attacks with beginning of relief within 4 hours experienced a relapse based on the IS score and the pain/swelling or treatment benefit VAS.

The median time to minimal symptoms at all anatomical locations was 4, 4 and 8 hours after the start of treatment for the IS score, the pain/swelling VAS, and the treatment benefit VAS, respectively. The median time to minimal symptoms tended to be longer for non-abdominal locations (6, 8 and 10 hours for the IS score, the pain/swelling VAS, and the treatment benefit VAS, respectively) than for abdominal locations (2, 2 and 1 hours for the IS score, the pain/swelling VAS, and the treatment benefit VAS, respectively).

The data of these two small open-label studies support the findings from the two RCT studies.

#### **Study 1205 OLE and study 1304 OLE**

The 1205 OLE and 1304 OLE study phase allowed the open label extension treatment of acute angioedema attacks in HAE patients screened or treated in the RCT phase of study 1205 RCT or 1304 RCT respectively. The OLE phase also allowed new HAE patients to be screened and enrolled for treatment of acute attacks in the study after the RCT phase closed.

The study design for the OLE studies was similar to the RCT phase, except that:

- In the OLE phase, HAE patients could be treated multiple times for subsequent new acute angioedema attacks and there was only a single rhC1INH treatment arm

In the 1205 OLE the initial rhC1INH treatment was 50 U/kg body weight.

This initial 50 U/kg body weight dose could be followed by an additional 50 U/kg body weight at the discretion of the investigator and depending on the patient's clinical response within 4 hours after administration of the initial treatment. The maximum amount of rhC1INH that could be given to a patient for an acute attack was 100 U/kg body weight.

In the 1304 OLE the initial rhC1INH treatment was a fixed dose of a single 2100 U vial.

This initial fixed dose could be followed by an additional one or two 2100 U vial(s) at the discretion of the investigator and depending on the patient's clinical response within 4 hours after administration of the initial treatment. The maximum amount of rhC1INH that could be given to a patient for an acute attack was 3 x 2100 U vials (6300 U).

Between 04 September 2008 and 01 March 2009, 21 HAE patients were treated in Study 1205 OLE phase for 35 acute angioedema attacks with rhC1INH and 33 HAE patients were treated in study 1304 OLE phase for 70 acute angioedema attacks with rhC1INH.

The analyses of the primary (Table 22 and 23) and secondary efficacy endpoints (time to beginning of relief of symptoms and time to minimal symptoms, respectively) corroborated the RCT results. Response rates were consistent over time.

**Table 22. Median Time (minutes) to Beginning of Relief of Symptoms (FAS [mITT]) (Overall Severity VAS Score) (1205 OLE)**

	<b>Attack 1</b> <b>(N=27)</b>	<b>Attack 2</b> <b>(N=25)</b>	<b>Attack 3</b> <b>(N=13)</b>	<b>Attack 4</b> <b>(N=7)</b>	<b>Attack 5</b> <b>(N=4)</b>
<i>Median</i>	64.0	63.0	52.0	242.0	106.5
<i>(95% CI)</i>	(56.0, 88.0)	(41.0, 67.0)	(37.0, 65.0)	(40.0, 271.0)	(20.0, -)

*Note: 11 patients who received treatment in the RCT phase of the study were considered to have had their first rhC1INH-treated attack in that phase; this attack was not included in any summaries in the OLE phase. Their second rhC1INH-treated attack (first in OLE phase) was summarized together with other patients' second rhC1INH-treated attack in the OLE).*



**Table 23. Median Time (minutes) to Beginning of Relief of Symptoms (FAS [mITT]) (Overall VAS) (1304 OLE)**

	<b>Attack 1 (N=36)</b>	<b>Attack 2 (N=17)</b>	<b>Attack 3 (N=8)</b>	<b>Attack 4 (N=3)</b>	<b>Attack 5 (N=2)</b>
Median	60.0	60.0	120.0	62.0	46.0
(95% CI)	(34.0, 120.0)	(31.0, 121.0)	(20.0, 719.0)	(32.0, 958.0)	(31.0, 61.0)

*Note: 4 patients who received rhC1INH in the RCT phase of the study were considered to have had their first rhC1INH treated attack in that phase; this attack was not included in any summaries in the OLE phase. Their second rhC1INH treated attack [first in OLE] was summarized together with other patients' second rhC1INH treated attack in the OLE.*

In study 1205 OLE, efficacy was less pronounced in patients treated for their fourth or fifth attack, however, numbers are small. In spite of the lower dose used in study 1304 OLE, the outcome with regards to both the primary and the secondary endpoint was consistent with the findings in the RCT study. In this study no tendency of an attenuated effect with repeated treatments was observed as compared to study 1205 OLE.

The applicant addressed this during the assessment and provided further efficacy data which demonstrated that efficacy was similar over repeated attacks and that there was no trend for waning efficacy on repeat treatment.

The rate of therapeutic failures and the other exploratory analyses were in line with the primary and secondary endpoint findings.

#### **2.4.8. Discussion on clinical efficacy**

The randomised controlled trials (RCTs) 1205 and 1304 are considered as the pivotal studies. Study 1101 provides information on dose-finding, whereas studies 1202 and 1203, as well as the open-label extensions (OLEs) of studies 1205 and 1304 (referred to as 1205 OLE and 1304 OLE) are regarded as supportive. The supportive studies allowed repeated treatment and studies 1205 OLE and 1304 OLE, further allowed one additional dosing during the same attack.

The PK/PD data from study 1101 showed that both the 100 U/kg and the 50 U/kg dose were able to increase C1INH above the lower normal limit. Both the 100 U/kg and the 50 U/kg dose were chosen for the pivotal trials. This is of importance since the lowest dose only restored C1INH levels for about two hours and it was not known whether this would be sufficient to alleviate an attack. The highest dose, on the other hand, resulted in supra-normal levels for about 2-3 hours which may be unnecessary. The choice of doses is thus considered adequate. Within the open-label extension the option of giving a second dose of 50 U/kg was tested. This is an adequate way of handling the possibility that some patients may need a longer restoration of C1INH levels than two hours to treat an attack.

A very similar study design was used in both RCT studies (1205 and 1304). The rationale for performing placebo-controlled trials is acceptable and in line with the recommendations given in the CHMP scientific advice. The inclusion and exclusion criteria are acceptable reflecting the target population, especially since patients with peripheral attacks were included. Exclusion of patients experiencing a life-threatening attack is important since the study was placebo-controlled.

Both studies were designed to show superiority for rhC1INH compared to placebo.

The primary and secondary endpoints are mainly in line with the scientific advice given by the CHMP, and are considered to be clinically relevant. The use of the VAS score in the evaluation of treatment of HAE attacks has been accepted in other applications for marketing authorisation.

Considering the small number of patients, the treatment groups were rather well balanced with regards to age, sex and BMI. The only exception is the placebo group in study 1205, where only one male patient was included. Data in special populations is very limited since only a total of four patients were included in the age groups < 18 years and five patients > 65 years were included.

In the RCT studies, no patients with laryngeal oedema were included in the active treatment groups. The majority of patients were included had abdominal or peripheral attacks.

Notably, a total of ten patients had previously received treatment with (plasma derived) C1 inhibitor.

No patients discontinued due to adverse events. Most discontinuations were due to the fact that patients entered the OLE phase of the study before the day 90 follow-up. Overall, the only

discontinuation due to lack of effect occurred in one of the placebo groups. One patient was lost to follow-up and one patient withdrew consent.

In study 1205, both doses showed significantly better effect than placebo, the median time to beginning of relief of symptoms for the 50 U/kg dose being twice as long as for the higher dose although the 95% CI for these medians were overlapping. The outcome of the secondary endpoint (median time to minimal symptoms) was not statistically significant in the mITT population, although shorter and in the same range for both doses tested when compared to placebo. There were no therapeutic failures in the active treatment groups. The results for the exploratory endpoints were all in favour of the active treatment, although the treatment effect was not as evident when evaluated by the investigator's score (IS). More failures were seen in the placebo treated group.

In study 1304, where only the 100 U/kg dose was tested, the active treatment showed consistently significant better effects than placebo, both with regards to the primary and secondary endpoint. The time to beginning of relief in the active treatment group was in the same range as in study 1205 in spite of the somewhat different definition of the primary endpoint in study 1205 (symptom relief with persistence). The time to relief in the placebo group was considerably longer in study 1304 than in study 1205. The applicant's explanation is that in study 1205, patients had a longer time from start of symptoms until presentation for treatment. This explanation is considered plausible. There were three patients with treatment failure in the active treatment group as opposed to none in study 1205.

Sensitivity analyses of the primary endpoint confirm the primary results in both studies. The efficacy findings in the pivotal studies appear to be robust and consistent in spite of the small number of patients.

Studies 1202 and 1203 allowed re-treatment. The VAS score used was not identical to the one used in the RCT trials. Outcomes were comparable to those reported in the RCT studies. Seven patients were treated twice.

The OLE part of study 1205 allowed both a second administration of rhC1INH, and repeated treatments in case of new HAE attack. The findings with regards to both the primary and secondary endpoint are consistent with the findings in the RCT part of the trial in patients up to the third treatment. Efficacy is less pronounced in patients treated for their fourth or fifth attack, however, numbers are small. The applicant addressed this during the assessment and provided further efficacy data which demonstrated that efficacy was similar over repeated attacks and that there was no trend for waning efficacy on repeat treatment.

A different dosing was used in the OLE part of study 1304 where patients received a single vial containing 2100 U (corresponding to a dose of 18-40 U/kg) with the option of a second dose. Repeated treatment in case of a new attack was allowed. In spite of the lower dose, the outcome with regards to both the primary and the secondary endpoint was consistent with the findings in the RCT study. In this study no tendency of an attenuated effect with repeated treatments was observed.

Pooled data from both OLE studies were analysed for consistency of the treatment effect in repeated attacks. The pooled analysis does not evoke any concerns on attenuation of the effect with repeated treatments.

When all data from both the RCT and OLE phases of studies 1205 and 1304 were pooled with regards to the need of an additional dose or therapeutic failure it was observed that the proportion of patients experiencing treatment failure was similar between the two higher doses (100 U/kg and 50 U/kg) and somewhat higher in the group that received the lowest dose (18-40 U/kg). The patients treated with the lowest dose also more often needed a second dose. These findings further support the proposed posology since similar success rates are achieved using this strategy (50 U/kg with an option of a second dose) as in the group receiving a single dose of 100 U/kg. The majority of patients appear to be successfully treated with 50 U/kg and only about 10 % need an additional dose.

In the open-label studies the initial treatment dose was to be administered within 1 hour after eligibility of the angioedema attack was confirmed. At the discretion of the investigator and depending upon the patient's clinical response, an additional iv dose could be administered within 4 hours from the initial dose. The applicant was asked to discuss whether this strategy should be reflected in the posology section of the SPC and whether there are any characteristics in the patient's response that could identify those who either need a second dose or are non-responders. The response during the assessment demonstrated that there is no need to recommend a 1hr interval between presentation and treatment of an acute attack and that this time interval was to allow time for the various study procedures. The majority of cases improved within 4hrs and only 10% required an additional 50U/kg dose. In addition section 5.1 of the SmPC was revised to include relevant information on the observed time to beginning of relief and information on how many patients that were treated with an additional dose.

## 2.4.9. Conclusions on the clinical efficacy

In conclusion, the results of the pivotal and supportive studies are consistent and indicate a beneficial effect of rhC1INH in the treatment of HAE attacks. The initially proposed posology is supported by the findings. The proposed posology with a cut-off weight of >84kg for a flat dose of 4,200 U (two vials) was further addressed by the applicant. The applicant identified and reviewed the relevant factors to support the proposal for a fixed dose of 4200U (2 vials) in patients with body weight 84 kg or greater. This is supported by the PK model, efficacy in subject  $\geq 84$ kg as well as by calculation based on the literature about relationship between plasma volume, bodyweight and height. The proposed weight cut-off of 84kg for the fixed dose of 4200U is accepted.

## 2.4.10. Clinical safety

### 2.4.10.1. Patient exposure

Up to the database cut-off of 03 September 2008, 144 subjects (14 healthy volunteers, 12 asymptomatic and 119 symptomatic HAE patients) had been exposed to a total of 300 administrations of rhC1INH. One HAE patient participated in both Studies 1101 and 1304.

In addition to the data presented in this summary analysis of safety, an additional 105 acute angioedema attacks were treated with rhC1INH in the 1304 and 1205 OLE studies between 04 September 2008 and 01 March 2009. Thirty-four patients, who had been treated with rhC1INH before 04 September 2008 were treated for 72 subsequent new acute angioedema attacks in the period from 04 September 2008 up to 01 March 2009. An additional 20 patients, who received their first treatment with rhC1INH in the period from 04 September 2008 up to 01 March 2009, were treated for 33 first and subsequent new acute angioedema attacks.

**Table 24 Overview of rhC1INH Administrations**

	Based on Database Cut-off of 03 September 2008	Including Open Label Extension Data Until 01 March 2009
Healthy Volunteers	59	59
Asymptomatic HAE Patients	24	24
HAE Patients; Treatments of Acute Attacks	217	322
<b>Total Administrations</b>	<b>300</b>	<b>405</b>

Healthy Volunteer administrations from Study 1106 and the Asymptomatic HAE Patient administrations from 1101 are not included in the combined safety analysis

**Table 25 Patient Disposition – Allocation to Dose Groups (Full Safety Analysis Set)**

	rhC1INH					Total (N=119)	Saline Solution (N=29)
	100 U/kg Single dose (N=43)	50 U/kg Additional dose (N=6)	50 U/kg Single dose (N=44)	18- 40 U/kg Additional dose (N=22)	18-40 U/kg Single dose (N=26)		
Study							
1202	6	0	0	0	0	6	0
1203	15	0	0	0	0	15	0
1205 RCT	13	0	12	0	0	25	13
1205 OLE	0	7	72	0	0	79	0
1304 RCT	16	0	0	0	0	16	16
1304 OLE	0	0	0	26	50	76	0
<b>Total</b>	<b>50</b>	<b>7</b>	<b>84</b>	<b>26</b>	<b>50</b>	<b>217</b>	<b>29</b>

OLE=open-label extension, RCT= Randomized Controlled Trial

Counting in columns was by attack and not by patient

In all the dose administered was based on the patients' body weight (expressed in U/kg), except for Study 1304 OLE where the patients received a set dose of a single 2100 U vial of rhC1INH. Converted to a dose in U/kg, body weight, the dose received ranged from 18 U/kg to 40 U/kg for the patients in this treatment arm.

A total of 38 patients have been given at least three treatments of rhC1INH. The particular problems with the intermittent nature of administration of this protein (to a population not on

immunosuppression) which has potentially high immunogenicity due to HRI and differential glycosylation of the rhC1INH, means that a relatively large safety database was required.

#### **2.4.10.2. Adverse events**

##### Studies 1101 and 1106

Studies 1101 (asymptomatic HAE patients) and 1106 (healthy volunteer subjects) were not included in the combined safety analysis. For completeness, a brief summary of safety has been included for these 2 studies.

During the course of Study 1101, 14 possibly related treatment emergent adverse events (TEAEs) were reported, 9 presented as headache, 2 as abdominal pain, one as a vasovagal reaction and 2 as local hematoma or skin reaction. In addition, one acute angioedema attack was reported as an unrelated serious adverse event (SAE). None of the AEs were judged as having a definite or probable relationship to study drug administration. All AEs occurred on single occasions or intermittently, none were persistent. The 3 intermittent TEAEs were considered related to pre-existing disorders.

During the course of Study 1106, a total of 57 TEAEs occurred, which were more or less equally distributed over the 5 rhC1INH administration periods. One female healthy volunteer subject developed a serious generalised allergic reaction following first exposure to rhC1INH that was reported as a drug related SAE and considered to result from a pre-existing but undisclosed allergy to rabbits. In this study, all AEs occurred on single occasions or intermittently and none was persistent. Intermittent and repetitive single occasion TEAEs were considered in most cases as related to pre-existent disorders. Most of the AEs occurring after study drug administration were reported as unlikely or definitely not related to treatment as most were considered to be related to general procedures associated with a clinical trial, such as food restriction, and insertion of i.v. cannulas. In addition, some AEs were related to a pre-existing condition (eg tension headaches and migraine), or to the (winter) season during which the study was conducted (eg, upper respiratory tract infections). Of the 4 AEs (7% of all TEAEs) that were reported as possibly related to the study medication, one presented as headache, 2 as pruritis, and one as taste perversion.

##### Combined safety analysis

A combined safety analysis was performed using the RCT and the Full Safety Analysis Sets. The RCT Safety Analysis Set included data resulting from a single treatment during the RCT phases of Studies 1205 and 1304. The Full Safety Analysis Set included AE data from the 6 clinical studies in symptomatic HAE patients (single and repeat treatments of subsequent new acute angioedema attacks per patient).

**Table 26. Summary of Treatment Emergent Adverse Events (All Attacks) (Full Safety Analysis Set)**

	rhC1INH					Total N=119	Saline Solution N = 29
	100 U/kg N = 43	50 U/kg <sup>a</sup> N = 6	50 U/kg <sup>b</sup> N = 44	18-40 U/kg <sup>a</sup> N = 22	18-40 U/kg <sup>b</sup> N = 26		
Total number of attacks treated	50	7	84	26	50	217	29
Total number of TEAEs	59	2	68	8	13	150	33
<b>Patients with at least:</b>							
1 TEAE	18 (42%)	2 (33%)	23 (52%)	7 (32%)	8 (31%)	55 (46%)	14 (48%)
1 Treatment related TEAE	2 (5%)	1 (17%)	3 (7%)	2 (9%)	1 (4%)	8 (7%)	3 (10%)
1 Severe TEAE	2 (5%)	0	7 (16%)	1 (5%)	2 (8%)	12 (10%)	6 (21%)
1 Serious TEAE	2 (5%)	0	2 (5%)	0	1 (4%)	5 (4%)	3 (10%)
1 TEAE leading to Permanent Discontinuation	0	0	0	0	0	0	0

<sup>a</sup> additional dose, <sup>b</sup> single dose

TEAE = Treatment emergent adverse event

Treatment related = possible, probable and definite relationship to study treatment

The most common adverse events reported were infections (mainly upper respiratory infections and sinusitis); these adverse events were more common in the active treatment group. Rash and pruritis was also more common in the active treatment groups (a total of 5 reports). Headache and abdominal was also commonly reported, with the same rate in actively and placebo-treated patients.

The overall rate of TEAEs did not differ between treatment groups including the placebo group. Due to the small numbers, it is not possible to assess whether there the TEAEs are dose-dependent. No specific pattern can be observed.

#### **2.4.10.3. Serious adverse event/deaths/other significant events**

No deaths were observed during any of the trials.

In the combined safety analysis, the incidence of serious adverse events (SAEs) was higher in the Saline Solution dose group (3/29 patients, 10%) than in the rhC1INH treatment groups, either individually (range 0% to 5%) or when combined (5/119 patients, 4%). In study 1106, one treatment emergent SAE was reported by one patient. The SAE severe allergic reaction occurred during the first administration of rhC1INH. The onset of the first symptoms (episode) emerged approximately 3 minutes after starting the administration of rhC1INH at 100 U/kg. The SAE was judged to be a severe allergic reaction to the study preparation in a subject with a (in retrospect known) pre-existent rabbit dander/hair allergy. Apart from this reaction, none of the reported SAEs appear directly related to the treatment.

#### **2.4.10.4. Laboratory findings**

No influence on laboratory parameters or vital signs, including ECG was observed..

#### **2.4.10.5. Immunogenicity**

As for any recombinant product, antibodies may be raised against recombinant C1 inhibitor and to host related impurities. Therefore, extensive immunogenicity testing has been undertaken throughout the rhC1INH clinical development program. The immunogenicity testing has looked for the development of antibodies against pdC1INH, rhC1INH, and HRI. A schedule for plasma sample collection was pre-specified in every clinical study protocol. In addition, although not foreseen in any of the clinical study

protocols, immunogenicity testing to look for the presence of IgE antibodies against rabbit, cow and other animal allergens has been undertaken on plasma samples collected from the majority of healthy volunteer and HAE patients exposed to rhC1INH.

These immunogenicity testing findings indicated:

- No persistent antibody responses above cut off levels to pdC1INH, rhC1INH, in symptomatic HAE patients following first or subsequent repeat treatment exposure to rhC1INH at doses up to 100 U/kg body weight (N.B., up to 12 exposures for one patient in the integrated analysis)

**Concerning Antibodies to C1 INH:**

The applicant provided immunogenicity testing data undertaken beyond March 2009, i.e. all available immunogenicity testing data from administrations of rhC1INH through October 2009. From the results the applicant's position that the antibodies were not clinically relevant in terms of efficacy is supported. Data on safety and all AEs of cases who had antibodies to C1INH was provided and this data demonstrated that no AEs were considered likely related to the presence of antibodies. Two cases of injection site reactions occurred, but in both subjects subsequent infusions were not associated with any AE. These data support the applicant's conclusion that there was no apparent significant clinical safety concern and no relationship was observed to adverse events.

- No neutralizing antibodies to C1INH were found in any of the symptomatic HAE patients following first or repeat exposure to rhC1INH

**Concerning anti-HRI antibodies:**

The applicant provided all available immunogenicity testing data from administrations of rhC1INH through October 2009. Overall, there were some findings of positive pre- and post-exposure anti-HRI antibodies in both healthy volunteer subjects and HAE patients who received rhC1INH as treatment for several acute angioedema attacks. Most of these anti-HRI antibodies were not positive in the displacement assay. In the remaining cases, where there was confirmation of anti-HRI antibodies by the displacement assay, there was no apparent significant clinical safety concern.

- No persistent anti-HRI responses were found in the symptomatic HAE patients included in the open label and RCT clinical studies up to 03 September 2008.

The applicant also committed to make available validated testing for antibody development to C1INH and HRI in cases with clinical features suggestive of an antibody response. This proposal is strongly supported. Expedited reporting of such cases has been agreed by the applicant and educational materials will be made available.

A post hoc analysis of available plasma samples was carried out to test for the presence of IgE antibodies against rabbit and cow milk allergens, and the rhC1INH clinical safety database was searched for AEs potentially indicating allergic reactions. All laboratory testing for IgE antibodies was performed using the ImmunoCap Allergy Blood Test system (Phadiatop, Uppsala, Sweden). Both datasets were compared.

In summary, the IgE antibody testing findings were as follows:

- The highest pre-existing IgE antibody level against rabbit dander (epithelium) allergens was found in the healthy volunteer subject who developed an anaphylactic reaction following exposure to rhC1INH in Phase 1 Study 1106.
- It is considered probable that elevated IgE against rabbit dander indicates an increased risk for adverse allergic reactions following exposure to rhC1INH.
- Apart from IgE antibodies against rabbit dander and possibly rabbit urine, no relationship was noted between pre-existing IgE antibodies against a wide range of animal allergens and reported AEs.
- This retrospective analysis did not indicate that pre-existing IgE antibodies to animal allergens other than rabbit dander, constitute a potential risk for adverse allergic reactions following exposure to rhC1INH. In particular, the applicant maintains that there was no indication of any risk due to the presence of pre-existing IgE against cow milk allergens.



However these cases with IgE antibodies to cow's milk did not have clinical evidence of cow's milk allergy. IgE to allergens can be present in the absence of clinical symptoms. A warning has been added to section 4.4 of the SPC to alert the prescribing physician about the lack of information available and the possible cross-reactivity of cow's milk-specific IgE to rhC1INH in patients with clinical evidence of cow's milk allergy.

- On the data available from this retrospective analysis, it was concluded that single and repeat exposure to up to 100 U/ kg body weight rhC1INH did not induce detectable IgE antibody responses against rabbit or other animal allergens.

It was proposed that the SPC should reflect that commercially available tests could be used to evaluate the potential risk for allergic reactions due to allergy to rabbits. The applicant has revised section 4.4 of the SPC with the suggested commercially available test which was utilised in the clinical programme and is widely available.

#### **2.4.10.6. Thrombogenicity**

Asymptomatic HAE patients have mild activation of coagulation and fibrinolysis as reflected by increased circulating levels of parameters such as F1+2 fragment, thrombin-antithrombin III (TAT) complexes and plasmin- $\alpha$ 2-antiplasmin (PAP) complexes. These activation processes further enhance during acute angioedema attacks and there are data indicating that infusion of pdC1INH can diminish increased platelet aggregability and decrease factor XIIa and F1+2 fragment levels in patients with HAE.

A concern about a possible risk for thromboembolic complications arises from the published reports with off-label administration of high dose pdC1INH (500-1050 U/kg, which is 25 to 50 times higher than the recommended dose for an angioedema attack) in neonates at risk for capillary leak syndrome who underwent cardiosurgery with extracorporeal circulation for major cardiovascular malformations.

Laboratory testing was undertaken to investigate the effects of rhC1INH on activation of coagulation and of fibrinolysis in symptomatic HAE patients. Samples collected from 25 HAE patients were included in this testing.

Overall, it is concluded from the laboratory testing that has been undertaken to assess the effects of rhC1INH on activation of coagulation and of fibrinolysis and the detailed review of published nonclinical and clinical data that there is no evidence to support a concern about thromboembolic risk arising from the proposed use of rhC1INH in the treatment of acute angioedema attacks in HAE patients for the following reasons:

1. The findings on coagulation and fibrinolytic parameters in HAE patients treated with rhC1INH indicated no effect of rhC1INH on activation of coagulation and fibrinolysis in HAE patients at the doses administered.
2. Up to 01 March 2009, no thromboembolic adverse events following administration of rhC1INH have been reported from the clinical program of rhC1INH in HAE patients (405 administrations of rhC1INH at doses ranging from appr. 18-120 U/kg body weight). The maximum number of treatments received by a single patient is 20, 14 HAE patients have received 5 administrations or more.

#### **2.4.10.7. Safety in special populations**

No separate analysis has been conducted for special populations.

The very limited experience of treating paediatric patients with rhC1INH does not indicate a different profile of AEs compared to the adult population.

#### **2.4.10.8. Safety related to drug-drug interactions and other interactions**

No drug interaction studies were performed in this clinical program. rhC1INH is the recombinant analogue of endogenous C1INH. Literature data indicate an interaction of tissue type plasminogen activator (tPA) and C1INH product. Interactions with other drugs are not anticipated due to the nature and metabolism of the product..



#### **2.4.10.9. Discontinuation due to adverse events**

No patients in the phase II and III trials were discontinued due to AEs. During the phase I trials, one patient was withdrawn from the study after reporting systemic pruritus within 72 hours of the first dose of rhC1INH and was withdrawn from the study on Day 22.

#### **2.4.10.10. Post marketing experience**

No post-marketing experience data were available, as the product had not yet been placed on the market in the European Union or in any other countries.

### **2.5. Discussion on clinical safety**

The safety database includes 119 patients that have been treated for a total of 217 attacks as well as safety data from the two phase I studies include 14 healthy volunteers and 12 asymptomatic HAE patients. Altogether 300 treatments/doses of rhC1INH have been given within the study program up to September 2008. A further 105 treatments have been administered in the ongoing open-label extensions up to March 2009. The database also includes patients that have been treated for repeated attacks. The majority of treatments have been given according to the proposed posology.

In the phase I studies 1101 and 1106, very few adverse events were reported. In study 1106, headache was the only AE that was consistently reported in four out of five treatment periods. One anaphylactic reaction was observed, highlighting the importance of identification of patients at risk for allergic reactions.

In the RCT studies 1205 and 1304, the overall rate of TEAEs does not differ between treatment groups including the placebo group. Due to the small numbers in each group, no specific pattern can be found. Due to the small numbers, it is impossible to assess whether there the TEAEs are dose-dependent. Overall, the rate of TEAEs was similar or slightly lower than in the placebo treated group.

The pattern of adverse events does not evoke any new safety concerns. The most common adverse events reported were infections (mainly upper respiratory infections and sinusitis); these adverse events were more common in the active treatment group, Rash and pruritus was also more common in the active treatment groups (a total of 5 reports). Headache and abdominal pain was also commonly reported, with the same rate in actively and placebo-treated patients. No deaths occurred during any of the clinical studies. No influence on laboratory parameters or vital signs, including ECG was observed.

The data from the OLE parts of studies 1205 and 1304 supports the previously described safety findings. No new safety concerns have emerged.

Apart from the acute anaphylactic reaction recorded in study 1106, none of the reported SAEs appear directly related to the treatment.

Very few non-Caucasian subjects were included in the studies. As judged from the biochemical data, no patients with severe renal or hepatic impairment were included in the RCT safety population. The lack of data is reflected in the revised SPC provided in the responses to the Day 120 LoQ.

The program for evaluating the immunogenic potential of rhC1INH is considered to be satisfactory.

In addition the applicant's plan to make immunogenicity testing available for cases who present with features suggestive of an antibody response (to HRIs or C1 INH) will enable close monitoring of such events.

As the product is purified rhC1INH from rabbit milk, the different glycosylation of rhC1INH compared with pdC1INH and also the range of HRIs present in the transgenic product can lead to clinical reactions in cases with pre-formed IgE antibodies and can also lead to the development of antibodies (to HRIs and C1 INH) on repeated administration.

Pre-existing IgE to HRIs present in the product can lead to a serious allergic reaction on first administration as was seen in the HV with rabbit allergy. Repeated administrations of rhC1INH can lead to an immune reaction and antibody responses against rhC1INH with possible cross-reactivity to pdC1INH and also to antibody responses to HRIs.

Pre-existing IgE antibodies to HRIs in rabbit milk caused a generalised allergic reaction in one healthy volunteer. The presence of IgE to rabbit dander was implicated in this case. As the safety database is

limited the applicant further discussed the range of allergens to be tested prior to starting a patient on rhC1INH. Prior to initiation of treatment the optimal allergy screen would be an IgE to rabbit milk, however as this is not available the applicant's proposal to test for IgE to rabbit dander in section 4.4 of the SPC is endorsed.

Regarding the rhC1INH itself, the applicant has developed assays to measure antibody responses to rhC1INH and pdC1INH. The timing and development of antibodies to rhC1INH in subjects in all clinical studies was further discussed by the applicant. The requested data for timelines of treatments, results of positive assays and efficacy was provided. From the results the applicant's position that the antibodies were not clinically relevant in terms of efficacy is supported. Data on safety in these cases was provided and did not suggest any safety concerns in cases who developed antibodies to C1INH.

Regarding anti-HRIs, patients that were shown to have increased levels of anti-HRI antibodies were retreated without infusions reactions. So far, there has been no indication that the antibodies detected are of clinical relevance. Further data was provided by the applicant during the assessment. The data supported the applicant's position that no consistent pattern of anti-HRI development was seen on repeated administrations of rhC1INH. No clinically significant AEs were associated with anti-HRIs and the applicant's proposal to test patients with clinical features suggestive of development of anti-HRIs will provide further long term information on this point.

Concerns have been raised that rhC1INH, which is given in higher concentrations than pdC1INH, would have a thrombogenic potential. This has been evaluated by the applicant during the clinical development without indications that this may be the case.

## ***2.6. Conclusions on the clinical safety***

The safety data has highlighted the possibility for a systemic allergic reaction in a patient with pre-existing rabbit allergy. This has been clearly highlighted, and the suggested tests to use for detection of such antibodies are described in section 4.4 of the revised SPC.

Other important safety issue identified relate to the development of and the possible clinical consequences of antibodies (IgG, IgM IgA) to rhC1INH and to HRIs. From the updated analysis of subjects who developed anti-HRIs, provided by the applicant during the assessment, no clinical consequences have been identified thus far. From the updated information on cases that had anti-C1INH antibodies detected, no effect on efficacy or safety was noted.

An additional issue which has been addressed in section 4.4 of the SPC is the potential for cross-reactivity of IgE present in patients with clinical evidence of cow's milk allergy to rabbit milk HRIs.

## ***2.7. Pharmacovigilance***

The applicant provided a pharmacovigilance system in section 1.8.1 of Module 1.

### **2.7.1. Detailed description of the pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### **2.7.2. Risk management plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table summary of the risk management plan:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
<b>Important identified risk</b>		
Allergic reaction due to pre-existing IgE against rabbit allergens	Routine pharmacovigilance Post Approval Safety Study	<p><u>Routine risk minimization activities.</u></p> <p>Section 4.3 of the SPC (Contraindications) includes "<i>Known or suspected allergy to rabbits</i>" as contraindication.</p> <p>Section 4.4 of the SPC (Warnings and Precautions) includes the following: <i>Conestat alfa rhC1INH is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating treatment with Ruconest, all HAE patients should be tested for the presence of IgE antibodies against rabbit allergens using a validated test for IgE antibodies against rabbit epithelium (dander) e.g. ImmunoCap system, Phadia, Sweden. Only patients who have been shown to have negative results for such test should be treated with Ruconest. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.</i></p> <p><i>As with any intravenously administered protein product, hypersensitivity reactions cannot be excluded.</i></p> <p><i>Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout the administration period. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur after administration, they should alert their physician.</i></p> <p><i>In case of anaphylactic reactions or shock, emergency standard medical treatment should be administered.</i></p> <p><i>And Section 4.2 of the SPC states: "Patients who have not previously received Ruconest should be tested for the presence of IgE antibodies against rabbit epithelium (dander) prior to initiation of Ruconest. See section 4.4."</i></p> <p><u>Additional risk minimization activities:</u></p> <p>Educational Materials will further enhance the understanding of the risks and proposed measures associated with allergy to rabbit allergens.</p> <p>The Patient Alert Card will stress the importance of monitoring for clinical signs and symptoms of hypersensitivity</p>

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
<b>Important potential risks</b>		
Allergic reaction due to cross reaction with IgE antibodies against cow milk	Routine pharmacovigilance Post Approval Safety Study Prick test protocol	<p><u>Routine risk minimization activities.</u> Section 4.4 of the SPC (Warnings and Precautions) includes a specific warning for patients with clinical cow milk allergy and general information regarding hypersensitivity reactions: <i>Although cross-reactivity between cow milk and rabbit milk is considered unlikely, the possibility of such a cross-reactivity in a patient who has evidence of clinical allergy to cow milk cannot be excluded.</i></p> <p><u>Additional risk minimization activities.</u> A protocol for a Prick test will be made available in the Educational Materials to provide a practical means to the treating physician to detect cross reacting antibodies.</p>
Allergic reaction due to the <u>formation</u> of IgE antibodies against rabbit allergens	Routine pharmacovigilance Post Approval Safety Study	<p><u>Routine risk minimization activities.</u> Section 4.4 of the SPC (Warnings and Precautions) includes information regarding hypersensitivity reactions (see above under important identified risk).</p> <p><u>Additional risk minimization activities.</u> Educational Materials will further enhance the understanding of the risks and proposed measures associated with allergy to rabbit allergens.</p> <p>The Patient Alert Card will stress the importance of monitoring for clinical signs and symptoms of hypersensitivity</p>
Hypersensitivity due to formation of anti-Host Related Impurities (HRI) antibodies	Routine pharmacovigilance Post Approval Safety Study Immunogenicity tests (anti HRI antibodies)	<p><u>Routine risk minimization activities.</u> Section 4.4 of the SPC (Warnings and Precautions) includes information regarding hypersensitivity reactions (see above under important identified risk).</p> <p><u>Additional risk minimization activities.</u> Educational Materials will further enhance the recognition, diagnosis and management of hypersensitivity reactions associated with anti HRI antibodies.</p> <p>Availability of immunogenicity tests will allow the physician to diagnose the presence of anti HRI antibodies</p> <p>The Patient Alert Card will stress the importance of monitoring for clinical signs and symptoms of hypersensitivity</p>
Induction of acquired angioedema due to the formation anti-C1INH antibodies	Routine pharmacovigilance Post Approval Safety Study Immunogenicity tests (anti C1INH antibodies and detection of neutralising antibodies )	<p><u>Routine risk minimization activities.</u> <u>None specific</u> Section 4.4 of the SPC (Warnings and Precautions) includes general information regarding the monitoring for hypersensitivity reactions (see above under important identified risk).</p>

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		<u>Additional risk minimization activities.</u> Educational Materials will further enhance the recognition, diagnosis and management of acquired angioedema due to the formation of anti C1INH neutralising antibodies.
Thromboembolic complications	Routine pharmacovigilance Post Approval Safety Study	Routine risk minimization activities.
Paediatrics	Paediatric Investigational Plan. Routine pharmacovigilance	Routine risk minimization activities.  The following information is included in SPC Section 4.2 (Posology): <i>The safety and efficacy of Ruconest in children (age 0 to 12 years) has not yet been established. Currently available data on adolescents (age 13 to 17 years) are described in section 5.1, but no recommendation on a posology can be made.</i>
Pregnant and lactating women	Routine pharmacovigilance	Routine risk minimization activities.  The following information is included in SPC Section 4.6 (Pregnancy and lactation): <i>There is no experience about the use of Ruconest in pregnant and breast-feeding women. In one animal study reproductive toxicity was observed (see section 5.3).</i>  <i>Ruconest is not recommended for use during pregnancy and breast-feeding, unless the treating physician judges the benefits to outweigh the possible risks.</i>

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

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

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Ruconest are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for Ruconest
- Educational material for the physician.
- Copies of the patient card to be given to patients before they receive Ruconest

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

- That Ruconest should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema and should be administered by a health care professional.
- That patients treated with Ruconest should be monitored for clinical signs and symptoms of hypersensitivity during administration. Emergency medical treatment should be available immediately to be administered in case of anaphylactic reactions or shock.

- The fact that Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins (Host Related Impurities, HRI).
- That Ruconest is contra indicated in all patients with known or suspected rabbit allergy or with positive serum IgE antibodies against rabbit dander due to the risk of major allergic reactions, therefore:
  - Before initiating treatment with Ruconest all patients should be tested for the presence of IgE antibodies against rabbit epithelium (dander). Only patients who have been shown to have negative test results should be treated with Ruconest. The patients should receive a patient card that documents the negative result.
  - IgE testing should be repeated once a year or after 10 treatments, whichever occurs first. In addition, IgE testing should be repeated if symptoms of rabbit allergy develop.
  - Information about the appropriate methodology to be used for laboratory testing of serum IgE antibodies against rabbit epithelium (dander)
- That patients with clinical evidence of cow's milk allergy may have antibodies cross reacting with the rabbit milk impurities in Ruconest.
  - A protocol for performing a skin prick test (SPT) with Ruconest and an intravenous test dosing schedule in patients with a negative skin prick test, including criteria for interpreting results, for patients with clinical features of cow's milk allergy.
- The need to inform patients about the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, and that they should alert their physician if these symptoms occur.
- The potential risk of an immune complex-mediated type III hypersensitivity reaction due to the formation of antibodies directed against Host Related Impurities (HRI). Advice about the immunogenicity laboratory testing program for detecting these antibodies for following up suspected immune complex-mediated disease, and about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.
- The risk of formation of anti-C1INH antibodies and therefore the potential risk of formation of neutralising antibodies. Advice about the immunogenicity laboratory testing program for these antibodies provided by the company for following up suspected emergence of neutralising antibodies and information about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.

The patient card should contain the following key elements:

- That they are receiving Ruconest for treatment of acute attack of hereditary angioedema
- That Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins
- That they have been tested negative for IgE anti rabbit (dander) within the last year.
  - The patient card should include an area where patients can record the results of their last IgE anti Rabbit (dander) and the date of the test
  - A reminder that IgE anti rabbit (dander) testing should be repeated once a year or after 10 treatments, whichever occurs first. In addition, IgE testing should be repeated if symptoms of rabbit allergy develop.
  - The patient card should include an area where patients can record the date and dose of every treatment by Ruconest (highlighting every tenth treatment)
- The importance of monitoring for clinical signs and symptoms of hypersensitivity and that patients should alert their doctor if they develop such symptoms during or after receiving Ruconest.

- That patients treated with Ruconest should be monitored for clinical signs and symptoms of hypersensitivity during administration. Emergency medical treatment should be available immediately to be administered in case of anaphylactic reactions or shock.
- That they should be asked to carry the card and always show it to any health care professional treating them for acute attacks of hereditary angioedema.

#### **2.7.2.1. User consultation**

The user testing was conducted appropriately and three rounds were performed, initially a pilot phase (3 subjects) followed by a Stage 1 (10 subjects). Following Stage 1, minor modifications were made to the PIL. The final Stage included another 10 subjects. All questions met the criteria that 16/20 subjects should be able to locate and understand the questions. The questions were relevant to the action of the drug, and to the main safety concerns and what actions to take in the event of problems.

The overall layout and readability of the PIL were considered satisfactory by the participants. The conclusions from the report were clear and concise.

### **2.7.3. Benefit-risk balance**

#### **2.7.3.1. Benefits**

##### **2.7.3.1.1. Beneficial effects**

A beneficial and clinically relevant effect was shown for rhC1INH in the primary endpoint, time to beginning of relief, in both randomised studies compared to placebo. The data were statistically robust and supported by the outcome of the secondary endpoint and by pharmacodynamic data. Exploratory endpoints were also in most parts in favour of rhC1INH. The median time to beginning of relief observed is comparable to that reported for plasma-derived C1INH and also for icatibant.

Dose-finding was based on previous experience with plasma-derived C1INH and from pharmacokinetic and pharmacodynamic studies in asymptomatic HAE patient. Two doses (50 and 100 U/kg) were evaluated within the RCT studies and this choice is considered adequate. The data from the RCT studies support the choice to continue the clinical programme with the 50 U/kg dose with the option to give an additional dose within four hours from the first administration. The posology to administer a dose of 50 U/kg in adults up to 84kg, and a dose of 4,200 U in adults over 84 Kg, i.e. a weight-based cut-off of 84 kg is endorsed.

The effect of treatment on patients with severe laryngeal oedema across all clinical studies have been analysed and the data indicate that rhC1INH is efficacious also in these attacks, however, time to beginning of relief appears to be somewhat longer than in other locations. Additional efficacy data provided support the proposed dose of 50U/kg demonstrating that the median time to beginning of relief of symptoms was the similar for potentially life-threatening attacks (PLA) as for all attacks, Therefore the proposed dose of 50 U/kg for PLA attacks as for other sites is endorsed.

##### **2.7.3.1.2. Uncertainty in the knowledge about the beneficial effects.**

The effect of rhC1INH appears to be similar for different anatomical locations of the attack, and also across studied subgroups. However, the available data are limited.

Efficacy has been studied in patients receiving treatment for up to 20 HAE attacks. Nevertheless, uncertainties remain as to whether the efficacy will wane on long term repeated administration in subjects who develop antibodies against rhC1INH.

Information from treatment in special populations is limited or lacking.

#### **2.7.3.2. Risks**

##### **2.7.3.2.1. Unfavourable effects**

The safety data base is still limited. In total, 165 subjects (14 healthy volunteers, 12 asymptomatic and 139 symptomatic HAE patients) had been exposed to a total of 405 administrations of rhC1INH.



The major risk already identified is the risk of allergic reactions in patients with known or unknown allergy to rabbits. One healthy volunteer experienced a serious allergic reaction to rhC1INH and was shown to have high IgE titres against rabbit allergens. Once identified, this risk may be possible to handle by preventive measures such as testing patients before exposure. This information on the use of commercially available tests to identify patients has been added to the SPC.

Recombinant protein products such as rhC1INH administered to human subjects may elicit antibodies against the recombinant protein, its endogenous counterpart, and against HRI in the drug product. The immunogenic potential of rhC1INH has been studied within the clinical programme and methods to detect antibodies have been developed. Although increased levels of antibodies sporadically have been detected, there has been no indication this far that they are of clinical relevance in terms of either efficacy or safety.

Concerns have been raised that rhC1INH, which is given in higher concentrations than pdC1INH, would have a thrombogenic potential. This has been evaluated by the applicant during the clinical development without indications that this may be the case.

The pattern of other adverse events does not evoke any new safety concerns. The most common adverse events reported were infections (mainly upper respiratory infections and sinusitis); these adverse events were more common in the active treatment group. Rash and pruritis was also more common in the active treatment groups (a total of 5 reports). Headache and abdominal pain was also commonly reported, with the same rate in actively and placebo-treated patients. No deaths occurred during any of the clinical studies. Apart from the allergic reaction discussed above, none of the reported SAEs appear directly related to the treatment.

#### **2.7.3.2.2. Uncertainty in the knowledge about the unfavourable effects**

The safety database is limited and further safety data will have to be collected in a post-authorisation safety study. Such measures have been proposed by the applicant. In addition the applicant will make available immunogenicity testing (for anti-C1INH and anti-HRI antibodies) for cases who present with features suggestive of an immune response. The applicant is also developing a skin prick test for rhC1INH. Both of these plans are strongly supported. In view of the complexity of the planned immunogenicity testing the applicant is requested to provide educational materials for this.

Antibody development to rhC1INH could lead to reduction in efficacy, and if cross-reactive to pdC1INH might lead to worsening of HAE and even reduction of loss of efficacy from pdC1INH treatment. Although there is no evidence of this from the efficacy data available to date, it remains a potential problem.

A further concern is the possible cross-reactivity between cow's milk and rabbit milk. Because the homology between these species is low and similar to the homology of camel and horse milk to cow's milk, the likelihood for cross-reactivity is predicted to be low. However cross-reactivities can occur with serious consequences and therefore a warning in section 4.4 of the SPC has been added for those with clinical evidence of cow's milk allergy.

#### **2.7.3.3. Benefit-risk balance**

##### **2.7.3.3.1. Importance of favourable and unfavourable effects**

rhC1INH is intended for the treatment of acute HAE attacks a rare and potentially life-threatening condition. Efficacy has been clearly demonstrated by generating clinically relevant and statistically robust data. The importance of these favourable effects is supported through:

- continued availability of supply due to independence of donor plasma;
- targeting the additional mediators of swelling in angioedema other than bradykinin;
- not being a blood-derived product thereby removing the potential risk of blood-born pathogens.

rhC1INH unfavourable effects relate to the fact that pre-existing allergy to rabbit dander was identified as the probable cause of the severe allergic reaction in the healthy volunteer. Patients who are rabbit allergic are those who are likely to have a major allergic reaction on their first treatment with rhC1INH. This very serious event, particularly if it occurs in an attack of laryngeal oedema could be fatal. Avoiding treating such cases is very important and the identification of such cases in clinical practice will be central to the safe use of the product. This should be achieved with the contraindication in section 4.3 and the further advice in section 4.4 of the SPC.

The importance of anti-rhC1INH would be the potential reduction in efficacy with rhC1INH and possibly also with pdC1INH treatment. The availability of alternative treatment with icatibant makes this possibility one in which the patient will still be able to receive treatment. Further information from the PASS study will help to address these uncertainties.

The importance of anti-HRIs is that these antibodies may lead to infusion reactions and serum-sickness symptoms. These effects would lead patients to discontinue rhC1INH and switch to another treatment.

#### **2.7.3.3.2. Benefit-risk balance**

Efficacy has been clearly demonstrated for the treatment of this rare and potentially life-threatening condition. Antibody development to rhC1INH and to HRI has not been demonstrated to result in clinical sequelae to date. The importance of these unfavourable effects is considered to be limited to those who have IgE to rabbit allergens and to those who mount an immune response to rhC1INH and/or HRIs.

Important for clinical practice is to avoid using the product in patients who are rabbit allergic due to potentially serious allergic reactions. This very serious event, particularly if it occurs in an attack of laryngeal oedema could be fatal. Avoiding treating such cases is very important and the identification of such cases in clinical practice will be central to the safe use of the product. Rabbit allergy constitutes a contraindication and the SPC proposes that before initiating treatment with rhC1INH, patients should be tested for the presence of IgE antibodies against rabbit allergens using a validated test for IgE antibodies against rabbit epithelium (dander) e.g. ImmunoCap system. Only patients who have been shown to have negative results for such tests, should be treated with rhC1INH. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.

A potential risk of cross-reactivity of IgE specific for cow's milk in those who have clinical evidence of IgE-mediated cow's milk allergy remains. This has been addressed in the SPC.

#### **2.7.3.4. Discussion on the benefit-risk balance**

The benefit of rhC1INH is a ready supply of a new treatment for acute attacks in HAE for which efficacy has been clearly demonstrated. For the safety concerns that have been identified (namely allergic reaction in those with pre-formed IgE antibody to rabbit dander) it is considered possible to minimise the risk of such events occurring by having rabbit allergy as a contraindication and by the requirement for a negative test for IgE to rabbit dander to be obtained in a patient prior to initiation of treatment. These points are clearly highlighted in the SPC.

Specific educational material for healthcare professionals as well as patient alert cards will be provided by the applicant.

The potential for a patient to develop antibodies to rhC1INH and/or to HRIs following repeated treatment remains a potential risk and further information on this will be made available post authorisation. In particular, the applicant commits to make anti-C1INH antibody tests available for any HAE patient on Ruconest meeting any of the following criteria:

- a) In two consecutive acute angioedema attacks there is a need for a dose greater than 50U/kg rhC1INH in any HAE patient that previously responded to treatment with 50 U/kg rhC1INH.
- b) In two consecutive acute angioedema attacks a failure to respond to rhC1INH treatment within 4 hours despite adequate dosing of 50 U/kg in any HAE patient who previously responded to treatment with 50 U/kg rhC1INH.

In addition, the applicant commits to make anti HRI antibody tests available for any HAE patient on Ruconest meeting any of the following criteria:

1. Type III hypersensitivity reaction (skin, joints or kidney symptoms) in temporal relation with a Ruconest administration which after investigation of other causes cannot be explained by exposure and reaction to other allergens.
2. Type III hypersensitivity in temporal relation with two consecutive administrations of Ruconest.

The company also commits to expedited reporting for cases concerning development of antibodies to C1INH and/or HRIs.

An important element of the long-term risk management strategy is the commitment to perform a post authorisation safety study, for which the protocol will be agreed with the CHMP prior to study start. This study should also include follow-up of HAE patients repeatedly treated with rhC1INH for acute angioedema. In addition to the testing provided in the PASS study the applicant commits to make certain antibody tests (anti-C1INH and HRI) available for patients who have not consented to the PASS study and who fulfil the criteria for further immunogenicity investigation.

These data will be important for the monitoring of the benefit risk balance.

In conclusion, the benefit risk balance is considered positive.

#### **2.7.3.5. Risk management plan**

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

the following additional risk minimisation activities were required:

See section 3.7.2 Risk Management Plan.

#### **2.7.4. Similarity with authorised orphan medicinal products**

The CHMP is of the opinion that Ruconest is not similar to Firazyr within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1

#### **2.7.5. Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ruconest in the "treatment acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency" was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Ruconest not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Firazyr for the same therapeutic indication.