Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

From:	Laura Polakowski, MD, MSPH Medical Officer, Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
To:	Elena Karnaukhova Chair, Review Committee Office of Blood Research and Review
Through:	Wei Hua, MD, PhD, MS, MHS Chief, Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA Michael Nguyen, MD Deputy Director, Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
Subject:	Pharmacovigilance Plan Review
Applicant:	Pharming, NV
Product:	Ruconest™, Recombinant (Human) C1 Esterase Inhibitor (rhC1INH)
Proposed Indication:	Ruconest is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients
Current Indication:	Not applicable in US
Submission type:	Original BLA
BLA number/Submission Date:	STN 125495/0.0, Submitted April 16, 2013
PVP Submission Date:	Original-April 16, 2013 Amendment 3 (Sequence 0003, 125495/0.4)-May 30, 2013 Amendment 14 (Sequence 0014, 125495/0.15)-October 30, 2013
Action Due Date:	Original-April 16, 2014 After Major Amendment-July 16, 2014

1 INTRODUCTION

1.1 Product Description

Ruconest is a recombinant human complement component 1 (C1) esterase inhibitor (rhC1INH: International Nonproprietary Name: conestat alfa) purified from the milk of rabbits expressing the gene encoding for human C1INH. The ---------(b)(4)--------- of the recombinant form of C1INH is identical to that of human C1INH. The formulated bulk drug substance rhC1INH contains the active ingredient in ----------(b)(4)----------. None of the excipients used is of human or animal origin. The drug product is manufactured by sterile filtration and aseptic filling of the formulated bulk drug substance into glass vials, followed by lyophilization. Each vial contains 2,100 International Units (IU) of rhC1INH activity in -(b)(4)- protein. The drug ---(b)(4)---- is reconstituted with 14 mL water for intravenous (iv) injection, resulting in a solution with a strength of approximately 150 IU/mL. According to the manufacturer, the drug product is sterile, non-pyrogenic, and preservative-free.

1.2 Rationale for Development, Indications and Usage

Hereditary angioedema (HAE) is a rare, serious, autosomal-dominant genetic disorder with an estimated prevalence of one in 50,000. Clinically, patients with HAE experience recurrent acute attacks of soft tissue swelling that can affect multiple anatomic regions, including the gastrointestinal tract, facial tissues, vocal cords and larynx, oropharynx, urogenital region, and/or the arms and legs. These acute attacks are associated with considerable morbidity and they often require hospitalization and immediate medical intervention. Laryngeal attacks can be life-threatening due to the risk of asphyxiation. Patients with HAE have an insufficient plasma concentration of functional C1INH, a serine protease inhibitor (serpin) produced mainly in the liver. In the setting of low functional C1INH, C1 activation causes cleavage of complement component 4 (C4). The diagnosis of HAE in untreated patients is confirmed by the presence of reduced C1INH activity levels and low plasma levels of C4.

In the US, currently available medications for HAE include the plasma-derived (pd) C1INH products Cinryze®, for routine prophylaxis against angioedema attacks, and Berinert®, for treatment of acute angioedema attacks. In addition to the pdC1INH products for HAE, two non-blood-derived drugs have been approved by the FDA for treatment of acute angioedema attacks: ecallantide (Kalbitor®), a kallikrein inhibitor, and icatibant (Firazyr®), a bradykinin receptor antagonist. Human plasma-derived C1INH products carry a risk of human infectious disease transmission and are dependent on adequate donor supply. The non-blood-derived drugs carry a risk of antibody response (i.e., Immunoglobulin E (IgE) and other subtypes) and anaphylaxis (ecallantide), injection site reactions (icatibant), and possible worsening or relapse of attack symptoms (icatibant).

Recognizing the need for a safe, effective, and widely-available therapeutic alternative to the existing HAE treatments, Pharming developed and established the expression of rhC1INH in the mammary glands of transgenic rabbits, thereby avoiding the risk of human infectious disease transmission and ensuring an adequate supply of the product not dependent upon plasma donation, as well as offering an alternative to non-blood-derived drug treatments.

Ruconest is indicated for the treatment of acute attacks of HAE in adult and adolescent patients ≥13 years of age. The proposed clinical dose of rhC1INH for the treatment of acute HAE attacks is a single iv injection of 50 IU/kg body weight, up to a maximum of 4,200 IU for those ≥84kg in body weight, with an option for a second administration of the same dose in case of an insufficient clinical response.

Ruconest is approved for use in the European Union (EU) (since October 28, 2010) and is indicated for treatment of acute angioedema attacks in adults with HAE due to C1 esterase inhibitor deficiency.

1.3 Contraindications, Warnings, and Precautions

Foreign labeling for Ruconest™ states the following contraindications, special warnings and precautions for use:

Contraindications

- Known or suspected allergy to rabbits
- Hypersensitivity to the active substance or to any of the excipients

Special warnings and precautions for use

- Conestat alfa is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating treatment with Ruconest, patients should be tested for the presence of IgE antibodies against rabbit allergens using a validated test for IgE antibodies against rabbit epithelium (dander). Only patients who have been shown to have negative results for such a test, should be treated with Ruconest. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.
- As with any intravenously administered protein product, hypersensitivity reactions cannot be excluded. 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, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur after administration, they should alert their physician.
- In case of anaphylactic reactions or shock, emergency medical treatment should be administered.
- 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.

1.4 Pertinent Regulatory History

1.4.1 Regulatory History in Foreign Countries

Ruconest™ was granted marketing authorization in the EU on October 28, 2010. Review procedures in Turkey, Israel, Malaysia, Singapore and South Korea are ongoing.

1.4.2 Regulatory History in the US

Orphan Designation was granted by the Food and Drug Administration (FDA) for rhC1INH for the treatment of acute attacks of angioedema on February 23, 1999. A pre-Investigational New Drug (IND) meeting with the Center for Biologics Evaluation and Research (CBER) was held on February 5, 2004, followed by an IND submission to CBER on June 25, 2004. IND BB-11785 went into effect on December 16, 2004. Responsibility for review and continuing oversight of rhC1INH was transferred to the Center for Drug Evaluation and Research (CDER), Division of Pulmonary and Allergy Products, Office of Drug Evaluation II on July 12, 2004. CDER granted rhC1INH Fast Track designation on July 21, 2006. In 2008, responsibility for the IND was transferred back to the Division of Blood Applications, Office of Blood Research and Review (OBRR), CBER. In January 2010, a pre-Biologics License Application (BLA) meeting was held with CBER to discuss nonclinical and clinical topics. Pharming filed a BLA in December 2010, which FDA refused to file. Pharming and FDA reached agreement on August 2, 2011, under a Special Protocol Assessment (SPA), on an additional controlled clinical study (Study 1310), which, if successful, would be the basis for approval. Preliminary results of the randomized controlled trial (RCT) phase and preliminary interim results of the open-label extension (OLE) phase of Study 1310 were provided to FDA in a pre-BLA meeting background information package. In its response on December 21, 2012, FDA agreed that the results of Study 1310 would form the basis for submission and review of a BLA for rhC1INH.

1.5 Worldwide Distribution Data and Post-Marketing (non-study) Exposure

Ruconest is currently marketed in the EU. During the most recent reporting period (October 28, 2010 – April 28, 2013), (b)(4) vials of Ruconest were distributed in 16 countries. No spontaneous Adverse Drug Reaction

reports were received from any sources during this reporting period. Four spontaneous case reports were received. No SAEs were associated with any of these case reports.

- One case report concerned an underdose of Ruconest: the patient received 2,100 IU of Ruconest for treatment of an abdominal and leg angioedema attack; per the Summary of Product Characteristics of Ruconest, the (53kg) patient should have received 2,650 IU, based on administration of 50 IU/kg for patients <84 kg.
- Two case reports concerned off-label use:
    - A 48-year old female patient with HAE used Ruconest (2,100 IU, three times per week) for prophylaxis of HAE attacks and experienced nausea, abdominal pain, headache, and difficulty sleeping. She experienced two breakthrough angioedema attacks during Ruconest therapy. Ruconest therapy was discontinued, but the symptoms remained ongoing.
    - A female patient used Ruconest (age and dose not reported) for prophylaxis of HAE attacks.
- One case report concerned a pregnancy: a female patient, age 21 years, received eight administrations of Ruconest 2,100 IU for face and neck swelling beginning in the 19th week of pregnancy. The outcome of the pregnancy was a full-term, live birth of a healthy male infant.

A post-approval HAE Registry is currently being conducted in the EU. In brief, the study design is a non-interventional treatment registry of HAE patients in the EU treated with a C1 esterase inhibitor, either pdC1INH or rhC1INH. As of February 21, 2013, 36 patients with HAE were screened, and four of these patients received 12 rhC1INH treatments. The Registry will remain open until the target number of 300 doses in the rhC1INH arm is reached, consisting of 100 patients followed up for at least three exposures to rhC1INH each.

1.6 Objectives/Scope of the Review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed in the US, and to evaluate the pharmacovigilance plan (PVP) submitted by Pharming, NV for the Ruconest BLA.

2 MATERIALS REVIEWED

Date	Source	Document Type	Document(s) Reviewed
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 1.2, Cover Letters: Original Submission & Attachment 2
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 1.14.1, Labeling: Draft Labeling & Foreign Labeling
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 1.16, Risk Management Plans: Pharmacovigilance Plan, Version 4.0, dated March 5, 2013
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.2, Introduction
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.3.S, Drug Substance: General Information
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.3.P, Drug Product: Description and Composition, Pharmaceutical Development
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.3.A, Appendices: Adventitious Agents Safety Evaluation
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.4, Non-clinical Overview
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.5, Clinical Overview
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.7.3, Clinical Summary: Summary of Clinical Efficacy
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.7.4, Clinical Summary: Summary of Clinical Safety
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 2.7.6, Synopses of Individual Studies

Date	Source	Document Type	Document(s) Reviewed
4/15/2013	Pharming	BLA Sequence 0000	125495/0/0; Module 5.3.3, Reports of Human Pharmacokinetic (PK) Studies •Subsection 5.3.3.1: Healthy Subject PK and Initial Tolerability Study Reports ➢ Study 1106 Phase I study in healthy subjects •Subsection 5.3.3.2: Patient PK and Initial Tolerability Study Reports ➢ Study 1101 Phase I study in asymptomatic HAE patients •Subsection 5.3.3.5: Population PK Study Reports ➢ Population PK of rhC1INH from studies 1101, 1106, 1202, 1203, 1205 & 1304
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 5.3.5, Reports of Efficacy and Safety Studies •Subsection 5.3.5.1: Study Reports of Controlled Clinical Studies ➢ Study 1205 RCT ➢ Study 1304 RCT ➢ Study 1310 RCT •Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies ➢ Study 1202/1203 OLE ➢ Study 1205 OLE ➢ Study 1207 OLE ➢ Study 1304 OLE ➢ Study 1310 OLE (preliminary results) •Subsection 5.3.5.3: Reports of Analyses of Data from >1 Study ➢ Integrated Summary of Safety (ISS), including all patient narratives •Subsection 5.3.5.4: Other Study Reports ➢ CDR-002 IgE Antibody – Immunogenicity of rhC1INH ➢ CDR-007 Thrombogenicity – Evaluation of the potential risk for thromboembolic side effects in relation to treatment with rhC1INH
4/15/2013	Pharming	BLA Sequence 0000	125495/0.0; Module 5.3.6, Reports of Postmarketing Experience
5/13/2013	Pharming	BLA Sequence 0003	125495/0.4; Module 1.11.2, Safety Information Amendment: Pharmacovigilance Plan, Response to Request for Information
5/13/2013	Pharming	BLA Sequence 0003	125495/0.4; Module 1.16, Risk Management Plan, Version 5.0, dated May 23, 2013
5/30/2013	FDA	OBRR Clinical Reviewer	Refuse to File memo discussed in filing meeting on May 31, 2013
9/26/2013	FDA	OBRR Clinical Reviewer	Draft Mid-Cycle Clinical Review Memo, distributed and discussed at mid-cycle meeting, September 26, 2013
---	Other	References	Medical literature review *(see detailed listing at end of report)* •Aoyama et al, 1992 •Chandler et al, 1997 •Choi et al, 2007 •Coplan et al, 2011 •Cugno et al, 1993 •Cugno et al, 1997 •Cugno et al, 2009 •Eldering et al, 1992 •Gandhi et al, 2012 •Ghazi & Grant, 2013 •Gurewich & Pannell, 2009 •Horstick et al, 2001 •Huisman et al, 1995 •Merlini et al, 1994 •Shmagel & Chereshnev, 2009 •Sulikowski & Patston, 2001
10/14/2013	Pharming	BLA Sequence 0011	125495/0.12; Module 5.3.5, Reports of Efficacy and Safety Studies •Subsection 5.3.5.5: Reports of Analyses of Data from >1 Study ➢ Integrated Summary of Safety (ISS), including all additional patient narratives (for 1310 OLE) ➢ 120-day Safety Update
10/30/2013	Pharming	BLA Sequence 0014	125495/0.15; Module 1.11.2, Response to Information Request on Pharmacovigilance Plan

3 PHARMACOVIGILANCE PLAN REVIEW

3.1 Non-Clinical Safety Findings

- No obvious or potential safety risks in animal studies, including rat, dog and monkey toxicity studies.
- Thrombogenic side effects, which were seen in one study of pdC1INH products, were monitored in all toxicity studies for rhC1INH and no significant effects on hematological parameters were observed after multiple administrations of daily doses up to 50-fold, 12.5-fold or 80-fold the human dose in rats, dogs, and monkeys, respectively.

3.2 Clinical Safety Database

The Sponsor presented safety data analyses for three controlled / randomized controlled trial (RCT) studies (Study 1205 RCT, Study 1304 RCT, and Study 1310 RCT) and seven uncontrolled / open-label extension (OLE) studies (Study 1101, Study 1106, Study 1202/1203 OLE, Study 1205 OLE, Study 1207 OLE, and Study 1304 OLE, as well as preliminary results for Study 1310 OLE). Both RCT and OLE components of two of the studies (1205 and 1310) involved patients in the US. All of the clinical studies included in this submission used the Ruconest product.

All clinical studies monitored participants for safety for 97 days following each dose of study drug. If a patient was treated for a new angioedema attack prior to completion of the assessments for the previous attack, a new follow-up period was begun at the time of the new treatment. All safety assessments that occurred after treatment of the new attack were then attributed to the new attack and were not included from that time forward in the summaries of the assessments for the previous attack(s).

For patients who participated in both an RCT and an OLE study/phase, each treatment-emergent adverse event (TEAE) was attributed to the study/phase in which the patient received the most recent dose of study drug. For those patients in the RCT phase of Study 1310 who received a double-blind dose of saline followed by an open-label rescue dose of rhC1INH, any TEAEs that commenced after administration of the rescue dose were assigned to the rhC1INH dose group and were not included in the summaries for the saline group.

Patients who did not complete all assessments through Day 90 in an RCT study/phase due to receipt of rhC1INH for treatment of a subsequent attack during an OLE study/phase were considered to have completed the RCT study/phase. All other patients who did not complete all assessments through Day 90 were considered to have been discontinued early (censored) from the study.

Patients were screened for antibodies to host-related impurities (HRI) and C1INH before receiving rhC1INH treatments and at scheduled intervals after each dose. Corresponding clinical signs and symptoms of hypersensitivity were monitored. Anti-HRI antibodies could potentially induce type I or type III hypersensitivity reactions; anti-C1INH antibodies could theoretically induce type III hypersensitivity reactions or could form neutralizing antibodies, potentially reducing rhC1INH efficacy. More information on these potential safety issues is discussed in Sections 3.3.2.1–3.3.2.3.

Published studies have shown that during an acute HAE attack, prior to any treatment, baseline levels of D-dimer, prothrombin activation fragment F1+2, thrombin-antithrombin (TAT) complexes and plasmin-antiplasmin (PAP) complexes are elevated while activated partial thromboplastin time (aPTT) is lower in most patients, indicating an activation of coagulation and fibrinolysis.[1-3] Due to observations of thromboembolic events (TEE) with the use of pdC1INH products (see also Section 3.3.2.4), further evaluation of this risk with rhC1INH was performed in Study 1310 and these indices were measured.

3.2.1 Sponsor Analysis

Table 1. Summary of Clinical Safety Studies for rhC1INH

Study #; Region	Study Objectives	Study Design; Patient Population	# of Subjects	# Subjects/Exposure	Key Safety Findings (SAEs)
1205 RCT US, Canada	Efficacy, Safety, Tolerability, PK/PD	Phase 2, Randomized, double-blind, placebo-controlled, multicenter study; HAE patients ≥12 yrs of age experiencing an acute angioedema attack	38 25 received rhC1INH	▪ rhC1INH 50 IU/kg single dose: 12/38 (32%) patients ▪ rhC1INH 100 IU/kg single dose: 13/38 (34%) patients ▪ Saline single dose: 13/38 (34%) patients	▪ No deaths ▪ rhC1INH 50 IU/kg: 1 patient (33 yr old female) with HAE attack ▪ rhC1INH 100 IU/kg: 1 patient (66 yr old female) with severe colitis, Day 31 (assessed as unrelated to rhC1INH) ▪ Saline: None
1304 RCT Italy, Spain, UK, Israel, Romania	Efficacy, Safety, Tolerability	Phase 3, Randomized, double-blind, placebo-controlled, multicenter study; HAE patients ≥16 yrs of age experiencing an acute angioedema attack	32 16 received rhC1INH	▪ rhC1INH 100 IU/kg single dose: 16/32 (50%) patients ▪ Saline single dose: 16/32 (50%) patients	▪ No deaths ▪ rhC1INH 100 IU/kg: 1 patient (41 yr old female) with 2 events of laryngeal edema, Days 2 & 95 ▪ Saline: 1 patient (64 yr old male) with prostate biopsy; 1 patient (44 yr old female) with biliary colic; 1 patient (71 yr old female) with kidney stone & removal (all assessed as unrelated to rhC1INH)
1310 RCT US, South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, Serbia	Efficacy, Safety	Phase 3, Randomized, double-blind, placebo-controlled, multicenter study; HAE patients ≥13 yrs of age experiencing an acute angioedema attack	74 56 received rhC1INH	▪ rhC1INH 50 IU/kg single dose: 38/74 (51%) patients ▪ rhC1INH 50 IU/kg single dose + additional dose: 5/74 (7%) patients ▪ Saline single dose: 18/74 (24%) patients ▪ Saline + rhC1INH 50IU/kg (rescue medication): 13/74 (18%) patients	▪ No deaths ▪ rhC1INH 50 IU/kg: 1 patient (43 yr old male) with severe abdominal hernia, Day 79 (assessed as unrelated to rhC1INH) ▪ rhC1INH 50 IU/kg + add'l dose: None ▪ Saline single dose: None ▪ Saline + rhC1INH 50 IU/kg: None
1202/1203 OLE The Netherlands, Hungary, Poland, Spain, UK	Efficacy, Safety, Tolerability, Immunogenicity, PK/PD	Phase 2, Open-label studies; HAE patients 16–65 years of age (1202) or 16–70 years of age (1203) experiencing acute angioedema attacks	14	▪ rhC1INH 100 IU/kg single dose per treated attack w/ multiple attacks per patient: 7 (50%) treated x 1 attack 7 (50%) treated x 2 attacks	▪ No deaths ▪ rhC1INH 100 IU/kg: 1 patient (45 yr old female) with mild colicky abdominal pain, Day 1 (assessed as unlikely related to rhC1INH)
1205 OLE US, Canada	Efficacy, Safety, Tolerability, Immunogenicity, PK/PD	Phase 2, Open-label phase of Study 1205; HAE patients ≥12 years of age experiencing acute angioedema attacks	62	▪ rhC1INH 50 IU/kg single dose per treated attack + optional second 50 IU/kg dose ▪ rhC1INH 50IU/kg single dose: 151/168 (90%) attacks ▪ rhC1INH 50IU/kg + add'l dose: 17/168 (10%) attacks	▪ No deaths ▪ rhC1INH 50 IU/kg single dose: 1 patient (33 yr old female) with hypersensitivity reaction (throat swelling, itchy lips) – possibly related to rhC1INH; 6 patients with HAE attacks; 1 patient (57 yr old female) with vertigo; 1 patient (28 yr old male) with pneumonia & arm swelling; 1 patient (62 yr old female) with 2 episodes of UTI & E.coli sepsis (all assessed as unlikely related to rhC1INH) ▪ rhC1INH 50 IU/kg dose + add'l dose: 2 patients with HAE attacks

Study #; Region	Study Objectives	Study Design; Patient Population	# of Subjects	# Subjects/Exposure	Key Safety Findings (SAEs)
1304 OLE Italy, Spain, UK, Israel, Romania, Argentina	Efficacy, Safety, Tolerability, Immunogenicity, PK/PD	Phase 3, Open-label phase of Study 1304; HAE patients ≥16 years of age experiencing acute angioedema attacks	57	▪ rhC1INH 2100 IU single dose per treated attack + optional second 2100 IU or 4200 IU dose if inadequate clinical response within 4 hrs ▪ rhC1INH 2100 IU single dose: 110/194 (57%) attacks ▪ rhC1INH 2100 IU + add'l dose, 84/194 (43%) attacks	▪ No deaths ▪ rhC1INH 2100 IU single dose: 1 patient (58 yr old male) with severe MI, Day 73 (assessed as unrelated to rhC1INH) ▪ rhC1INH 2100 IU single dose + add'l 2100 IU dose: None ▪ rhC1INH 2100 IU single dose + add'l 2400 IU dose: 1 patient (27 yr old male) with tonsillitis (assessed as unrelated to rhC1INH)
1310 OLE US, South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, Serbia	Efficacy, Safety	Phase 3, Open-label phase of Study 1310; HAE patients ≥13 yrs of age experiencing acute angioedema attacks	44	▪ rhC1INH 50 IU/kg single dose (patients <84kg) or 2400 IU (patients ≥84kg) per treated attack + optional second dose ▪ rhC1INH 50 IU/kg: 215/224 (96%) attacks; ▪ rhC1INH 50 IU/kg + add'l dose: 9/224 (4%) attacks	▪ No deaths ▪ rhC1INH 50 IU/kg single dose: 1 patient (68 yr old female) with moderate angioedema attack requiring hospitalization, Day 25 ▪ rhC1INH 50 IU/kg dose + add'l dose: None
1101 The Netherlands	Safety, Tolerability, PK/PD	Phase 1 Open-label exploratory study; Asymptomatic HAE patients 18–65 years of age	12	▪ 2 ascending doses of rhC1INH; interdose interval ≥5 weeks 3/12 (25%) patients per group: ▪ Gp A: rhC1INH 6.25 & 25 IU/kg ▪ Gp B: rhC1INH 12.5 & 50 IU/kg ▪ Gp C: rhC1INH 25 & 100 IU/kg ▪ Gp D: rhC1INH 50 & 100 IU/kg	▪ No deaths ▪ rHC1INH 6.25 IU/kg: 1 patient (33 yr old male) with severe abdominal HAE attack, Day 71 (assessed as unlikely related to rhC1INH) ▪ No other doses w/ an SAE
1207 Romania, Poland, Israel	Efficacy, Safety, Tolerability, PK/PD	Phase 2 Open-label study; Asymptomatic HAE patients ≥18 years of age	25	▪ Single weekly dose of rhC1INH 50 IU/kg x 8 weeks; 50 IU/kg optional dose for breakthrough attacks + 50IU/kg optional second dose, if indicated	▪ 1 death (50 yr old female) due to laryngeal edema 25 days after the patient's last dose of rhC1INH (assessed as unrelated to rhC1INH) ▪ 1 patient (21 yr old female) with appendicitis 4 days after last dose of rhC1INH (assessed as unrelated to rhC1INH)
1106 The Netherlands	Safety, Tolerability, PK, Immunogenicity	Phase 1 Open-label study; Healthy volunteer subjects 18–65 years of age	14	▪ 5 doses of rhC1INH 100 IU/kg; at 3-week interdose intervals ▪ 1 dose: 2 subjects ▪ 2 doses: 1 subject ▪ 5 doses: 11 subjects	▪ No deaths ▪ 1 patient (20 yr old female) with severe allergic reaction (anaphylaxis) commencing 2-3 minutes after start of iv injection of rhC1INH (1st dose) in subject with previously-undisclosed history of allergy to rabbit dander/hair (considered related to rhC1INH)

Abbreviations: HAE – hereditary angioedema; HRI – host-related impurities; MI – myocardial infarction; OLE – open-label extension; PD – pharmacodynamics; PK – pharmacokinetics; RCT – randomized controlled trial; SAEs – serious adverse events; UTI – urinary tract infection

3.2.1.1 Controlled / Randomized Controlled Trial (RCT) Studies

3.2.1.1.1 Study 1205 RCT

This study was a randomized, placebo-controlled, double-blind Phase 2 study of the safety and efficacy of rhC1INH for the treatment of acute attacks in patients with HAE.

- **Objectives**
  - To assess the safety and tolerability of rhC1INH in symptomatic patients with HAE
  - To assess the efficacy of rhC1INH in the treatment of acute attacks in HAE patients

    - To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of rhC1INH in symptomatic patients
- **Study Design**
    - Randomized, saline-controlled, double-blind, multi-center
    - Treatment with single, double-blind dose of rhC1INH 50 IU/kg, rhC1INH 100 IU/kg, or saline (placebo) (1:1:1 randomization)
- **Study Population**
    - Participating countries: US (26 sites), Canada (4 sites)
    - HAE patients ≥12 years of age, presenting with an acute angioedema attack
    - 39 patients randomized, 38 patients treated
    - 32 patients completed, 6 patients discontinued early
    - Primary safety analysis population: All treated patients, analyzed in accordance with treatment received
- **Key Safety Results**
    - Exposure
        - rhC1INH 50 IU/kg single dose, 12/38 (32%) patients
        - rhC1INH 100 IU/kg single dose, 13/38 (34%) patients
        - Saline single dose, 13/38 (34%) patients
    - TEAEs
        - rhC1INH 50 IU/kg, 4/12 (33%) patients
        - rhC1INH 100 IU/kg, 5/13 (38%) patients
        - Saline, 6/13 (46%) patients
    - Most common TEAE: pain (abdominal pain and/or headache)
    - Serious Adverse Events (SAEs)
        - No deaths
        - rhC1INH 50 IU/kg: 1 patient (33 yr old female) with new acute HAE attack
        - rhC1INH 100 IU/kg: 1 patient (66 yr old female) with severe colitis, Day 31 (assessed as unrelated to rhC1INH)
        - Saline: None
    - All rhC1INH-treated patients negative for anti-C1INH antibodies after treatment; one rhC1INH-treated patient confirmed for anti-host-related-impurities (HRI) antibodies on Day 22 only, but no clinical symptoms of hypersensitivity
    - Safety conclusion: rhC1INH 50 IU/kg or rhC1INH 100 IU/kg was generally safe and well-tolerated

3.2.1.1.2 Study 1304 RCT

This study was a randomized, placebo-controlled, double-blind phase 3 study of the efficacy and safety of rhC1INH for the treatment of acute attacks in patients with HAE.

- **Objectives**
    - 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
- **Study Design**
    - Randomized, saline-controlled, double-blind, multi-center
    - Treatment with single, double-blind dose of rhC1INH 100 IU/kg or saline (placebo) (1:1 randomization)
- **Study Population**
    - Participating countries: Italy, Spain, UK, Israel, Romania
    - HAE patients, ≥16 years of age, presenting with an acute angioedema attack
    - 34 patients randomized, 32 patients treated
    - 30 patients completed, 2 patients discontinued early

    - Primary safety analysis population: All treated patients, analyzed in accordance with treatment received
- **Key Safety Results**
    - Exposure
        - rhC1INH 100 IU/kg single dose, 16/32 (50%) patients
        - Saline single dose, 16/32 (50%) patients
    - TEAEs
        - rhC1INH 100 IU/kg, 2/16 (13%) patients
        - Saline, 8/16 (50%) patients
    - Most common TEAE: pain (abdominal pain and/or headache)
    - SAEs
        - No deaths
        - rhC1INH 100 IU/kg: 1 patient (41 yr old female) with 2 events of laryngeal edema, Days 2 & 95
        - Saline: 1 patient (64 yr old male) with prostate biopsy; 1 patient (44 yr old female) with biliary colic; 1 patient (71 yr old female) with kidney stone & removal (all assessed as unrelated to rhC1INH)
    - All rhC1INH-treated patients negative for anti-C1INH Immunoglobulin M (IgM) and Immunoglobulin A (IgA) antibodies after treatment; 2 rhC1INH-treated patients with isolated anti-rhC1INH Immunoglobulin (IgG) antibodies after treatment; 1 saline-treated patient with isolated anti-HRI antibodies after treatment, but none with clinical symptoms of hypersensitivity
    - Safety conclusion: rhC1INH 100 IU/kg was generally safe and well-tolerated

3.2.1.1.3 Study 1310 RCT (Pivotal Trial)

This is a phase 3 randomized, double-blind, placebo-controlled study with an open-label extension evaluating the efficacy, safety and immunogenicity of rhC1INH for the treatment of acute attacks of angioedema in patients with HAE.

- **Objectives**
    - To evaluate efficacy and safety of rhC1INH 50 IU/kg when used for the treatment of acute angioedema attacks in patients with HAE
    - To assess efficacy, safety, and immunogenicity of rhC1INH when used for the repeated treatment of acute angioedema attacks in patients with HAE
- **Study Design**
    - Randomized, saline-controlled, double-blind, multi-center
    - Treatment with single, double-blind dose of rhC1INH 50 IU/kg (for patients <84 kg, or rhC1INH 4,200 IU for patients ≥84 kg [“rhC1INH 50 IU/kg”]) or saline (placebo)
    - (3:2 randomization), plus a rescue open-label dose of the same size in the event of inadequate clinical response within four hours
- **Study Population**
    - Participating countries: US, South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, Serbia
    - HAE patients, ≥13 years of age (≥18 years of age outside the US and Canada), presenting with an acute angioedema attack
    - 75 patients randomized, 74 patients treated
    - 73 patients completed, 1 patient discontinued early
    - Primary safety analysis population: All treated patients, analyzed in accordance with treatment received
- **Key Safety Results**
    - Exposure
        - rhC1INH 50 IU/kg single dose, 38/74 (51%) patients
        - rhC1INH 50 IU/kg single dose + additional dose , 5/74 (7%) patients

        - Saline single dose, 18/74 (24%) patients
        - Saline + rhC1INH 50IU/kg (rescue medication), 13/74 (18%) patients
    - TEAEs
        - rhC1INH 50 IU/kg, 18/56 (32%) patients
        - Saline, 10/18 (56%) patients
    - Most common TEAEs: nasopharyngitis, urinary tract infection, diarrhea
    - SAEs
        - No deaths
        - rhC1INH 50 IU/kg single dose: 1 patient (43 yr old male) with severe abdominal hernia, Day 79 (assessed as unrelated to rhC1INH)
        - rhC1INH 50 IU/kg single dose + additional dose: None
        - Saline single dose: None
        - Saline + rhC1INH 50 IU/kg: None
    - No confirmed anti-C1INH antibodies and no neutralizing antibodies after treatment in rhC1INH-treated patients; 7 patients with anti-HRI antibodies after treatment, none with clinical symptoms of hypersensitivity
    - Safety conclusion: rhC1INH 50 IU/kg (for patients <84kg, or rhC1INH 4,200 IU for patients ≥ 84kg) was generally safe and well-tolerated

3.2.1.2 Uncontrolled / Open-Label Extension (OLE) Studies

3.2.1.2.1 Open-Label Studies in Symptomatic HAE Patients

3.2.1.2.1.1 Study 1202/1203

Study 1202 is a phase 2 exploratory, open-label study of the safety and efficacy of rhC1INH for the treatment of acute attacks in patients with HAE. Study 1203 is a phase 2/3 study of the efficacy and safety of rhC1INH for the treatment of acute attacks in patients with HAE. Results of both studies were analyzed together.

- **Objectives**
    - To explore the efficacy of rhC1INH in the treatment of acute attacks in patients with HAE
    - To assess the safety and tolerability of rhC1INH in symptomatic patients with HAE
    - To assess the PK and pharmacodynamics (PD) of rhC1INH in symptomatic patients
- **Study Design**
    - Open-label, multi-center
    - Treatment of each eligible attack with a single, open-label dose of rhC1INH 100 IU/kg
- **Study Population**
    - Participating countries: The Netherlands, Hungary, Poland, Spain, UK
    - HAE patients, ≥13 years of age (≥18 years of age outside the US and Canada), presenting with an acute angioedema attack
    - HAE patients, 18-65 years of age (Study 1202) or 16-70 years of age (Study 1203), presenting with an acute angioedema attack(s)
    - 14 patients treated for a combined total of 21 attacks
    - 13 patients completed, 1 patient discontinued early
    - Safety analysis population = All treated patients
- **Key Safety Results**
    - Exposure: rhC1INH 100 IU/kg single dose, 21/21 (100%) attacks
    - TEAEs: 11/14 (79%) patients, including urticarial behind right ear (1 patient);
    - Most common TEAEs: new acute angioedema attack, nasopharyngitis, upper respiratory infection, headache, erythematous rash
    - SAEs
        - No deaths
        - rhC1INH 100 IU/kg: 1 patient (45 yr old female) with colicky abdominal pain, Day 1 (assessed as unlikely related to rhC1INH)

- No patients developed anti-C1INH or anti-HRI antibodies
- Safety conclusion: rhC1INH 100 IU/kg was generally safe and well-tolerated

3.2.1.2.1.2 Study 1205 OLE

This is an open-label extension of Study 1205 RCT, examining the safety and efficacy of rhC1INH for the treatment of acute attacks in patients with HAE.

- **Objectives**
  - To assess the safety, tolerability, and effects of rhC1INH in treating subsequent attacks of HAE
- **Study Design**
  - OLE phase of Study 1205 RCT; open-label, multi-center
  - Treatment of each eligible angioedema attack with open-label rhC1INH 50 IU/kg, plus an additional equivalent open-label dose of rhC1INH 50 IU/kg in the event of inadequate clinical response within 4 hours
- **Study Population**
  - Participating countries: US, Canada
  - HAE patients, ≥12 years of age, presenting with an acute angioedema attack(s)
  - 62 patients treated for a combined total of 168 attacks (23 patients were treated in Study 1205 RCT prior to entry into Study 1205 OLE)
  - 52 patients completed, 6 patients discontinued early, 4 patients lost to follow-up
  - Primary safety analysis population: All patients treated in Study 1205 OLE
- **Key Safety Results**
  - Exposure:
    - rhC1INH 50 IU/kg single dose, 151/168 (90%) attacks
    - rhC1INH 50 IU/kg + additional dose, 17/168 (10%) attacks
  - TEAEs: 39/62 (63%) patients across all attacks; frequency did not increase with number of treated attacks
  - Most common TEAEs: headache, nasopharyngitis
  - SAEs
    - No deaths
    - rhC1INH 50 IU/kg single dose: 1 patient (33 yr old female) with hypersensitivity reaction (throat swelling, itchy lips) – possibly related to rhC1INH; 6 patients with HAE attacks; 1 patient (57 yr old female) with vertigo; 1 patient (28 yr old male) with pneumonia & arm swelling; 1 patient (62 yr old female) with 2 episodes of UTI & E.coli sepsis (all assessed as unlikely related to rhC1INH)
    - rhC1INH 50 IU/kg dose + add'l dose: 2 patients with HAE attacks
  - 3 patients had occasional, isolated confirmed antibodies after treatment, but none with clinical symptoms of hypersensitivity
  - Safety conclusion: rhC1INH 50 IU/kg was generally safe and well-tolerated when used for treatment of repeated angioedema attacks

3.2.1.2.1.3 Study 1304 OLE

This study is an open-label extension of Study 1304 RCT, examining the efficacy and safety of rhC1INH for the treatment of acute attacks in patients with HAE.

- **Objectives**
  - To assess the safety, tolerability, and efficacy, as well as the PK and PD of rhC1INH in the open-label treatment of subsequent attacks of HAE
- **Study Design**
  - OLE phase of Study 1304 RCT; open-label, multi-center
  - Treatment of each eligible angioedema attack with open-label rhC1INH 2,100, plus an additional equivalent open-label dose of rhC1INH 2,100 IU in the event of inadequate clinical response within 4 hours

- **Study Population**
  - Participating countries: Italy, Spain, UK, Israel, Romania, Argentina
  - HAE patients, ≥16 years of age, presenting with an acute angioedema attack(s)
  - 57 patients treated for a combined total of 194 attacks (14 patients were treated in Study 1304 RCT prior to entry into Study 1304 OLE)
  - 57 patients completed, no patients discontinued early
  - Primary safety analysis population: All patients treated in Study 1304 OLE
- **Key Safety Results**
  - Exposure: rhC1INH 2100 IU, 110/194 (57%) attacks; rhC1INH 2100 IU + additional dose, 84/194 (43%) attacks
  - TEAEs: 27/57 (47%) patients across all attacks; frequency did not increase with number of treated attacks
  - Most common TEAEs: abdominal pain, nausea, headache
  - SAEs
    - No deaths
    - rhC1INH 2100 IU single dose: 1 patient (58 yr old male) with severe MI, Day 73 (assessed as unrelated to rhC1INH)
    - rhC1INH 2100 IU single dose + add'l 2100 IU dose: None
    - rhC1INH 2100 IU single dose + add'l 2400 IU dose: 1 patient (27 yr old male) with tonsillitis (assessed as unrelated to rhC1INH)
  - 17 patients had occasional confirmed antibodies post-treatment, but none had clinical symptoms of hypersensitivity
  - Safety conclusion: rhC1INH was generally safe and well tolerated when used for treatment of repeated angioedema attacks

3.2.1.2.1.4 Study 1310 OLE

This is an open-label extension of Study 1310 RCT, evaluating the efficacy, safety and immunogenicity of rhC1INH for the treatment of acute attacks of angioedema in patients with HAE.

- **Objectives**
  - To assess efficacy, safety, and immunogenicity of rhC1INH when used for the repeated treatment of acute angioedema attacks in patients with HAE
- **Study Design**
  - OLE phase of Study 1310 RCT; open-label, multi-center
  - Treatment of each eligible angioedema attack with open-label rhC1INH 50 IU/kg (for patients <84 kg, or rhC1INH 4200 IU for patients ≥84 kg ["rhC1INH 50 IU/kg"]), plus an additional equivalent open-label dose in the event of inadequate clinical response within 1 hour
- **Study Population** (through September 14, 2012 data cut-off)
  - Participating countries: US, South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, Serbia
  - HAE patients, ≥13 years of age (≥18 years of age outside the US and Canada), presenting with an acute angioedema attack(s)
  - 44 patients treated for a combined total of 224 attacks
  - 5 patients discontinued early
  - Primary safety analysis population: All patients treated in the OLE Phase of Study 1310
- **Key Safety Results**
  - Exposure: rhC1INH 50 IU/kg, 215/224(96%) attacks; rhC1INH 50 IU/kg + additional dose, 9/224 (4%) attacks
  - TEAEs: 30/44 (68%) patients across all attacks; frequency did not increase with number of treated attacks
  - Most common TEAEs: fibrin D-dimer increased, nasopharyngitis, headache, new acute angioedema attack
  - SAEs

        - No deaths
        - rhC1INH 50 IU/kg single dose: 1 patient (68 yr old female) with moderate angioedema attack requiring hospitalization, Day 25
        - rhC1INH 50 IU/kg dose + add'l dose: None
    - 5 patients had confirmed anti-rhC1INH IgG antibodies after treatment and no change in efficacy was noted in these patients; no patients had neutralizing antibodies after treatment; 16 patients had confirmed anti-HRI antibodies after treatment, but none had clinical symptoms of hypersensitivity
    - Safety conclusion: rhC1INH 50 IU/kg (for patients <84 kg, or rhC1INH 4,200 IU for patients ≥84 kg) was generally safe and well tolerated when used for treatment of repeated angioedema attacks

3.2.1.2.2 Open-Label Studies in Asymptomatic HAE Patients

3.2.1.2.2.1 Study 1101

This is a phase 1 exploratory study of the safety, tolerability, PK and PD of ascending intravenous doses of rhC1INH in asymptomatic patients with HAE.

- **Objectives**
    - To assess the safety and tolerability of rhC1INH
    - To assess the PK of ascending doses of rhC1INH
    - To explore the PD of rhC1INH
    - To define the appropriate doses to be used in Phase 2 efficacy studies
- **Study Design**
    - Open-label, single center
    - Administration of 2 single, open-label doses (≥five-week inter-dose interval) of rhC1INH: 6.25, 12.5, 25, 50, or 100 IU/kg
- **Study Population**
    - Participating Country: The Netherlands
    - Asymptomatic HAE patients, 18-65 years of age
    - 12 patients treated, 12 patients completed, 0 patients discontinued early
- **Key Safety Results**
    - Exposure: rhC1INH 6.25 IU/kg (N=3); rhC1INH 12.5 IU/kg (N=3); rhC1INH 25 IU/kg (N=6); rhC1INH 50 IU/kg (N=6); rhC1INH 100 IU/kg (N=6)
    - TEAEs considered possibly related to rhC1INH: headache (9 events), abdominal pain (2 events), local hematoma or skin reaction (2 events), vasovagal reaction (1 event)
    - SAEs
        - No deaths
        - rHC1INH 6.25 IU/kg: 1 patient (33 yr old male) with severe abdominal HAE attack, Day 71 (considered unlikely related to rhC1INH)
    - All patients negative for anti-C1INH, anti-HRI, and neutralizing antibodies post-treatment. No allergic reactions.
    - Safety conclusion: rhC1INH 6.25-100 IU/kg was generally safe and well tolerated in asymptomatic HAE patients

3.2.1.2.2.2 Study 1207

This is an open-label exploratory phase 2 study of the safety and prophylactic effect of weekly 50 IU/kg rhC1INH treatment in asymptomatic patients with HAE.

- **Objectives**
    - To evaluate the occurrence of HAE attacks under prophylactic administration of rhC1INH (50 IU/kg/week)
    - To evaluate PK/PD parameters, immunogenicity, and safety on repeated administration of rhC1INH

- **Study Design**
  - Open-label, multi-center
  - Treatment with 8 weekly, open-label doses of rhC1INH 50 IU/kg; acute breakthrough attacks each could be treated with 1 or 2 doses of rhC1INH 50 IU/kg; maximum totalrhC1INH doses per patient was 15
- **Study Population**
  - Participating countries: Romania, Poland, Israel
  - Asymptomatic HAE patients experiencing HAE attacks at least every 2 weeks, ≥18 years of age
  - 25 patients treated, 24 patients completed, 1 patient was discontinued early
- **Key Safety Results**
  - Exposure: rhC1INH 50 IU/kg, 8 to 11 doses (N=25)
  - TEAEs considered possibly related to rhC1INH: dry mouth (1 event), dizziness (1 event), hypotension (1 event), anxiety (1 event)
  - SAEs
    - 1 death (50 yr old female) due to laryngeal edema 25 days after the patient's last dose of rhC1INH (considered not related to rhC1INH)
    - 1 (21 yr old female) patient with appendicitis 4 days after the last dose of rhC1INH (considered not related to rhC1INH)
  - Isolated anti-C1INH antibodies after treatment; all patients negative for neutralizing antibodies. Confirmed anti-HRI antibodies in 11/25 (44%) patients after treatment, without associated clinical symptoms of hypersensitivity
  - Safety conclusion: 8 weekly injections of rhC1INH 50 IU/kg were generally safe and well tolerated in HAE patients

3.2.1.2.3 Open-Label Studies in Healthy Volunteers

3.2.1.2.3.1 Study 1106

This is a phase 1 study of the safety, tolerability, immunogenicity and PK of repeated intravenous doses of rhC1INH in healthy subjects.

- **Objectives**
  - To assess the safety, tolerability, and immunosafety of rhC1INH on repeated dosing in healthy volunteers
  - To assess the PK of rhC1INH in healthy volunteers
- **Study Design**
  - Open-label, single center
  - Administration of 5 single, open-label doses of rhC1INH 100 IU/kg (3-week interdose interval)
- **Study Population**
  - Participating country: The Netherlands
  - HV subjects, 18 to 65 years of age
  - 14 subjects treated, 11 subjects completed, 3 subjects discontinued early
- **Key Safety Results**
  - Exposure: rhC1INH 100 IU/kg, 5 doses (N=11); rhC1INH 100 IU/kg, 2 doses (N=1);
  - rhC1INH 100 IU/kg, 1 dose (N=2)
  - TEAEs considered possibly related to rhC1INH: pruritus (2 events), headache (1 event), taste perversion (1 event)
  - SAEs
    - No deaths
    - 1 (20 yr old female) subject with severe allergic reaction (anaphylaxis) commencing 2-3 minutes after start of iv injection of rhC1INH in subject with previously-undisclosed history of allergy to rabbit dander/hair (considered related to rhC1INH)
  - 4 patients with anti-HRI antibodies (with 2 (50%) prior to any rhC1INH doses), but none of these with clinical symptoms of hypersensitivity

- Safety conclusion: rhC1INH 100 IU/kg was generally safe and well tolerated in healthy volunteer subjects; rabbit allergy can potentially induce type I hypersensitivity reactions

3.2.1.3 Other Studies

3.2.1.3.1 CDR-002 IgE Antibody – Immunogenicity of rhC1INH

- **Objectives**
  - To look for any relationship between pre-existing IgE antibodies against a panel of animal-derived allergens, particularly from rabbit and from cow milk, and reported hypersensitivity-type reactions following single or repeated exposure to rhC1INH in healthy volunteer subjects and HAE patients
  - To assess the potential of rhC1INH to induce IgE antibodies against rabbit or cow milk allergens in healthy volunteer subjects and HAE patients following single or repeated exposure to rhC1INH.
- **Methods**
  - Plasma samples from the healthy volunteer subjects and HAE patients that participated in the clinical development program of rhC1INH were tested for the presence of IgE antibodies against a pre-specified panel of animal-derived allergens and the clinical safety database was searched for AEs with a possible allergic basis.
  - Possible allergic AEs were defined as TEAEs with symptoms suggesting an underlying allergic basis that occurred within 7 days after exposure to rhC1INH.
  - IgE testing**:** Plasma samples collected up to 90 days after first or subsequent rhC1INH administrations from 137 healthy volunteer subjects and HAE patients that were exposed to rhC1INH in the clinical development study program of rhC1INH (Studies 1101, 1106, 1202/1203, 1205, and 1304) up to September 3, 2009, were included in the retrospective analysis.
  - Pre-exposure (screening) plasma samples collected at study screening visits or just prior to exposure to rhC1INH were tested for the presence of pre-existing IgE antibodies against the selected panel of animal-derived allergens (i.e., rabbit, rat, mouse, guinea pig, hamster, cow, cat, dog and horse dander/epithelium allergens, among others).
  - Pre-exposure plasma samples were tested for the presence of pre-existing IgE antibodies against common inhaled environmental allergens to confirm or exclude the diagnosis of an atopic constitution.
  - Post-exposure plasma samples collected at Day 22 and Day 90 after each subject's last exposure to rhC1INH were tested for IgE antibodies against rabbit dander and rabbit meat allergens, and against cow milk allergens to evaluate the potential of rhC1INH to induce IgE antibodies against these allergens.
- **Results**
  - Up to September 3, 2009, 144 subjects (healthy volunteers and HAE patients) had been exposed to rhC1INH in the clinical development study program. Pre- and post-exposure plasma samples were available from 137 of these subjects.
  - Possible allergic AEs: 12 subjects (8.8%) including 1 SAE, which occurred in an adult female healthy volunteer (Study 1106) with pre-existing (undisclosed) rabbit allergy who developed an anaphylactic reaction immediately following first exposure to rhC1INH at a dose of 100 IU/kg.
  - Atopic constitution: 66.7% of subjects who reported an AE with a possible allergic basis versus 41.6% of subjects who did not report an AE with a possible allergic basis.
  - Pre-existing IgE
    - Of 113 subjects without any positive IgE test results at screening, 9 (8.8%) with possible allergic basis AE
    - At screening, 24 (17.5%) subjects with ≥1 positive IgE antibody test result
    - 3 of 24 (12.5%) reported TEAEs meeting criteria of possible allergic basis AE

        - 1 healthy volunteer subject with an anaphylactic reaction immediately following her first exposure to rhC1INH (had highest IgE level against rabbit epithelium, dander and urine allergens; also had IgE to guinea pig epithelium and cat dander, but these allergens found in 6/24 subjects without allergic reaction to rhC1INH, thus these were considered unlikely to be involved in any allergic basis AE resulting from exposure to rhC1INH)
        - 1 healthy volunteer subject with flu-like symptoms 3 days after a second exposure to rhC1INh (IgE against rabbit dander)
        - 1 asymptomatic HAE patient with pre-existing elevated IgE against cat allergens but negative for IgE against any rabbit or cow milk allergens. This patient's AE, conjunctivitis and rhinitis, occurred 3 days after exposure to rhC1INH but soon after exposure to a cat. Hence, cat allergy was considered the likely cause of the reported symptoms. No other subjects found to have raised IgE antibody levels against cat allergens reported allergic type reactions following exposure to rhC1INH.
    - 3/24 subjects had IgE against cow milk. None developed an allergic type AE upon exposure to rhC1INH.
    - Induction of IgE
        - 0/12 subjects who reported a possible allergic basis AE following exposure to rhC1INH had an increase in post-exposure IgE levels to rabbit or cow milk allergens.
        - 0/24 subjects at screening with at least one positive IgE antibody against any animal allergens tested had an increase in post-exposure IgE levels to rabbit or cow milk allergens.
        - 3/113 subjects previously below threshold for rabbit and cow milk allergens had above threshold IgE against rabbit or cow milk allergens post-study exposure to rhC1INH. None of these three subjects developed an allergic AE upon first or repeated exposure to rhC1INH.
- **Conclusions**
    - The highest pre-existing IgE antibody level against rabbit dander allergens was found in the healthy volunteer subject who developed an anaphylactic reaction following exposure to rhC1INH. 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 urine, no relationship was noted between pre-existing IgE antibodies against a wide range of animal allergens and reported allergic type basis AEs. This retrospective analysis does 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, there was no indication of any risk due to the presence of pre-existing IgE against cow milk allergens. From these data, it is concluded that single and repeat exposure up to 100 IU/kg body weight rhC1INH did not induce detectable IgE antibody responses against rabbit or other animal allergens.

3.2.1.3.2 CDR-007 Thrombogenicity in Relation to Treatment with rhC1INH

C1INH products are generally well tolerated. However, during off-label administration of very high doses of the pdC1INH product, Berinert®, among neonates with cardiac malformations, a greater risk of thromboembolic complications was noted. This study was implemented to address concerns over this potential "class effect" with rhC1INH.

Major conclusions of this evaluation are as follows:

- There is no evidence to support an increase in thromboembolic risk arising from the proposed use of rhC1INH in the treatment of acute angioedema attacks in HAE patients for the following reasons:

- The inhibitory spectrum of C1INH predicts that C1INH not only affects fibrinolytic proteases but also coagulation proteases *in vivo*.
- Except for a paper by Horstick et al,[4] of which the conclusions regarding thromboembolic side effects of pdC1INH are based on a misinterpretation of the experimental data (where clots noted in coronary venous blood in pigs were not evidence of thromboembolic side effects but rather clotting in blood samples taken from non-heparanized animals), none of the published preclinical studies on pdC1INH, given at up to 20 times the recommended dose for angioedema attacks, mention thrombogenic side effects of C1INH.
- The Sponsor's submission states there is no evidence in the medical literature for an increased risk of TEE with C1INH therapy in HAE. Based on the mechanism of action of C1INH, a lower risk of TEE would be expected compared to fibrinolytic inhibitors.
    - Reviewer's note: This conclusion did not include the 2012 publication of a study by Gandhi et al, in which case reports of TEE associated with the use of the C1INH products in HAE patients were extracted from the FDA Adverse Event Reporting System (AERS) database and found to occur with greater-than-expected frequency; all reports occurred with the use of the pdC1INH product, Cinryze.[5]
- A review of the literature does not provide evidence for a thrombogenic risk of C1INH products in other diseases, even when given at significantly higher doses than the recommended dose for the treatment of angioedema attacks in HAE patients. The exception is severely ill neonates treated with pdC1INH at extremely high doses of 500-1050 U/kg. However, these observations in neonates were uncontrolled in a setting with known underlying risk for thromboembolism, and are confounded by clinical factors.
- The preclinical program of rhC1INH did not raise concerns about an increased risk for thromboembolic complications.
- The findings on coagulation and fibrinolytic parameters in HAE patients treated with rhC1INH indicate no effect of rhC1INH on activation of coagulation and fibrinolysis in HAE patients at the doses administered.
- Up to March 1, 2009, no TEE related to the administration of rhC1INH had been reported from the clinical program of rhC1INH in HAE patients (405 administrations of rhC1INH at doses ranging from 18-120 IU/kg body weight). The maximum number of treatments received by a single patient was 20, and 14 patients had received 5 administrations or more.
- From March 1, 2009 through September 13, 2013, no TEE have occurred during the clinical studies of rhC1INH. The maximum number of treatments received by a single patient was 24.

3.2.1.3.3 Study 1113 Phase 1 Study to Assess Immunogenicity of rhC1INH in Subjects with Allergies to Cow's Milk or Rabbits

Study 1113 is being conducted as a follow-up measure for the European Medicines Association (EMA) to assess the negative predictive value of a skin prick test in 25 subjects with allergies to cow's milk or rabbits. Following confirmation of sensitization by a skin prick test with cow's milk and/or rabbit dander, subjects receive a skin prick test with increasing concentrations of rhC1INH followed by intracutaneous skin testing with increasing concentrations of rhC1INH and blood sample collection to assess basophil activation. Those subjects who test negative for the skin prick test and intracutaneous skin testing are asked to return at two weeks or later for a subcutaneous challenge with four increasing doses of rhC1INH.

As of September 13, 2013, 20 subjects have been enrolled, of which 17 subjects have completed all study procedures, two subjects remain ongoing, and one subject was lost to follow-up. Of the 17 subjects who have completed the study, seven had rabbit allergies, six subjects had cow's milk allergies, and four subjects had allergies to both rabbits and cow's milk. None of the 17 subjects who've completed the study have had a positive reaction to subcutaneous challenge and no SAEs have been reported.

3.2.1.3.4 Study 1209 Phase 2, Open-Label Study of rhC1INH in Pediatric Patients with HAE

As part of the Pediatric Investigation Plan prepared for the EU, the Sponsor has agreed to study the safety and immunogenicity of rhC1INH for the treatment of acute HAE attacks in children (Study 1209). This study will evaluate the pharmacokinetics/pharmacodynamics, safety, immunogenicity and efficacy of rhC1INH for the treatment of acute attacks among HAE patients from 2 up to and including 13 years of age. A summary of the protocol for Study 1209 and preliminary enrollment numbers follows.

Table 2. Study 1209 Protocol Summary

Objectives
• To assess the clinical safety, immunogenicity, and tolerability of rhC1INH in the treatment of acute angioedema attacks among HAE patients 2−13 years of age • To assess the pharmacokinetics and pharmacodynamics of rhC1INH in the treatment of acute angioedema attacks among HAE patients 2−13 years of age • To assess the efficacy of rhC1INH in the treatment of acute angioedema attacks among 2−13 year old HAE patients
Study Design
• An open-label, multicenter clinical study • Treatment with rhC1INH 50 IU/kg (for patients <84 kg, or rhC1INH 4200 IU for patients ≥ 84 kg): a second dose can be provided, at the investigator's discretion, in case of insufficient therapeutic response • Four hours after study medication administration, the patient may be discharged from the clinic if the investigator judges the patient's condition well enough • The investigator will schedule a telephone contact at 24 hours after study medication administration; Follow up visits are planned at Day 28 and Day 90 • Multiple attacks can be treated, provided a minimum 24-hour interval between subsequent treated attacks and a maximum of 10 attacks per patient in the study • Safety and tolerability by standard criteria (vital signs, ECG, adverse events, routine laboratory safety parameters and immunogenicity [anti-host related impurities and anti C1INH antibodies]) • Pharmacokinetic and pharmacodynamic parameters (C1INH activity and C4 in plasma) during treatment for the first attack • Efficacy parameters and endpoints (time to beginning of relief, time to minimal symptoms, time to complete resolution)
Study Population
• Patients eligible for treatment with rhC1INH if they present to the clinic within 5 hours of onset with an acute attack of at least moderate severity • Patients 2−13 years of age suffering from HAE (baseline plasma levels of C1INH activity < 50%) • The study will continue until at least 20 patients have been enrolled • As of September 13, 2013, 20 patients were enrolled, of which one patient was lost to follow-up and one subject was withdrawn, both prior to receiving treatment in the study. Three patients (8, 12 & 13 years of age) have been treated for a total of 12 angioedema attacks. No SAEs or AEs leading to discontinuation have been reported.

3.3 Safety Concerns Within the Pharmacovigilance Plan

3.3.1 Important Identified Safety Issues

3.3.1.1 Type I Hypersensitivity Reaction Due to Pre-Existing IgE Antibodies Reacting With HRI

Type I hypersensitivity reactions occur when allergens combine with specific IgE antibodies that are bound to membrane receptors on tissue mast cells and blood basophils. The antigen-antibody reaction causes the release of potent vasoactive and inflammatory mediators, which produce vasodilation, increased capillary

permeability, glandular hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils and other inflammatory cells. Examples of type I hypersensitivity reactions include atopic diseases (allergic rhinitis, conjunctivitis, and asthma) and some cases of urticaria and systemic anaphylaxis. These reactions can be associated with severe respiratory problems and/or shock. Ruconest (rhC1INH) is purified from the milk of rabbits expressing the gene encoding for human C1INH. In this regard, sensitization to rabbit allergens resulting in pre-existing IgE antibodies could plausibly cause a type I hypersensitivity reaction to host-related impurities (HRI) in someone receiving rhC1INH.

One SAE of an anaphylactic reaction was reported in a 20-year-old Caucasian female healthy volunteer in Study 1106 who omitted disclosure of a known clinically significant allergy to rabbits during the screening procedures. This SAE was experienced two minutes after start of the rhC1INH injection, which is consistent with an allergic reaction mediated by pre-existing IgE. Levels of IgE against rabbit dander were one order of magnitude higher (39.6 kU/L) than the patient's highest pre-existing level of IgE against rabbit dander (4.9 kU/L).

The prevalence of rabbit allergy in the general population (sensitization to rabbit allergens) is less than 1%. However, in animal laboratory workers with exposure to rabbits, allergic reactions may be around 30%.[6,7] Based on the rhC1INH clinical trial experience, five of 144 participants from whom samples have been taken, had pre-existing IgE against rabbit epithelium. Only one of these participants developed an anaphylactic reaction.

Type I hypersensitivity reactions due to pre-existing IgE antibodies reacting with HRI can be prevented by including a Contraindication and Warning in the package insert (PI) for patients with known allergy to rabbits or rabbit-derived products.

3.3.2 Important Potential Safety Issues

3.3.2.1 Type I Hypersensitivity Reaction Due to Formation of IgE Antibodies Reacting With HRI

HRI contained in rhC1INH could theoretically induce formation of IgEs against these impurities, resulting in a type I hypersensitivity reaction. Archived plasma samples of subjects enrolled in the clinical program of rhC1INH were analyzed to investigate the potential for the induction of IgE against rabbit or milk antigens following administration of rhC1INH. No clinically relevant induction of IgE production by rhC1INH was observed.

Assays to detect IgE antibodies to rhC1INH, rabbit milk, and rabbit HRI have not been developed because 1) only one individual developed an allergic (anaphylactic) reaction following exposure to rhC1INH, but this would have been prevented if the individual had disclosed her past history of allergy and, 2) the development of assays to detect IgE antibodies to rhC1INH, rabbit milk, and rabbit HRIs would require positive control samples from individuals who have experienced an allergic reaction following exposure to rhC1INH, which are currently not available. A specific test against a specific antigen could be developed if a clinically relevant antigen had been identified. To date, with a single case of anaphylaxis, it is impossible to comment on the clinical relevance of potential antigens.

3.3.2.2 Type III Hypersensitivity Reaction Due to Formation of Antibodies Against C1INH or HRI

Type III hypersensitivity reactions occur when antigen-antibody immune complexes deposit in vessels or tissue and activate complement, thus initiating a sequence of events that results in release of proteolytic enzymes and permeability factors, thereby producing acute inflammation. An example of a Type III hypersensitivity reaction is rheumatoid arthritis. The formation of antibodies other than IgE (i.e., IgG, IgM, IgA) is expected to be of limited (if any) clinical relevance. In the rhC1INH clinical program, there were no clinical symptoms associated with the occasional presence of anti-HRI antibodies. A theoretical risk associated with antibodies other than IgE is the formation of immune complexes between the antigen and the antibodies. Although such antigen-antibody complexes are generally effectively removed, in certain circumstances immune complexes

may induce pathological responses known as type III hypersensitivity reactions.[8] Because rhC1INH only contains traces (part per million) of HRI, precipitation of HRI immune complexes is unlikely to occur.

Another potential effect of the formation of anti-C1INH antibodies is the formation of neutralizing antibodies, which could theoretically reduce the efficacy of rhC1INH. While not an adverse reaction, such an effect is potentially important (see next Section).

The formation of antibodies (IgG, IgM, IgA) against C1INH or HRI was monitored for all HAE patients and healthy volunteer subjects participating in the clinical development program of rhC1INH. Occasionally, samples screened positive for anti-HRI antibodies, but these were not associated with clinical symptoms. The clinical consequence of the formation of antibodies other than IgE therefore remains unknown.

In Study 1101, none of the 12 asymptomatic HAE patients receiving two repeat administrations of rhC1INH doses ranging from 6.25 to 100 IU/kg had confirmed positive anti-C1INH or anti-HRI antibodies. In Study 1106, eleven healthy volunteer subjects received five rhC1INH doses of 100 IU/kg, once every three weeks. Four patients had confirmed positive anti-pdC1INH antibodies at any time-point and one patient had confirmed anti-HRI antibodies. In Study 1207, 10 of 25 asymptomatic HAE patients receiving eight weekly injections of 100 IU/kg had confirmed positive samples for anti-HRI antibodies at the end of the study period. Two of 25 patients had confirmed positive anti-C1INH antibodies; none of the patients with confirmed anti-C1INH antibodies demonstrated reduced efficacy of rhC1INH. In 155 symptomatic patients, anti-C1INH antibodies confirmed by -----(b)(4)----- assay were detected in six patients. Two of these patients had anti-C1INH antibodies before first exposure to rhC1INH. Five of the 155 patients had anti-HRI antibody results confirmed in a -----(b)(4)----- assay at any time-point. One of those five patients had confirmed anti-HRI antibody results before first exposure to rhC1INH.

Following treatment with rhC1INH, patients should be monitored for clinical symptoms of type III hypersensitivity reactions (skin, joint, kidney) and, if such symptoms are observed, the patients should be withdrawn from rhC1INH treatment.

3.3.2.3 Induction of Acquired Angioedema Due to Formation of Neutralizing Antibodies Against C1INH

Neutralizing antibodies against C1INH may result in a reduced response to rhC1INH treatment and could also neutralize endogenous C1INH. The potential clinical impact of neutralizing antibodies against C1INH would be similar to that of acquired angioedema. Formation of antibodies would develop gradually and the patient would notice “lack of efficacy” as an early symptom. Angioedema attacks could still be treated with higher doses or ecallantide.

As mentioned in Section 3.3.2.2, there is a theoretical risk that patients may develop neutralizing antibodies against C1INH affecting the efficacy of rhC1INH. Antibody formation to C1INH was monitored, and occasional values above cutoff were observed. Eight patients had anti-C1INH antibodies confirmed by -----(b)(4)----- assay, but no neutralizing antibodies were detected.

In patients receiving rhC1INH, induction of acquired angioedema due to formation of neutralizing antibodies against C1INH could be prevented by withdrawing the patient from rhC1INH treatment if the formation of neutralizing antibodies is suspected.

3.3.2.4 Thromboembolic Complications

It has been hypothesized that the inhibiting effects of C1INH on the activity of fibrinolytic proteases may cause thromboembolic side effects.[4] However, a review of the biochemical properties of C1INH indicates that the inhibitory effect of C1INH on fibrinolytic proteases is at best weak and of doubtful physiological relevance.[9,10]

At the time of licensure, TEE had been identified as of particular or potential relevance in patients who received the plasma-derived C1INH product, Berinert. Prior to licensure of Berinert or Cinryze, several fatal

TEE had been observed in a clinical trial in Europe of neonatal and pediatric cardiac patients where Berinert was administered for an indication other than HAE. Upon licensure in the US, the labels for both products included a warning that TEE had been reported in off-label use at high doses. In addition, Cinryze approval included a post-market requirement (PMR) to conduct a clinical trial to evaluate higher-than-labeled dose schedules for prophylaxis, and the occurrence of TEE. Berinert approval included three PMRs: 1) an open-label uncontrolled study to assess inhibitory antibody formation in subjects with congenital C1INH deficiency and acute HAE attacks treated with Berinert; 2) a study evaluating long-term safety data in subjects exposed to repeated doses; and 3) a registry of patients treated with Berinert for any indication for observation of TEE and other adverse events.

In May 2010, a FDAAA Section 921 posting of a potential signal of serious risk of "thromboembolic events in patients with certain thrombogenic risk factors" was triggered for pdC1INH. This posting was based on eight reports of TEE after receipt of Cinryze that were detected through the Adverse Event Reporting System (AERS), FDA's national passive surveillance system that receives reports for drugs and non-vaccine biologics submitted through MedWatch. In all cases, there were alternative explanations for the reported TEE, such as known coagulation disorders, pregnancy, or cardiac septal defect. As a result, the Warnings and Precautions and Adverse Reactions sections of the labels for Berinert and Cinryze (labeling approved December 22, 2011 and January 9, 2012, respectively) were updated with additional information about TEE, including the statement that TEE have been reported in patients receiving Berinert or Cinryze.

To date, no TEE related to the administration of rhC1INH have been reported in clinical trials of rhC1INH. In these studies, 236 participants received 997 administrations of rhC1INH at doses ranging from approximately 6.25 to 120 IU/kg. Further, coagulation and fibrinolysis were studied in symptomatic HAE patients receiving rhC1INH (see observed changes to specific indices in next paragraph). The nonclinical development program of rhC1INH also did not show an increased risk for thromboembolism. In toxicology studies in rats, dogs, and monkeys, repeated daily doses of rhC1INH up to 40-fold the licensure clinical dose of 50 IU/kg had no meaningful effect on coagulation parameters (prothrombin time and aPTT) or histopathology evaluations. The results of these studies indicate no increased risk of TEE with administration of rhC1INH. An *in vitro* study confirmed the lack of these effects at plasma concentrations of rhC1INH up to 10 IU/mL, a plasma concentration greater than five times those expected after a single administration of rhC1INH 50 IU/kg. Consequently, the risk of thromboembolic complications in HAE patients at the recommended rhC1INH dose is not supported by *ex vivo* data and clinical observations.

A study to evaluate the effects of rhC1INH on coagulation and fibrinolysis in patients treated with rhC1INH 50 IU/kg, 100 IU/kg, or saline was conducted. The results of this study confirm studies published in the literature[1-3] showing that during an acute HAE attack, prior to any treatment, baseline levels of D-dimer, prothrombin activation fragment F1+2, thrombin-antithrombin (TAT) complexes and plasmin-antiplasmin (PAP) complexes were elevated in most patients, while activated partial thromboplastin time (aPTT) was lower than normal. These findings indicate activation of coagulation and fibrinolysis due to the ongoing acute HAE attack. After administration of rhC1INH, no clear increases in levels of F1+2 fragment or TAT complexes were observed. In fact, F1+2 levels tended to decrease during the course of the attack in the patients who received rhC1INH whereas they remained stable in the group who received saline. Four of the seven HAE patients in the saline group had lower F1+2 levels at 4 hours compared with baseline, versus eight of the nine patients in each rhC1INH group. Parameters such as F1+2 are particularly relevant, since these are significantly elevated in acute thrombotic conditions such as myocardial infarction.[11] Also, no decrease of PAP complexes occurred in the groups receiving rhC1INH, ruling out significant inhibition of fibrinolysis by rhC1INH. Due to observations of TEE with the use of plasma-derived C1INH products, further evaluation of this risk with rhC1INH was performed in Study 1310. D-dimer concentrations were measured at Baseline, 2 hours, and Day 7 following study drug administration in the randomized control trial (RCT) and OLE Phases of the study. In the RCT Safety Analysis Set, Baseline and 2 hour D-dimer concentrations were elevated in both the rhC1INH and saline groups. By Day 7, median values decreased in both groups. As reported in the literature[3], the early high D-dimer

concentrations likely reflect the ongoing HAE attack, which is associated with activation of both coagulation and fibrinolysis. Similar trends were observed in the OLE Safety Analysis Set.

3.3.3 Important Missing Information

3.3.3.1 Data on Pregnant or Nursing Women

Pregnant and breast-feeding women were excluded from the clinical studies of rhC1INH. To date, there are no formal data on the safety of rhC1INH in pregnant or breast-feeding women. However, there were five women who became pregnant during the clinical studies. Three of these women (21, 30 & 38 years of age) gave birth to healthy infants with no overt sequelae; one woman (18 years of age) was diagnosed as pregnant 3 days after receipt of dose 8 (2,100 IU) of 18 total doses and experienced a spontaneous abortion 22 days post-dose 8; and one woman (29 years of age) withdrew from the study 53 days after dose 1 and was lost to follow-up.

3.3.3.2 Other Populations Not Studied in the Pre-Approval Phase or Thus Far in Non-US Postmarketing Studies

3.3.3.2.1 Pediatric Patients

The safety and efficacy of rhC1INH in children (0−12 years of age) has not yet been established. Overall, 17 adolescent HAE patients (13−17 years of age) were treated with rhC1INH in clinical trials for a combined total of 52 acute angioedema attacks. There was no indication that adolescent patients reacted differently to treatment with rhC1INH as compared with adult patients (e.g., the proportion of adolescent patients experiencing AEs across all attacks was similar to that of the adult patients). Thus, adolescent patients (ages 13−17 years) are not excluded from the proposed license indication.

The Sponsor is currently enrolling children in Study 1209, which will assess the pharmacokinetics, pharmacodynamics, clinical safety, tolerability, immunogenicity and efficacy of rhC1INH among children 2−13 years of age (See Section 3.2.1.3.4). As of September 13, 2013, 20 patients have been enrolled, one of whom was lost to follow-up and another who was withdrawn.

3.3.3.2.2 Elderly

Seven patients 65 years of age or older were treated with rhC1INH in clinical studies. No evidence was apparent to indicate that patients 65 or older would react differently to treatment with rhC1INH as compared with younger patients. Therefore, elderly patients are not excluded from the proposed license indication.

3.3.3.2.3 Patients With Renal or Hepatic Impairment

No dosage adjustment is necessary for patients with renal impairment, since rhC1INH does not undergo renal clearance. There is no clinical experience with the use of rhC1INH in patients with hepatic impairment. Hepatic impairment may prolong the plasma half-life of rhC1INH, but this is not considered to be of clinical significance. No recommendation on rhC1INH dose adjustment for patients with hepatic impairment can be made.

3.3.3.2.4 Patients With Cardiac Impairment or Other Conditions or Treatment

Patients with co-morbid conditions that, in the opinion of the Investigator, might interfere with the evaluation of safety were excluded from participation in the clinical studies of rhC1INH. As treatment involves a "replacement" therapy with C1INH activity through a recombinant analog of the human plasma protein C1INH, it is unlikely that administration of rhC1INH would involve any particular risk for patients with co-morbid conditions. Therefore, there is generally no clinical basis to exclude patients with cardiac impairment or other co-morbid conditions.

Patients with a history of anaphylaxis, severe allergies, viral hepatitis, human immunodeficiency virus, abnormalities in routine laboratory parameters, and/or addiction to narcotics were excluded from the clinical studies of rhC1INH. In addition, patients taking disallowed concomitant medications (i.e., medications that

could interfere with the evaluation of safety and efficacy of rhC1INH), blood donors, pregnant women, or those participating in other clinical studies were also excluded from the clinical studies of rhC1INH. These exclusion criteria were set to improve the evaluation of the safety and efficacy of rhC1INH treatment. However, except for patients who are allergic to rhC1INH, patients with the aforementioned conditions do not necessarily need to be excluded from treatment with rhC1INH.

3.3.3.2.5 Patients of Different Ethnic Origins

HAE is a genetic disorder with an equal ethnic and gender distribution.[12] Most participants in the clinical studies of rhC1INH were Caucasian (95% among patients experiencing HAE attacks and 90% among asymptomatic patients and healthy volunteer subjects). The safety database for non-Caucasian participants in clinical trials of rhC1INH is currently not adequate to determine any differences in rhC1INH safety across patients or healthy volunteer subjects of different racial or ethnic backgrounds.

3.3.3.2.6 Acquired Angioedema Patients

The majority of patients with acquired angioedema have neutralizing antibodies against C1INH. Therefore, this patient population was excluded from the clinical trials of rhC1INH.

3.4 Additional Comments on Other Potential Safety Concerns

3.4.1 Pharmacological Class Effects

The principle risks with pdC1INH products are associated with blood borne transmissible agents, and therefore not applicable to rhC1INH. The potential safety issue of TEE is covered in Section 3.3.2.4. The principal risk associated with other recombinant human proteins is allergic reactions to HRI, which have been covered in Sections 3.3.1.1−3.3.2.3.

3.4.2 Identified and Potential Interactions, Including Food-Drug and Drug-Drug Interactions

No clinical food-drug or drug-drug interaction studies of rhC1INH or analyses of the effects of concomitant medications on the safety of rhC1INH have been performed to date. Data in the literature indicate an interaction of tissue-type plasminogen activator and high doses of exogenous C1INH-containing products.[10,13-15] The prescribing information will indicate that rhC1INH should only be used together with tissue-type plasminogen activator when the benefit outweighs the risk.

Interactions with chemical entity drugs, including medications frequently used in the management of HAE patients such as analgesics, androgens, and anti-fibrinolytics, are not anticipated due to the nature and metabolism of rhC1INH. As for recombinant proteins such as rhFactorVIII, rhFactorIX, rhFactorVII, and therapeutic monoclonal antibodies, no drug-drug interactions are expected; in addition, rhC1INH is not expected to alter binding of these biological products to albumin.

3.4.3 Adventitious Agent Safety

3.4.3.1 Non-Viral Adventitious Agents

The risk of transmissible spongiform encephalopathy (TSE) or prion disease through rabbit milk used in the manufacture of this product is assumed to be negligible, given that 1) TSE diseases have not been reported to occur naturally in rabbits; 2) precautions are taken to prevent accidental contamination of lab rabbit feed with meat and bone meal by compliance with European directives forbidding the incorporation of any animal protein into formulated diets; 3) the Spongiform Encephalopathy Advisory Committee has concluded that current scientific evidence is lacking to suggest any risk of TSE contamination via animal milk, regardless of geographical and species origin.

3.4.3.2 Viral Adventitious Agents

The risk of viral contamination of purified rhC1INH is minimized by using four complementary control principles: 1) control of animal facilities and animal husbandry; 2) animal health monitoring, including testing

for specific viruses; 3) screening of the skimmed milk -----(b)(4)----- for adventitious viral contaminants; and 4) viral clearance by the purification process.

3.5 Sponsors Proposed Actions and Timelines

3.5.1 Routine Pharmacovigilance Practices

- Team of medical and scientific professionals assigned to review all AE case reports associated with rhC1INH treatment
- Expedited reporting to the US FDA of all spontaneously reported serious, unexpected drug reactions associated with rhC1INH exposure
- Monthly review of global published medical and scientific literature associated with rhC1INH treatment
- Monthly reports summarizing individual case report metrics worldwide, both spontaneous, and those identified through the medical and scientific literature
- Continuous monitoring of AEs reported worldwide through frequent individual case reviews, signal detection activities, and benefit-risk evaluations
- Quarterly reviews of aggregate and cumulative AEs by the Sponsor's Risk Management Committee to monitor worldwide changes in the safety profile or the benefit-risk profile of the product
- At least annually, cumulative data analysis by the Sponsor's Safety Review Board of all serious cases worldwide based on the medical and scientific safety data gathered to date to ensure that the benefit-risk profile of rhC1INH remains positive and its risk mitigation is maximized
- Preparation of Periodic Adverse Experience Report (PAER) or Periodic Safety Update Report (PSUR) and Annual Reports
- Updates to label information in a timely fashion in response to new identified or potential safety concerns provided by the Sponsor or regulatory authorities
- Convening appropriate panels as needed for guidance in evaluating any potential safety signals
- Providing standard medical information letters for physicians to address frequently asked questions
- Risk communication to physicians, patients, and regulatory agencies when new clinically significant risks are identified or new mitigation plans are generated
- Evaluation of the Sponsor's PVP every 2 years to determine the effectiveness of 1) Risk mitigation in decreasing risk of treated patients; and 2) Enhanced safety surveillance to provide more data on identified and potential risks as well as safety in pregnant or nursing women treated with rhC1INH

3.5.2 Signal Detection

Signal detection methods will vary depending on the specific clinical study design. For signal detection conducted during future clinical studies of rhC1INH, all AEs for all patients will be analyzed for each unique System Organ Class and MedDRA Preferred Term by two approaches:

- Frequency and severity
    - Number and percentage of individual AEs
    - All AEs for all patients presented in a data listing, by severity, and by treatment group
- Temporal relationship and exposure
    - Time (hours or days, as appropriate) between the first dose of study drug and the onset of every AE presented in a data listing
    - Extent of exposure (e.g., number of doses prior to AE onset)
    - Change of AEs over time (e.g., by absolute time and by number of attacks)
    - Differences in AEs at initiation of treatment or withdrawal of treatment
    - Changes in severity or frequency of patients' preexisting conditions, if known, over time

Summary statistics (n, mean, standard deviation, median, minimum and maximum values) will be calculated as appropriate. Temporal associations of AEs, if identified with pdC1INH products in published reports, will be analyzed for rhC1INH as well.

Postmarketing signal detection of spontaneous and literature AE reports will be performed on a quarterly basis or more frequently, if unexpected potential risks are identified. The key goal of signal detection will be to identify AE rate imbalances and disproportionality using data from a variety of sources.

Data sources include:

- Case and case series review using HAE registry data and spontaneous reports, with focus on AEs that are rare, serious, and with high drug-attributable risk
- Passive surveillance using signals from the HAE registry (see Section 3.5.4.1) and spontaneous AE reports, as well as reports in the literature
- Active surveillance collected by the Sponsor from the health care provider, emergency room, or the patient (if self-administered) on a quarterly basis

Data analyses will include:

- Aggregate analyses by case counts (Reporting Rate)
- Data mining and Proportional Reporting Ratio (PRR) using HAE registry cases and those in FAERS

3.5.3 Benefit-Risk Evaluation

- Review of HAE, its epidemiology and pharmacology
- Review of benefits and risks in clinical trials, post-marketing spontaneous and literature reports of safety for rhC1INH, according to Benefit-Risk Action Team (BRAT) framework[16]
- Annual integrated benefit-risk assessments, based on the BRAT framework

3.5.4 Enhanced Pharmacovigilance

3.5.4.1 US HAE Registry

- **Primary Objective:** To evaluate the incidence of adverse events and time to beginning of symptom relief reported after single or repeated treatment with rhC1INH
- **Secondary Objective:** To characterize hypersensitivity reactions, thrombotic events, and the safety profile in pregnant and nursing women
- **Study Design:** This is a multicenter, open-label, observational study (registry) of rhC1INH, 50 IU/kg of body weight (body weight < 84 kg; 4200 IU for ≥ 84 kg), to evaluate the incidence of adverse events and time to symptom relief, as well as to characterize hypersensitivity reactions, thrombotic events, and the safety profile in pregnant and nursing women in the treatment of acute attacks of HAE in adult and adolescent patients. There are no restrictive patient entry criteria. Patients who are treated with pdC1INH for their HAE attacks are not eligible for enrollment; other medications taken with rhC1INH, including ecallantide and icatibant, will be allowed and recorded.
  Patients will obtain rhC1INH prescriptions from their healthcare provider (HCP) and will be directed to a specialty pharmacy in their locale. The HCP will obtain an informed consent from the patient for participation in the registry. For minors (≥ 13 but < 18 years old), assent will be obtained as well as parental informed consent.
  The study will conduct passive surveillance of adverse events (web-based entry) by patients and active surveillance of adverse events (scheduled telephone survey) of patients every three months by Sponsor or designee. Patients may be enrolled by a center specializing in the treatment of HAE or may be referred by their individual treating physician. Both self-administration and administration of rhC1INH by an HCP will be allowed. For patients treated in the emergency room or hospital; the Sponsor will obtain patient written permission for the HCP or hospital to release the patient's medical records pertaining to the attack.

Data will be collected regarding the patient's demographics, body weight, date of last treated HAE attack, date of onset of first symptoms of current attack, time of onset of first symptoms of current attack, location(s) of current attack, exposure (e.g., single dose or repeat dose), AEs, and time to beginning of symptom relief, improvement of symptoms within 24 hours after the treatment of an attack, and reduction in pain and swelling.
Multiple queries will occur when necessary to gather complete patient information. At least three follow-up attempts over a period of at least three months will be conducted using a variety of modalities.

- **Study Population:** The study population will be males and females, 13 years of age and older who have a current diagnosis of HAE and are being treated with rhC1INH. Patients who are treated with pdC1INH for their HAE attacks are not eligible for enrollment; HAE medications taken with rhC1INH will be allowed and recorded.
  The study will continue until either a) three years have elapsed, or b) 100 patients have enrolled, 35 of whom will be treated with rhC1INH for at least three attacks. If a patient becomes pregnant while being treated with rhC1INH, the woman will be required to meet with her health care provider to determine the benefits and risks potentially associated with continued treatment with rhC1INH during the pregnancy. Approval from her HCP will be required for her to continue her participation in the registry.
- **Test Product, Dose, and Mode of Administration:** Dosing of rhC1INH is 50 IU/kg (for body weight < 84 kg; 4,200 IU for ≥ 84 kg). The rhC1INH is provided as a lyophilized powder for reconstitution for injection in a 25 mL Type 1 glass vial. Each vial (2,100 IU) of rhC1INH is reconstituted by adding 14 mL sterile water for injection per vial to obtain a solution of 150 IU/mL. If the patient prefers to self-administer the drug, s/he will be trained by the HCP and instructed to begin self-administration immediately upon recognition of symptoms of an HAE attack.
- **Duration of Treatment:** The recommended dose of rhC1INH is 50 IU/kg, with a maximum of 4,200 IU, to be administered as a slow intravenous injection over approximately 5 minutes. In the majority of cases, a single dose of rhC1INH is sufficient to treat an acute angioedema attack. However, in case of an insufficient clinical response, an additional (second) dose can be administered at the recommended dose level for the patient's body weight. No more than two doses should be administered within a 24-hour period.
- **Efficacy Assessments:** Patient data will be collected on time to beginning of symptom relief, improvement of symptoms within 24 hours after treatment of an attack, and reduction in pain and swelling.
- **Safety Assessments:** Patient data will be collected on all serious adverse events experienced during and after treatment with rhC1INH for up to 30 days following their last treatment with rhC1INH. For adverse events of special interest (i.e., hypersensitivity,TEE), a data capture aid will be used to collect additional data to characterize the event and patient attributes at the time of the event. For women who are pregnant, a data capture aid will be used to collect additional data about the pregnancy, pregnancy outcome, and prior pregnancy history. Patient data for pregnant women will be collected until the outcome of the pregnancy is known. For women who are nursing, a data capture aid will be used to collect additional data on the approximate quantity of the breast milk, breast feeding difficulties, and any adverse events reported in the nursing infant. Patient data for nursing women will be collected until nursing ends.
- **Statistical Methods:** Safety and efficacy data will be summarized by descriptive statistics. Descriptive statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum value; categorical variables will be presented as counts and percentages. Data from the US Ruconest (rhC1INH) Patient Registry will be combined with its European HAE registry counterpart (Pharming Group NV, Protocol # C1 1412) which has proposed to enroll 300 patients treated with rhC1INH and an unrestricted number of patients treated with pdC1INH for a three year duration. As part of routine pharmacovigilance, benefit-risk evaluations will be performed annually or more

frequently when new identified risks are recognized. An integrated benefit-risk assessment will be conducted.

3.5.4.2 Data Capture Aids

- Used to collect supplemental data on spontaneous or literature-identified AEs associated with
  - Immunologic events
  - Thromboembolic events
  - Pregnant or nursing women in the US
- Will identify specified MedDRA terms in AE reports, then intake professional will solicit additional information using the Data Capture Aid for that AE or patient category
- All data collected by Data Capture Aids will be analyzed in the signal detection program as part of routine pharmacovigilance.
- Below is a list of MedDRA preferred terms that the Sponsor has proposed to use to capture AE cases in the first two categories above.

Table 3. Comprehensive List of MedDRA preferred terms

Events of Interest	MedDRA Preferred Terms	
Allergic reactions	HYPERSENSITIVITY PRURITIS RASH RASH PRURITIC RASH GENERALIZED RASH MACULAR	RASH PAPULAR DRUG ERUPTION EYE PRURITIS ALLERGIC COUGH ALLERGIC OEDEMA
Anaphylaxis	ANAPHYLACTIC REACTION ANAPHYLACTIC SHOCK ANAPHYLACTOID SHOCK FLUSHING	PALLOR SKIN WARM FEELING HOT
Shock	CARDIOGENIC SHOCK SENSATION OF FOREIGN BODY COLD SWEAT CYANOSIS SYNCOPE LOSS OF CONSCIOUSNESS	PULSE PRESSURE DECREASED HEART RATE INCREASED DIZZINESS PRESYNCOPE HYPOTENSION URINE OUTPUT DECREASED
Respiratory distress or difficulty breathing	GRUNTING NASAL FLARING CYANOSIS USE OF ACCESSORY RESPIRATORY MUSCLES RESPIRATORY RATE INCREASED	CARDIO-RESPIRATORY DISTRESS DYSPNOEA HYPONOEA PULMONARY OEDEMA NASAL OEDEMA
Angioedema	OEDEMA OEDEMA PERIPHERAL CONJUNCTIVAL OEDEMA	EYELID OEDEMA LIP OEDEMA FACE OEDEMA
Inspiratory stridor	LARYNGEAL OBSTRUCTION LARYNGEAL OEDEMA PHARYNGEAL OEDEMA	TONGUE OEDEMA PALATAL OEDEMA
Bilateral wheezing	ASTHMA BREATH SOUNDS ABNORMAL	
Urticaria	PRURITIS ALLERGIC DERMATITIS ALLERGIC	RASH PAPULAR
Serum sickness	TYPE III HYPERSENSITIVITY FEVER MALAISE SPLENOMEGALY LYMPHADENOPATHY PROTEINURIA	HAEMATURIA LEUKOCYTOCLASTIC VASCULITIS DIFFUSE VASCULITIS VASCULITIS RENAL FAILURE ACUTE RENAL FAILURE RENAL IMPAIRMENT
Delayed hypersensitivity reactions	TYPE IV HYPERSENSITIVITY CONTACT DERMATITIS	ECZEMA RASH PAPULAR
Thrombosis, including deep venous thrombosis	THROMBOPHLEBITIS PHLEBITIS VENOUS THROMBOSIS	SPINAL CORD INFARCTION SPINAL CORD ISCHEMIA ISCHEMIA

Events of Interest	MedDRA Preferred Terms	
	ARTERIAL THROMBOSIS CAROTID ARTERY THROMBOSIS INTRACARDIAC THROMBOSIS	PULMONARY HYPERTENSION CORONARY ARTERY THROMBOSIS
Pulmonary embolism	PLEURITIC PAIN PLEURISY HAEMOPTYSIS HYPOXIA RESPIRATORY RATE INCREASED	HEART RATE INCREASED CIRCULATORY COLLAPSE RESPIRATORY ARREST SUDDEN DEATH
Ischemic colitis	GASTROINTESTINAL ISCHEMIA INTESTINAL ISCHEMIA ABDOMINAL PAIN HAEMATOCHEZIA	DEFECATION URGENCY GASTROINTESTINAL HAEMORRHAGE DIARRHOEA HAEMORRHAGIC
Myocardial infarction	MYOCARDIAL ISCHEMIA CORONARY ARTERY THROMBOSIS ANGINA UNSTABLE CHEST PAIN	PAIN IN JAW HEART RATE IRREGULAR COLD SWEAT
Stroke	EMBOLIC STROKE CEREBRAL INFARCTION BRAIN STEM INFARCTION BRAINSTEM ISCHEMIA EMBOLIC CEREBRAL INFARCTON BASAL GANGLIA INFARCTION CEREBELLAR ISCHEMIA BLINDNESS UNILATERIAL SUDDEN VISUAL LOSS VIITH NERVE PARALYSIS	PARALYSIS MONOPLEGIA HEMIPARESIS GAIT DYSTURBANCE DIPLOPIA MENTAL IMPAIRMENT APHASIA LOSS OF CONSCIOUSNESS CONVULSION
Transient ischemic attack	BLINDNESS TRANSIENT HYPOAESTHESIA MUSCULAR WEAKNESS VIITH NERVE PARALYSIS	GAIT DISTURBANCE DIPLOPIA MENTAL IMPAIRMENT APHASIA
Cerebrovascular accidents (excluding device-related thrombosis)	EMBOLISM EMBOLISM ARTERIAL EMBOLISM VENOUS *See also Preferred Terms for STROKE*	

3.5.4.3 Enhanced Expedited SAE Reporting

- The Sponsor will provide FDA with 15-day expedited reports of all SAEs that are related to the identified or potential risks, regardless of event expectedness (i.e., both unexpected AND expected).

3.6 Action Plan for Safety Issues

Table 4. Pharmacovigilance Action Plan for Ruconest™

Important Identified Risks	Planned Pharmacovigilance Actions
Type I hypersensitivity reaction due to pre-existing IgE antibodies against host-related impurities (HRI).	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry • Risk Minimization Activities **USPI Contraindication in patients with a history of allergy to rabbits or rabbit-derived products **USPI Warnings and Precautions statement advising patients be closely monitored for hypersensitivity reactions throughout the administration period, with epinephrine available to treat any severe hypersensitivity reactions

Important Identified Risks	Planned Pharmacovigilance Actions
Type I hypersensitivity reaction due to the formation of IgE antibodies against HRI	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry
Type III hypersensitivity reaction due to the formation of antibodies against C1INH or HRI	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry
Acquired angioedema due to the formation of neutralizing antibodies against C1INH	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry
Thromboembolic complications	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry
Important Missing Information	**Planned Pharmacovigilance Actions**
Data on pregnant or nursing women	• Routine Pharmacovigilance • Signal Detection • Benefit-Risk Evaluation • Enhanced Safety Surveillance **Data Capture Aids **US HAE Registry
Data on younger children (<13 years of age); This application is for an indication of rhC1INH in adolescents and adults. However, safety data among children can be considered Important Missing Information in more comprehensive pharmacovigilance of this product	• Pediatric Investigation Plan (EU) ** Study 1209 of the pharmacokinetics/pharmacodynamics, safety, tolerability, immunogenicity and efficacy of rhC1INH for the treatment of acute HAE attacks among children 2−13 years of age (see Section 3.2.1.3.4)

4 REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

4.1 Clinical Review Memo

According to the draft clinical review memo, the following primary issues of concern were noted with this BLA. The results of the three efficacy studies, Study 1205 RCT, Study 1304 RCT, and Study 1310 RCT were not consistent with one another; a clinical dose effect was not demonstrated in Study 1205, and Study 1310 did not demonstrate clinical efficacy in female patients and in US patients. It was believed that the absence of numerical superiority for rhC1INH compared to saline in Study 1310 RCT for the primary efficacy endpoint in female patients and in patients enrolled in the US may be explained by differences in the time from attack onset until evaluation at the study center between patients in the US versus patients in the rest of the world. The OBRR clinical reviewer is recommending that prior to licensure the Sponsor conduct an additional clinical trial at US sites that is balanced for gender and demonstrates a clinical dose effect.

5 POSTLICENSURE SAFETY REVEIW

Ruconest is currently marketed in the EU. Throughout the reporting period (October 28, 2010 – April 28, 2013), (b)(4) vials of Ruconest were distributed in 16 countries. No spontaneous Adverse Drug Reaction reports were received from any sources during this reporting period. Four spontaneous case reports were received. No SAEs were associated with any of these case reports.

- One case report concerned an underdose of Ruconest: the patient received 2,100 IU of Ruconest for treatment of an abdominal and leg angioedema attack; per the Summary of Product Characteristics of Ruconest, the (53kg) patient should have received 2,650 IU, based on administration of 50 IU/kg for patients <84 kg.
- Two case reports concerned off-label use:
    - A 48-year old female patient with HAE used Ruconest (2,100 IU, three times per week) for prophylaxis of HAE attacks and experienced nausea, abdominal pain, headache, and difficulty sleeping. She experienced two breakthrough angioedema attacks during Ruconest therapy. Ruconest therapy was discontinued, but the symptoms remained ongoing.
    - A female patient used Ruconest (age and dose not reported) for prophylaxis of HAE attacks.
- One case report concerned a pregnancy: a female patient, age 21 years, received eight administrations of Ruconest 2,100 IU for face and neck swelling beginning in the 19th week of pregnancy. The outcome of the pregnancy was a full-term, live birth of a healthy male infant.

A post-approval HAE Registry is currently being conducted in the EU. In brief, the study design is a non-interventional treatment registry of HAE patients in the EU treated with a C1 esterase inhibitor, either pdC1INH or rhC1INH. As of February 21, 2013, 36 patients with HAE were screened, and four of these patients received 12 rhC1INH treatments. The Registry will remain open until the target number of 300 patients in the rhC1INH arm is reached, consisting of 100 patients followed up for at least three exposures to rhC1INH each.

6 INTEGRATED RISK ASSESSMENT

Based on the review of the pre-licensure safety data, the Sponsor's proposed pharmacovigilance plan, and the postmarketing safety reports from outside the US, at the time of this review, the OBE/DE reviewer has not identified any new safety concern that would warrant a REMS or a PMR study.

Important safety issues identified in the clinical studies by either the Sponsor or the FDA include the following:

- Type I Hypersensitivity Reaction Due to Pre-Existing IgE Antibodies Reacting With HRI
- Type I Hypersensitivity Reaction Due to Formation of IgE Antibodies Reacting With HRI
- Type III Hypersensitivity Reaction Due to Formation of Antibodies Against C1INH or HRI
- Induction of Acquired Angioedema Due to Formation of Neutralizing Antibodies Against C1INH
- Thromboembolic Complications
- Missing Information on Pregnant or Nursing Women
- Missing Information on Younger Children

Hypersensitivity reactions are plausible risks with receipt of rhC1INH. Among the 24 study subjects with pre-existing IgE antibodies, only three (12.5%) experienced allergic basis AEs: one healthy volunteer subject with a previously undisclosed rabbit allergy who experienced an anaphylactic reaction; one healthy volunteer subject with a rabbit allergy who experienced flu-like symptoms three days after receipt of a second rhC1INH dose; and one asymptomatic HAE patient with a cat allergy who experienced conjunctivitis and rhinitis three days after rhC1INH, but also soon after cat exposure and the symptoms were attributed to the cat exposure. Because of the potential (albeit rare) for hypersensitivity reactions to rhC1INH among those with pre-sensitization to rabbit allergens, foreign labeling for Ruconest includes contraindications, special warnings and precautions for those with known or suspected rabbit allergy or hypersensitivity to any component of the product.

Although the clinical studies for rhC1INH were relatively small (total n=236 who received rhC1INH), no TEE were reported. Indices measuring fibrinolysis and coagulation indicated activation of both processes by the ongoing acute HAE attack, as opposed to activation by receipt of rhC1INH. The nonclinical animal toxicology studies of rhC1INH also did not show an increased risk for thromboembolism. However, postmarketing reports of TEE after pdC1INH were the impetus for a May 2010 FDAAA Section 921 posting of a potential signal of serious risk of "thromboembolic events in patients with certain thrombogenic risk factors" after receipt of pdC1INH. In all eight case reports, there were alternative explanations for the reported TEE, such as known coagulation disorders, pregnancy, or cardiac septal defect. As a result, the Warnings and Precautions and Adverse Reactions sections of the labels for the two US licensed pdC1INH products, Berinert and Cinryze (labeling approved December 22, 2011 and January 9, 2012, respectively) were updated with additional information about TEE, including a statement that thrombotic events have been reported in patients who received pdC1INH. In order to further evaluate this possible "class effect" (i.e., increased risk of TEE) in rhC1INH recipients, enhanced surveillance to carefully monitor for TEE and other potential SAEs is planned.

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending the final clinical, statistical and product reviews. If any further safety concerns are identified, FDA may recommend further modification of the pharmacovigilance activities.

7 RECOMMENDATIONS

Based on the review of the pre-licensure safety data, the sponsor's proposed pharmacovigilance plan, and the post-marketing safety reports from outside the US, OBE/DE agrees with the Risk Management Plan as proposed by the Sponsor with the following actions for post-licensure safety surveillance activities of Ruconest:

- Routine pharmacovigilance
    - Adverse event reporting in accordance with 21 CFR 600.80
    - 15-day expedited reporting of all unexpected SAEs in the first three years after licensure, per 21 CFR 600.80 (c)(1)(i)
    - Quarterly signal detection analyses
    - Annual Benefit-Risk Evaluation
- Enhanced surveillance
    - 15-day expedited reporting of all SAEs related to the identified or potential risks of rhC1INH, regardless of event expectedness (i.e., both unexpected AND expected), in the first three years after licensure, per 21 CFR 600.80 (c)(1)(i)
    - Implementation of the US HAE Registry as a post-marketing commitment (PMC), according to the following schedule:
        - Registry Protocol Submission Date: January 16, 2015 (6 months from product licensure date)
        - Study Completion: July 16, 2018 (6 months for study start + 3 years duration from study start)
        - Final Study Report: January 16, 2019 (6 months from last patient, last visit)

      [Pharming agreed to this PMC and timeline in writing on July 15, 2014.]
    - Use of Data Capture Aids for AEs associated with immunologic responses, TE complications and those among pregnant or nursing women
    - Signal detection to identify cases with identified or potential risks of rhC1INH that Data Capture Aids can then be applied to; Please include the following MedDRA preferred terms (PTs) among the search terms used in this signal detection:

HYPERSENSITIVITY OR ALLERGIC REACTIONS	THROMBOEMBOLIC COMPLICATIONS
o Hypersensitivity o Serum sickness o Type I hypersensitivity o Type III immune complex mediated reaction o Anaphylactic reaction o Anaphylactic shock o Anaphylactoid reaction o Anaphylactoid shock o Angioedema o Urticaria o Bronchospasm o Wheezing	o Embolism o Embolism, venous o Thrombosis o Venous thrombosis o Deep vein thrombosis o Pulmonary embolism o Pulmonary thrombosis o Cerebrovascular accident o Colitis, ischaemic o Acute myocardial infarction o Angina pectoris o Angina, unstable o Myocardial infarction o Myocardial ischaemia o Embolic stroke o Ischaemic stroke o Transient ischaemic attack

- o Appendix 1 provides a more comprehensive list of MedDRA PTs that can be used to identify cases with the identified or potential risks of rhC1INH, as well as complications during pregnancy or breastfeeding. It is assumed that all listed PTs can be linked to their corresponding High Level Terms (HLTs), High Level Group Terms (HLGTs) and System Organ Class (SOC) terms, as well as corresponding Lowest Level Terms (LLTs). This list is an example that can be used at the Sponsor's discretion.

- As part of the product label, USPI Contraindication in patients with a history of allergy to rabbits or rabbit-derived products, with a Warnings and Precautions statement advising patients with such allergies be monitored closely for hypersensitivity reactions throughout rhC1INH administration, with epinephrine available to treat any severe hypersensitivity reactions.
- Regular (biannual) updates to pediatric Study 1209

The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS).

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Appendix 1. Relevant MedDRA or Non-MedDRA Verbatim Terms to Identified or Potential Risks of rhC1INH		
HYPERSENSITIVITY REACTIONS	**THROMBOEMBOLIC COMPLICATIONS**	**PREGNANCY OR NURSING WOMEN**
SOC: IMMUNE SYSTEM DISORDERS HLGT: Allergic conditions • HLT: Allergic conditions NEC o PT: Allergic bronchitis o PT: Allergic cough o PT: Allergic respiratory symptom o PT: Alveolitis, allergic o PT: Asthma o PT: Blepharitis, allergic o **PT: Bronchospasm** o PT: Dermatitis, allergic o PT: Erythema multiforme o PT: Eye allergy o **PT: Hypersensitivity** o PT: Immediate post-injection reaction o PT: Infusion site hypersensitivity o PT: Injection site hypersensitivity o PT: Laryngitis, allergic o PT: Multiple allergies o PT: Pruritis, allergic o PT: Reactive airways dysfunction syndrome o **PT: Serum sickness** o PT: Serum sickness-like reaction o PT: Skin reaction o PT: Stevens-Johnson syndrome o **PT: Type I hypersensitivity** o **PT: Type III immune complex mediated reaction** • HLT: Allergies to foods, food additives, drugs and other chemicals o PT: Administration related reaction o PT: Allergic colitis o PT: Drug eruption o PT: Drug hypersensitivity o PT: Drug reaction with eosinophilia and systemic symptoms o PT: Infusion related reaction o PT: Reaction to drug excipients o PT: Toxic Epidermal Necrolysis o PT: Toxic skin eruption • HLT: Anaphylactic responses o **PT: Anaphylactic reaction** o **PT: Anaphylactic shock** o **PT: Anaphylactoid reaction** o **PT: Anaphylactoid shock** o PT: First use syndrome • HLT: Angioedemas o **PT: Angioedema**	SOC: VASCULAR DISORDERS HLGT: Embolism and Thrombosis • HLT: Aortic embolism and thrombosis o PT: Aortic embolus o PT: Aortic thrombosis • HLT: Cerebrovascular embolism and thrombosis o All PTs in this category • HLT: Gastrointestinal embolism and thrombosis o All PTs in this category • HLT: Hepatic and portal embolism and thrombosis o PT: Hepatic artery embolism o PT: Hepatic artery thrombosis o PT: Hepatic vein thrombosis o PT: Portal vein thrombosis o PT: Splenic vein thrombosis • HLT: Non-site specific embolism and thrombosis o PT: Arterial thrombosis o PT: Disseminated intravascular coagulation o **PT: Embolism** o PT: Embolism, arterial o **PT: Embolism, venous** o PT: Microembolism o PT: Thrombophlebitis migrans o **PT: Thrombosis** o PT: Thrombotic microangiopathy o **PT: Venous thrombosis** • HLT: Peripheral embolism and thrombosis o PT: Axillary vein thrombosis o **PT: Deep vein thrombosis** o PT: Femoral artery embolism o PT: Iliac artery embolism o PT: Infusion site thrombosis o PT: Injection site thrombosis o PT: Jugular vein thrombosis o PT: Pelvic venous thrombosis o PT: Penile vein thrombosis o PT: Peripheral artery thrombosis o PT: Peripheral embolism o PT: Spinal artery embolism o PT: Subclavian artery embolism o PT: Subclavian artery thrombosis o PT: Subclavian vein thrombosis o PT: Thrombophlebitis o PT: Venous thrombosis, limb • HLT: Pulmonary embolism and thrombosis o PT: Pulmonary artery thrombosis o **PT: Pulmonary embolism** o PT: Pulmonary microemboli	SOC: PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS HLGTs: • Abortion and still birth • Foetal complications • Maternal complications of labour and delivery • Neonatal perinatal conditions • Placental, amniotic and cavity disorders (excl haemorrhages) • Postpartum and puerperal disorders Verbatim terms for pregnant women (non-MedDRA): • Pregnancy, labour, delivery and postpartum conditions Verbatim terms for lactation (non-MedDRA): • Lactation • Breastfeed • Nurse • Production or secretion of milk • Wet nurse • Suckle • Colostrum

Appendix 1. Relevant MedDRA or Non-MedDRA Verbatim Terms to Identified or Potential Risks of rhC1INH		
HYPERSENSITIVITY REACTIONS	**THROMBOEMBOLIC COMPLICATIONS**	**PREGNANCY OR NURSING WOMEN**
o PT: Circumoral oedema o PT: Eyelid oedema o PT: Face oedema o PT: Hereditary angioedema o PT: Idiopathic angioedema o PT: Laryngeal oedema o PT: Lip oedema o PT: Lip swelling o PT: Oculorespiratory syndrome o PT: Oedema, mouth o PT: Oropharyngeal swelling o PT: Periorbital oedema o PT: Pharyngeal oedema o PT: Small bowel angioedema o PT: Swelling face o PT: Swollen tongue o PT: Tongue edema • HLT: Atopic disorders o PT: Atopic keratoconjunctivitis o PT: Atopy o PT: Conjunctivitis, allergic o PT: Dermatitis, atopic o PT: Rhinitis, allergic • HLT: Urticarias o PT: Diffuse cutaneous mastocytosis o PT: Haemorrhagic urticaria o PT: Idiopathic urticaria o PT: Infusion site urticaria o PT: Injection site urticaria o **PT: Urticaria** o PT: Urticaria, papular o PT: Urticaria, physical SOC: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS HLGT: Bronchial disorders (excl neoplasms) • HLT: Bronchospasm and obstruction o PT: Asthma o PT: Asthmatic crisis o PT: Bronchial hyperreactivity o **PT: Bronchospasm** o PT: Reactive airways dysfunction syndrome o PT: Status asthmaticus o **PT: Wheezing** HLGT: Upper respiratory tract disorders (excl infections) • HLT: Laryngeal spasm, oedema and obstruction o PT: Laryngeal oedema o PT: Laryngospasm o PT: Laryngotracheal oedema o PT: Stridor • HLT: Pharyngeal disorders	o **PT: Pulmonary thrombosis** o PT: Pulmonary veno-occlusive disease o PT: Pulmonary venous thrombosis • HLT: Renal embolism and thrombosis o All PTs in this category • HLT: Retinal embolism and thrombosis o All PTs in this category • HLT: Site specific embolism and thrombosis NEC o PT: Arterial thrombosis o PT: Coronary artery embolism o PT: Coronary artery thrombosis o PT: Intracardiac thrombus o PT: Ovarian vein thrombosis • HLT: Vena caval embolism and thrombosis o All PTs in this category HLGT: Vascular disorders NEC • HLT: Cerebrovascular and spinal vascular disorders NEC o **PT: Cerebrovascular accident** o PT: Stroke in evolution • HLT: Non-site specific vascular disorders NEC o PT: Venoocclusive disease HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis • HLT: Gastrointestinal necrosis and vascular insufficiency o **PT: Colitis, ischaemic** SOC: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS HLGT: Pulmonary vascular disorders • HLT: Pulmonary thrombotic and embolic conditions o PT: Pulmonary artery thrombosis o PT: Pulmonary embolism o PT: Pulmonary infarction o PT: Pulmonary microemboli o PT: Pulmonary thrombosis o PT: Pulmonary venous thrombosis • HLT: Vascular pulmonary disorders NEC o PT: Pulmonary vein occlusion o PT: Pulmonary veno-occlusive disease SOC: CARDIAC DISORDERS HLGT: Coronary artery disorders • HLT: Coronary artery disorders NEC o PT: Coronary artery embolism o PT: Coronary artery occlusion o PT: Coronary artery thrombosis • HLT: Ischaemic coronary artery disorders o PT: Acute coronary syndrome o **PT: Acute myocardial infarction** o **PT: Angina pectoris**	

Appendix 1. Relevant MedDRA or Non-MedDRA Verbatim Terms to Identified or Potential Risks of rhC1INH		
HYPERSENSITIVITY REACTIONS	**THROMBOEMBOLIC COMPLICATIONS**	**PREGNANCY OR NURSING WOMEN**
o PT: Oropharyngeal spasm o PT: Oropharyngeal swelling o PT: Pharyngeal oedema	o **PT: Angina unstable** o PT: Chest discomfort o PT: Chest pain o **PT: Myocardial infarction** o **PT: Myocardial ischaemia** o PT: Papillary muscle infarction o PT: Postinfarction angina o **PT: Silent myocardial infarction** SOC: NERVOUS SYSTEM DISORDERS HLGT: Central nervous system vascular disorders • HLT: Central nervous system haemorrhages and cerebrovascular accidents o PT: Basal ganglia infarction o PT: Basal ganglia stroke o PT: Basilar artery occlusion o PT: Basilar artery thrombosis o PT: Brain stem infarction o PT: Brain stem ischaemia o PT: Brain stem stroke o PT: Brain stem thrombosis o PT: Carotid arterial embolus o PT: Carotid artery occlusion o PT: Carotid artery thrombosis o PT: Cerebellar artery occlusion o PT: Cerebellar artery thrombosis o PT: Cerebellar embolism o PT: Cebebellar infarction o PT: Cerebral ischaemia o PT: Cerebral thrombosis o **PT: Cerebrovascular accident** o PT: Embolic cerebral infarction o **PT: Embolic stroke** o **PT: Ischaemic stroke** o PT: Lacunar infarction o PT: Pituitary infarction o PT: Precerebral artery occlusion o PT: Stroke in evolution o PT: Thalamic infarction o PT: Thrombotic cerebral infarction o PT: Thrombotic stroke o PT: Vertebral artery occlusion o PT: Vertebral artery thrombosis • HLT: Cerebrovascular venous and sinus thrombosis o All PTs in this category • HLT: Transient cerebrovascular events o **PT: Transient ischaemic attack**	