Application Type	Original BLA
STN	BL 125495/0
CBER Received Date	April 16, 2013
PDUFA Goal Date	July 16, 2014
Division / Office	OBRR
Committee Chair	Elena Karnaukhova OBRR/DH/LPD
Clinical Reviewer(s)	Charles W Maplethorpe
Project Manager	Nannette Cagungun FDA/CBER/OBRR/DBA/RPMB
Priority Review	Standard Review
Reviewer Name(s)	Yuqun Abigail Luo
Review Completion Date / Stamped Date	May 16, 2014
Supervisory Concurrence	Boguang Zhen, PhD Branch Chief, FDA/CBER/OBE/DB/TEB Estelle Russek-Cohen, PhD Director, FDA/CBER/OBE/DB
Applicant	Pharming Group NV
Established Name	C1 Esterase Inhibitor (Recombinant)
(Proposed) Trade Name	Ruconest
Pharmacologic Class	ATC Code: B06AC04
Formulation(s), including Adjuvants, etc	<No Formulations>
Dosage Form(s) and Route(s) of Administration	2100 IU lyophilized powder for reconstitution for intravenous injection in a single use vial
Dosing Regimen	50 IU/kg for up to 84kg, 4200 IU for > 84kg, for a single HAE attack
Indication(s) and Intended Population(s)	Treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients

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GLOSSARY

BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CSR	Clinical study report
EIA	Efficacy Information Amendment
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAE	Hereditary Angioedema
HRI	Host-related impurities
HV	Healthy volunteer
IV	Intravenous
IS	Investigator Score (or Investigator Symptom Score)
ITT	Intent-to-Treat
MID	Minimally important difference
mITT	Modified Intent-to-Treat
OLE	Open Label Extension
OPL	Oropharyngeal-laryngeal
OSV	Overall Severity VAS score
PD	Pharmacodynamic
pdC1INH	Plasma derived human C1 esterase inhibitor
PK	Pharmacokinetic
PP	Per protocol
PRO	Patient Reported Outcome
RCT	Randomized, controlled trial
rhC1INH	Recombinant human C1 esterase inhibitor
ROW	Rest of World
RTF	Refused to File
SAP	Statistical Analysis Plan
TEQ	Treatment Effects Questionnaire
VAS	Visual Analog Scale

1. EXECUTIVE SUMMARY

Original BLA 125495/0 proposed the treatment of acute angioedema attacks in subjects with hereditary angioedema (HAE) with a single dose of 50 IU/kg of C1 Esterase Inhibitor (Recombinant), purified from the milk of transgenic rabbits, abbreviated as rhC1INH.

The supporting clinical database comprised eight clinical studies. Three of these studies, studies 1205, 1304, and 1310, each contained both an RCT and an OLE component. The RCT components were randomized, double-blind, and saline-controlled, treating single acute attacks in HAE subjects. The OLE components were uncontrolled open label extensions treating additional subsequent attacks. Study 1310 was conducted in US and Europe. Study 1205 was conducted in US and Canada. Study 1304 and all other studies were conducted in Europe.

Of the three RCT studies, study 1310RCT was considered the sole confirmatory study to support efficacy claims for the proposed indication. Studies 1205 and 1304, including the RCT components, were considered exploratory. Study 1205RCT was initially designed as an exploratory Phase 2 study to primarily evaluate safety; its statistical analysis plan was developed and finalized after study outcome became available. Study 1304RCT was conducted in Europe with 81% of subjects from sites at Italy, and the rhC1INH dose was 100 IU/kg, twice the dose proposed in the application. Therefore, the RCT component of study 1310 was selected for statistical review of the efficacy claims, and will be referred to simply as study 1310 in what follows. The protocol of study 1310 received FDA concurrence under special protocol assessment.

Study 1310 randomized 75 HAE subjects reporting with eligible acute attacks, at a 3:2 ratio, stratified by gender and the anatomical location of the angioedema attack, to receive 50 IU/kg rhC1INH or saline in a double-blind manner to treat the acute attacks. The study aimed to ensure roughly 50% of the subjects treated were from US. The primary efficacy endpoint was the time to beginning of relief of symptoms with persistence at the primary attack location, based on the Treatment Effect Questionnaire (TEQ), a patient reported outcome.

The primary efficacy endpoint was significantly shorter in the rhC1INH arm compared to the saline arm, with a median of 90 minutes versus 152 minutes, and a p-value of 0.031 from the pre-specified primary analysis of log-rank test stratified by the primary attack location.

The full safety database contained 236 subjects, including healthy volunteers (HV), asymptomatic HAE subjects, and HAE subjects experiencing acute attacks, exposed to a total of 940 administrations of rhC1INH at various doses, single or repeated. The rhC1INH 50 IU/kg single dose or 50 IU/kg single dose plus additional doses, the proposed rhC1INH dose in the application, were given to 145 subjects for 393 attacks.

One death was reported for a Romania HAE subject under rhC1INH prophylaxis treatment in study 1207, after experiencing a fatal laryngeal angioedema attack 25 days after the final dose of rhC1INH. This subject received eight weekly slow intravenous (iv) injections of rhC1INH 50 IU/kg. Two nonfatal serious adverse events (SAE) were assessed as probably or possibly related to rhC1INH. One HV subject in study 1106 experienced severe allergic reaction commencing three minutes after start of iv injection of rhC1INH. This subject had previously-undisclosed history of allergy to rabbit dander/hair. One HAE subject receiving a single dose of 50 IU/kg rhC1INH in study 1205OLE experienced hypersensitivity. The

remaining nonfatal SAEs were assessed as "unlikely", "definitely not", or "not related" in their relationship to study drug by the applicant.

Findings in subgroup efficacy analysis in study 1310 received further statistical consideration. Among the planned analyses for the primary efficacy endpoint, numerically similar response times between the rhC1INH arm and the saline arm were observed in two subgroups, female subjects and US subjects. Specifically, for female subjects, the median times to beginning of relief were 112.5 and 105.0 minutes in the rhC11INH and in the saline arm, respectively. For US subjects, the median times were 97.5 and 90.0 minutes in the rhC1INH versus the saline arm, respectively. The observed result in the female subgroup was confounded with that in the US subgroup due to chance imbalance in treatment group assignments when the two factors, gender (male versus female) and geographical region (US versus Rest of the World (ROW)), were considered together. Specifically, 11 out of the 22 US subjects assigned to the rhC1INH arm were females, while 14 out of the 16 US subjects assigned to the saline arm were females. Partly due to this chance imbalance, we focus further consideration of the subgroup analysis on the US subjects only.

The observed similarity in response times between the two arms in US subjects may reflect Type II error or confounding factors not considered in the study design, or it may reflect genuine lack of efficacy in the US subjects. It was not possible to discriminate between these two potential explanations with statistical reasoning based on the available data within the study, because the study was not powered for any subgroup analysis and the study size was small. Clinical judgment is required to assess which one of the two potential explanations is more plausible.

The applicant had submitted various post-hoc analyses to explore the role of potential confounding factors in explaining the results in the US subjects and to explore re-analysis of the data, including attack severity at baseline and rescue medication usage, among others. Statistical reasoning is of limited value due to the post-hoc nature of these additional analyses. Clinical judgment is required to assess the interpretation of these additional analyses.

Overall the sole confirmatory study showed statistically significant reduction in time to beginning of relief of symptoms with persistence, from a median of 152 minutes in the saline arm to 90 minutes in the rhC1INH arm (p=0.031). Approximately half of the subjects were treated at US sites. These subjects showed similar time to beginning of relief in the two arms, with a median of 97.5 minutes in the rhC1INH arm and of 90 minutes in the saline arm. The degree of concern over this observation and the likelihood that this observation reflects Type II errors instead of genuine lack of efficacy in the US subjects cannot be assessed statistically with available data and thus rely heavily on clinical judgment.

2. CLINICAL AND REGULATORY BACKGROUND

Ruconest® contains, as the active substance, recombinant human complement component 1 (C1) esterase inhibitor (C1INH), purified from the milk of transgenic rabbits expressing the gene encoding for human C1INH. Ruconest is supplied as a sterile, preservative-free, white/off-white lyophilized powder for reconstitution for injection. One IU of rhC1INH activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 mL of

pooled normal plasma. The International Nonproprietary Name is conestat alfa. Ruconest is also referred to as rhC1INH in what follows.

The proposed indication in this BLA for Ruconest is treatment for acute attacks of angioedema in subjects with hereditary angioedema (HAE). The proposed dose of rhC1INH is 50 IU/kg for subjects <84 kg and 4200 IU for subjects ≥84 kg, with an option for a second administration of the same dose in case of an insufficient clinical response.

2.1 Disease or Health-Related Condition(s) Studied

HAE is a rare, serious, autosomal-dominant genetic disorder with an estimated prevalence of one in 50,000. Clinically, HAE patient experience recurrent acute attacks of soft tissue swelling that can affect multiple anatomical regions, including the gastrointestinal tract, facial tissues, vocal cords and larynx, oropharynx, urogenital region, and/or the arms and legs.

HAE patient have an insufficient plasma concentration of functional C1INH. 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. The normal range of C1INH activity in the general population is 0.7 to 1.3 IU/mL (70% to 130% activity). The median plasma level of C1INH activity in HAE patient is approximately 0.2 IU/mL, or approximately 20% of the normal amount.

Most angioedema attacks occur at a single anatomical location, but 10% to 15% of attacks occur at multiple locations. Acute angioedema attacks that compromise the upper airway (laryngeal attacks), with an estimated frequency of <1% of all attacks, are the most clinically serious,

In the natural course of untreated acute angioedema attacks in HAE patients, the time to maximal symptoms and time to resolution vary by anatomical location. Peripheral edema can have a slower onset and can take longer to resolve as compared to swelling of submucosal tissue, both in untreated and plasma derived C1INH (pdC1INH) treated patients.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

In the US, currently available medications for HAE include the pdC1INH products Cinryze®, for routine prophylaxis against angioedema attacks, and Berinert®, for treatment of acute angioedema attacks. In addition to the pdC1INH products, two non-blood-derived drugs were recently approved by FDA for treatment of acute angioedema attacks: recombinant ecallantide (Kalbitor®), a kallikrein inhibitor, and icatibant (Firazyr®), a bradykinin receptor antagonist.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Ruconest was evaluated in eight clinical studies to characterize its safety, efficacy, immunogenicity, and pharmacokinetic/pharmacodynamic (PK/PD). On October 28, 2010, Ruconest® was granted marketing authorization in the European Union. It may be administered in an acute care setting by a trained health care professional, or it may be self-administered by patients who have been trained in proper administration procedures.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

A summary of the regulatory history related to this submission is given below.

- Orphan Designation was granted for Ruconest for the treatment of acute attacks of angioedema on February 23, 1999. Fast Track Designation was granted by Center for Drug Evaluation and Research (CDER) in July 2006.

- On October 28, 2010, European Commission granted marketing authorization to Ruconest for treatment of acute attacks caused by HAE, based on interim analyses outcomes of a Phase 3 study (study 1304) conducted in Europe and a Phase 2 study (study 1205) conducted in North America.

- On December 13, 2010, the applicant filed an original BLA, BL --(b)(4)--, of Ruconest for the same indication to FDA, supporting the efficacy claims by studies 1304 and 1205. FDA refused to file (RTF) the BLA in a letter dated February 24, 2011. Among the reasons for the RTF decision were the inadequacies of the studies to support a BLA filing and that "Insufficient numbers of subjects (a total of 12 subjects, four of whom had major protocol violations) have been evaluated in randomized, placebo-controlled trials (RCTs) to support the proposed dose at 50 U/kg under the proposed conditions of use of the product." The RTF letter also repeated FDA's request for the applicant to "submit a protocol for and conduct pre-licensure an additional phase 3 randomized, placebo-controlled study [RCT] to adequately support the evaluation of safety and efficacy of this product."

- The protocol for a Phase 3 confirmatory study, study 1310, was proposed by the applicant and received FDA Special Protocol Assessment (SPA) concurrence under IND 11785 on July 14, 2011. The original IND was submitted to Center for Biologics Evaluation and Research (CBER) in June 2004, transferred to CDER in July 2004, and then transferred back to CBER in August 2008. The Phase 2 study 1205 was conducted under this IND. Some information on study 1304, including its Statistical Analysis Plan (SAP), was also submitted to FDA for comment under this IND.

- On April 16, 2013, the applicant submitted this original BLA, BL 125495/0, for Ruconest to treat acute HAE attacks. On June 14, 2013, FDA informed the applicant that the BLA was filed and that the FDA identified, preliminarily, the following potential review issues regarding the confirmatory study 1310: the study did not demonstrate efficacy at sites in the US, which accounted for one-half of the total enrollment, and the study did not demonstrate efficacy for female subjects, which accounted for 63% of the enrollment. Several rounds of FDA information requests (IR) and applicant response amendments ensued, with one of the main clinical review issues being the aforementioned subgroup analysis results.

- On January 16, 2014, the Late Cycle Meeting (LCM) was held between FDA and the applicant. One outstanding clinical review issue was the observed results of Ruconest in the US with respect to the primary endpoint.

- On February 6, 2014, the applicant submitted an amendment following discussion with the clinical review discipline. This was characterized as a major amendment and extended the review action due date by three months to July 16, 2014.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical database of Ruconest submitted to the BLA included data from ten completed studies, studies 1101, 1106, 1202, 1203, 1205RCT (RCT: Randomized Controlled Trial), 1205OLE (OLE: Open-Label Extension), 1207, 1304RCT, 1304OLE, and the RCT phase of study 1310, together with interim data through a cut-off date of September 14, 2012 for the OLE phase of study 1310. See Section 5.3 for the Table of Studies. Only studies 1205 and 1310 included subjects in the US; all the other studies included only subjects in Europe.

Reviewer Comment #1: *The applicant treated studies 1205RCT, 1205OLE, 1304RCT, and 1304OLE as four separate studies; while considered study 1310, with both a RCT phase and an OLE phase, as a single study. The applicant made this distinction because new subjects were directly enrolled in studies 1205OLE and 1304OLE, whereas all 1310OLE subjects were previously exposed to study drug (rhC1INH or saline) in 1310RCT. At places of this review (e.g. Section 1, Executive Summary), this reviewer refers to the count of studies as eight instead of ten, by considering 1205RCT and 1205OLE as a single study, and 1304RCT and 1304OLE as a single study, to avoid potential confusion. This difference in counting the number of studies between the applicant and this reviewer does not materially impact the content and evaluation of actual submitted clinical database.*

The Ruconest clinical development program included 940 administrations of Ruconest in 236 subjects. A total of 205 symptomatic HAE subjects received Ruconest treatment for 650 acute angioedema attacks, including 39/205 (19%) subjects treated for at least five attacks. The maximum number of treated attacks was 39.

There were three randomized, double-blind, saline controlled studies, the RCT components of studies 1205, 1304, and 1310. Each of these studies also had an OLE component. The applicant and the Agency agreed that 1310RCT was the sole confirmatory study to support the efficacy claims for the proposed indication and dose, while 1205RCT and 1304RCT served as exploratory studies. Study 1205RCT was considered exploratory because it was initially designed as an exploratory phase 2 study to primarily evaluate safety with its statistical analysis plan (SAP) developed after study outcome became available. Study 1304RCT was considered exploratory because it was conducted in Europe with 81% of subjects from Italy sites, and the Ruconest dose was 100 IU/kg, twice the dose proposed in this application. In addition, studies 1205RCT and 1304RCT shared many design features that rendered them exploratory in efficacy considerations.

Therefore, of the three RCT studies, 1310RCT will be reviewed in detail in Section 6, Discussion of Individual Studies/Clinical Trials. Study 1205RCT will also be briefly discussed individually in Section 6, with the design and conduct features that rendered the study exploratory listed and its primary efficacy results included. Study 1304RCT will not be discussed further. Earlier phase studies did not materially impact the analysis or the conclusions of the review, therefore Section 7, Integrated Overview of Efficacy, will be omitted.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- Original submission under BLA 125495/0
    - Module 5.3.5.1: Clinical Study Reports (CSRs) for Study 1310, Study 1205 RCT, Study 1304 RCT and Tabulation Data
    - Module 5.3.5.3.1: Integrated Summary of Safety (ISS)
- Sequence 0005, Efficacy Information Amendment (EIA), dated July 29, 2013
- Sequence 0013, EIA, dated October 25, 2013
- Sequence 0016, EIA, dated November 13, 2013
- Sequence 0023, EIA, dated February 6, 2014.

5.3 Table of Studies/Clinical Trials

Type of Study	Protocol Number	Objective(s)	Study Design	Test Product: Dose* and Regimen	# Subjects (#Administrations) Sex	Population
PK	1106	PK, Safety, Tolerability, Immunogenicity	Open-label	rhC1INH 100 IU/kg, 5 doses at 3-week intervals	14 (59) 4M, 10F	Healthy Volunteer
PK	1101	PK/PD, Safety, Tolerability	Open-label	rhC1INH 6.25, 12.5, 25, 50, 100 IU/kg, 2 ascending doses, at least 5-week intervals	12 (24) 8M, 4F	Asymptomatic HAE
Efficacy	1207	Efficacy, Safety, Tolerability, PK/PD	Open-label prophylactic	rhC1INH 50 IU/kg once weekly for 8 weeks, with 50 IU/kg for acute attacks	25 (207) 5M, 20F	Asymptomatic HAE
Exploratory	1202	Efficacy, Safety, Tolerability, PK/PD	Open-label	rhC1INH 100 IU/kg One dose per acute attack.	4 (6)	Symptomatic HAE
Exploratory	1203	Efficacy, Safety, Tolerability, PK/PD	Open-label	rhC1INH 100 IU/kg One dose per acute attack.	10 (15) 4M, 10F (together with Study 1202)	Symptomatic HAE
Efficacy	1205 RCT	Efficacy, Safety, Tolerability, PK/PD	Randomized 1:1:1, double-blind, placebo-controlled, US, Canada	rhC1INH 50 or 100 IU/kg or Saline	38 (25 rhC1INH and 13 Saline) 10M, 28F	Symptomatic HAE
Efficacy	1304 RCT	Efficacy, Safety, Tolerability	Randomized (1:1), double-blind, placebo-controlled, ROW	rhC1INH 100 IU/kg or Saline	32 (16 rhC1INH and 16 Saline) 15M, 17F	Symptomatic HAE
Efficacy	1310 RCT+ OLE	Efficacy, Safety	Randomized (3:2), double-blind, placebo-controlled with open-label extension	rhC1INH 50 IU/kg (max 4200 IU) or Saline. OLE: rhC1INH 50 IU/kg (max 4200 IU). A 2nd dose may be given based upon clinical response	RCT: 74 (56 rhC1INH [including rescue] and 31 Saline) OLE[+]: 44 (170)	Symptomatic HAE

Type of Study	Protocol Number	Objective(s)	Study Design	Test Product: Dose* and Regimen	# Subjects (#Administrations) Sex	Population
					28M, 47F	
Efficacy	1205 OLE	Efficacy, Safety, Tolerability	Open-label extension	rhC1INH 50 IU/kg initial dose, a 2nd dose may be given based on clinical response	62 (168) 24M, 38F	Symptomatic HAE
Efficacy	1304 OLE	Efficacy, Safety, Tolerability, PK/PD	Open-label extension	rhC1INH 2100 IU initial dose, a 2nd dose may be given based on clinical response	57 (194) 20M, 37F	Symptomatic HAE

* Administered by intravenous infusion or slow intravenous infusion; + Up to September 14, 2012 data cut-off
Source: Adapted from eCTD Module 5.2 Tabular Listing of all Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Studies 1310 and 1205 (only the RCT components) are discussed individually in this section. Study 1310, the sole confirmatory study, is discussed in detail. Study 1205 is considered exploratory; the discussion herein focuses on some features in its design and conduct that are different from study 1310 and includes its primary efficacy results. See Section 5.1, Review Strategy, for the overall approach to the review.

6.1 Trial #1: Study 1310

Study 1310 is titled "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension Evaluating the Efficacy, Safety and Immunogenicity of Recombinant Human C1 Inhibitor for the Treatment of Acute Attacks of Angioedema in Patients with HAE." The version 7.0 protocol, submitted on July 18, 2011 as Amendment 75 to IND 11785, received FDA SPA concurrence on August 2, 2011.

The following documents formed the basis of this review. This reviewer also performed verification and additional statistical analyses using submitted Analysis Data Sets as needed.

1. Documents submitted under the initial sequence.

   o The Clinical Study Report (CSR, 2609 pages), dated February 25, 2013, with 152-page main text.

   o The Protocol (92 pages), Version 7.0, dated July 15, 2011.

   o The Statistical Analysis Plan (SAP, 77 pages), Version 13.0, dated July 15, 2011.

2. Sequence 0005 Efficacy Information Amendment (EIA, 75 pages) titled "Response to FDA Questions Regarding Subgroup Analysis in Study C1 1310", dated July 29, 2013.

3. Sequence 0016 EIA (101 pages) titled "Response to FDA Questions Regarding Statistical Issues Dated 23 October 2013", dated November 13, 2013.

4. Sequence 0023 EIA (33 pages) titled "Response to FDA Questions from Late-cycle Meeting on 16 January 2014", dated February 6, 2014.

Version 7.0 of the protocol was for implementation in the US, and version 7.1 of the protocol was for implementation in "Rest of the World" (ROW) other than the US. The two protocols were identical with one exception: the lower limit on age for enrollment was 13 years for US and 18 years for ROW. The applicant referred to version 7.0 and 7.1 of the protocol, in the development history of the protocol for study 1310, as Protocol Amendment 3. Protocol Amendment 3, compared to Protocol Amendment 2, incorporated substantial changes in study design (CSR, pp.69-71), including, but not limited to, rewording of the questionnaire forming the basis of the primary endpoint and changing time points at which questionnaires were to be administered. There were five subjects treated prior to the implementation of Protocol Amendment 3, 4 by rhC1INH and 1 by saline.

The applicant stated that version 13.0 of the SAP added clarification on the methodology proposed in the protocol, including the addition of some new analyses and further sensitivity analyses, but there were no substantial changes from the analyses proposed in Protocol Amendment 3. Version 15 of the SAP, dated June 06, 2012, made two minor changes compared to version 13.0, including updates of Table numbers and additional adverse event (AE) summaries. After the finalization of the SAP, the applicant added additional post-hoc analyses (CSR, p.72), which will be identified as such below if they appear in this review.

6.1.1 Objectives (Primary, Secondary, etc)

The objectives of Study 1310 were as follows.

1. To evaluate efficacy and safety of rhC1INH at a dose of 50 U/kg when used for the treatment of acute angioedema attacks in patients with HAE.

2. To assess efficacy, safety and immunogenicity of rhC1INH when used for the repeat treatment of acute angioedema attacks in patients with HAE.

6.1.2 Design Overview

Study 1310RCT was a randomized, double-blind, placebo-controlled, multi-center, multi-national study. A total of 75 eligible HAE subjects reporting to study centers with eligible acute angioedema attacks were centrally randomized, at a 3:2 ratio, to receive an intravenous (IV) injection of rhC1INH or saline to treat the acute attacks.

Reviewer Comment #2: *The study appeared adequate and well-controlled.*

6.1.3 Population

Eligibility consisted of subject eligibility and attack location eligibility, evaluated at the screening visit and the randomization visit, respectively.

Subject eligibility. Subjects started with a screening visit to confirm diagnosis of HAE. Subjects ≥18 years of age (≥13 years for subjects in the US and Canada) with confirmed diagnosis of HAE excluding acquired angioedema were eligible to enroll. The criteria for the diagnosis of HAE consisted of a medical history supported by central laboratory investigations. The medical history of subjects included any of the following:

- Self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, often recurrent and often lasting more than 12 hours and/or
- Recurrent self-remitting abdominal pain without clear organic etiology, often recurrent and often lasting more than 6 hours and/or
- Recurrent laryngeal edema
- Family members with recurrent angioedema and/or abdominal pain and/or laryngeal edema.

The central laboratory confirmed the diagnosis of HAE, defined as:

- < 50% of normal levels of functional C1INH
- Not abnormally low levels of C1q

- Absence of C1INH auto antibodies.

<u>Attack location eligibility</u>. An eligible subject would then report to a study center when he or she experienced an acute angioedema attack. This visit was termed the randomization visit. The time elapsed between the screening visit and the randomization visit could be many months. Upon reporting, subjects would be evaluated for attack location eligibility. Subjects with at least one eligible attack location would then be randomized and study medication would be prepared accordingly. Infusion would then start provided that at least one of the attack locations continued to satisfy location eligibility immediately prior to infusion; otherwise the subject would not receive the prepared study treatment. Table 1 lists important time points in the study procedures from screening until the end of infusion, which includes (for the randomization visit): (1) Presentation for evaluation and start of evaluation, (2) Randomization, (3) Baseline assessment after preparation of randomized study treatment and right before infusion of the study medication, and (4) Start of infusion of study medication (Time 0). Attack location eligibility evaluation comprised evaluations both prior to and after randomization. A subject would only be randomized if he or she had at least one abdominal, peripheral, facial, or oropharyngeal-laryngeal (OPL) location that met all the following three criteria.

1. Attack onset. The onset of symptoms at the attack location was within 5 hours before start time of evaluation.

2. Severity. Upon presentation, the symptomatic anatomical locations were assessed with a location-specific Visual Analog Scale (VAS) for severity. See Section 6.1.8, Endpoints and Criteria for Study Success, for information on the VAS. The subject was considered eligible for treatment if the Overall Severity VAS score (OSV) for the anatomical location at the time of initial evaluation was at least 50 mm (0 mm = no symptoms, 100 mm = extremely disabling).

3. No evidence of regression of symptoms at the location. Regression was defined as a decrease in the OSV of ≥20 mm at the location just prior to randomization compared with the initial OSV at Presentation.

After randomization, the pharmacist would prepare the study medication accordingly. Then just prior to infusion, the eligible location would be evaluated again with VAS. Study medication would be infused only when the location, at Baseline measurement, still met the severity criterion of VAS ≥ 50mm.

For subjects with multiple eligible attack locations, the primary attack location was defined as the eligible location with the highest OSV at Baseline. If the OSV was equal for two locations, the primary attack location was defined as the most clinically serious location. The order of clinical seriousness in decreasing order is OPL, facial, abdominal, and peripheral. This ordering was based primarily on the possibility of symptoms becoming life-threatening and secondarily on the degree of associated pain.

<u>Differential diagnosis of abdominal pain.</u> The Investigator was instructed to diligently consider the subject's history, review of systems, physical examination, and results of all available laboratory and non-invasive diagnostic tests to establish the likelihood that HAE was the cause of the abdominal pain with which the subject acutely presented. The

results of vital signs, stool hemoccult, and urinalysis were to be available to the Investigator prior to administration of study medication to subjects with abdominal symptoms. If the results suggested a symptom etiology other than HAE, the subject was not treated with study medication and further testing was performed. In particular, blood in urine or in stool would exclude the subject from randomization or from receiving study medication if already randomized.

Table 1.
Important time points in study procedures for study 1310 (Sources for some information: CSR pp.230-238, Table 14.1.8.1RCT)

Time Point (TP)	Procedure	Expected elapsed time relative to another TP	Actual elapsed time relative to another TP (mean, standard deviation) [min, 1st, 2nd, and 3rd quartiles, max]
#1	Screening		
#2	Attack Onset		From Screening (TP#1) (months) (4.3, 4.3) [0.5, 1.1, 2.0, 7.6, 16.0]
#3	Presentation for evaluation and start of evaluation	Within 5 hours of symptom onset of the primary attack location	From attack onset (TP#2), not symptom onset of primary attack location (minutes) (208, 173) (45, 135, 165, 228, 1090)
#4	Randomization		
#5	Baseline	Within 5 minutes prior to start of infusion	
#6	Start of Infusion (Time 0)	Within 1 hour of presentation (based on study 1205)	From Presentation (TP#3) (minutes) (65.9, 34.5) (20, 45, 59.5, 79.75, 210)
#7	End of Infusion	Around 5 minutes from start of infusion at a flow rate of 6ml/minute	From Start of Infusion (TP#6) (Time in minutes (number of subjects)) 3(2), 4(2), 5(59), 6(9), 7(1), 15(1)

6.1.4 Study Treatments or Agents Mandated by the Protocol

Randomized treatment consisted of one intravenous injection of rhC1INH at the dose of 50 IU/kg for subjects <84 kg or 4200 IU (2 vials) for subjects ≥84 kg, or an equivalent volume of saline. The rhC1INH treatment solutions to be injected were made from vials containing 350 mg (2100 IU) lyophilized material. Each vial was reconstituted with 14 mL water for injection prior to use. Batches MB002 and MD001 of rhC1INH were supplied by Pharming Technologies B.V. The saline solution to be infused consisted of NaCl 0.9% w/v with a total volume equivalent to the volume based on rhC1INH dosing.

Batches 14DK26 and 14EG31, manufactured by ----(b)(4)------ (for ROW), and 93652DK, manufactured by ---(b)(4)--- (for US), of normal saline were supplied by Pharming Technologies B.V.

6.1.6 Sites and Centers

A total of 26 centers participated in the trial, 16 in North America and 10 in ROW (8 in Europe and 2 in South Africa). Randomized subjects consisted of 38 subjects from 11 US centers, and 37 subjects from 8 European centers.

6.1.7 Surveillance/Monitoring

6.1.8 Endpoints and Criteria for Study Success

There is no objective clinical or laboratory assessment to evaluate the severity of the symptoms of acute angioedema attacks. Study 1310 assessed symptom severity and treatment effect with two patient reported outcome (PRO) measures, the Treatment Effect Questionnaire (TEQ) and the VAS, and one Investigator Symptom Score (IS) measure. The primary and secondary efficacy endpoints were time-to-event endpoints defined based on TEQ. The applicant also proposed a key exploratory efficacy endpoint and alternative efficacy endpoints analogous to the primary and secondary efficacy endpoint, but based instead on VAS. In what follows this reviewer summarizes the TEQ, VAS, and IS first, followed by the definitions of the efficacy endpoints.

TEQ (Protocol, p.83, 18.2 Appendix B) consisted of three questions administered before infusion, and three similar questions administered after infusion. The three questions before infusion were as follows.

1. Question 1: To what extent has the overall severity of your [abdominal] HAE attack changed since your arrival at the study center? The subject answered by selecting from a seven-point scale (Much worse, Worse, A little worse, Not changed, A little better, Better, Much better).

2. Question 2: Overall, has the intensity of your [abdominal] HAE attack symptoms begun to decrease noticeably since your arrival at the study center? The subject answered "Yes" or "No".

3. Question 3: At this moment, are your [abdominal] HAE attack symptoms minimal (barely noticeable)? The subject answered "Yes" or "No".

The word "abdominal" in the TEQ questions were replaced by the relevant attack location to which the TEQ was addressed.

The set of three questions after infusion replaced "… since your arrival at the study center" in Questions 1 and 2 above with "… since you received the infusion."

Separate VAS forms (Protocol, pp.78-82, 18.1 Appendix A) were given to subjects to express the severity of angioedema symptoms for five possible anatomical locations: abdominal, facial, urogenital, OPL, and peripheral locations. For each affected anatomical location, the subject answered a set of location-specific priming symptom

questions by marking how they felt on a 100mm line, with 0mm denoting no symptom and 100mm denoting extreme symptom. Then the subject answered the same "Overall Severity VAS" (OSV) question for all locations, "How severe are the angioedema symptoms now for this location? 0mm = no symptoms; 100mm = extremely disabling." The set of location-specific questions for an abdominal attack covered topics of feeling ill, abdominal pain, feeling bloated, and feeling nauseous; for a facial attack covered feeling ill, pain in face, and swelling of face; for an OPL attack covered feeling ill, pain in mouth or throat, swelling in mouth or throat, ease of breathing, speech affected, and difficulty in swallowing; for a peripheral attack covered swelling in extremities, pain in extremities, and difficulty using swollen extremities; for an urogenital attack covered feeling ill, pain in genital area, swelling in genital area, feeling nauseous, and ease of urination.

The applicant claimed that a reasonable minimally important difference (MID) based on the OSV would be 20mm and a conservative estimate of the MID would be 30 mm, based on a qualitative, semi-structured interview study of the content validity of the VAS instrument with 27 HAE subjects (17 in the United States and 10 in Italy), and a psychometric evaluation of the OSV based on data from 30 subjects in the European study 1304RCT.

Independent of the subject evaluation of severity, the Investigator assessed the severity of the subject's angioedema symptoms using an IS for each affected anatomical location. The IS (Protocol, p.84, 18.3 Appendix C) is a 6-point ordinal scale: 0 = no symptoms, 1 = almost no symptoms, 2 = mild symptoms, 3 = moderate symptoms, 4 = severe symptoms, 5 = life-threatening.

The primary efficacy endpoint was the time to beginning of relief of symptoms (based on Questions 1 and 2 of the TEQ, with persistence) at the primary attack location. The time to beginning of relief at the primary attack location was defined as the time between beginning of treatment administration (Time 0) and the first time point at which the subject reported the following:

- An answer of "A little better", "Better" or "Much better" to TEQ Question 1, and
- An answer of "Yes" to TEQ Question 2, and
- Persistence of improvement at the next assessment time (i.e., either the same or a better response to Question 1 and "Yes" to Question 2)

Censoring Event. Subjects who did not achieve beginning of relief of symptoms within the observation period (see assessment schedule below) were censored. If a subject received a disallowed concomitant medication or received open-label rhC1INH as rescue medication, prior to achieving beginning of relief of symptoms, the time to beginning of relief of symptoms was censored at the last time that the TEQ was assessed prior to the receipt of the disallowed concomitant medication or the rescue medication.

The secondary efficacy endpoint was the time to minimal symptoms at all locations based on Question 3 of the TEQ. Achieving minimal symptoms was defined as an answer of "Yes" to TEQ Question 3.

The applicant also considered therapeutic failure as a key exploratory endpoint. Therapeutic failure was defined as no response within 4 hours, relapse within 24 hours,

occurrence of acute angioedema attack at a new anatomical location within 24 hours and after beginning of relief, or use of a medication that could interfere with the assessment of efficacy. Medication and other therapy that could indicate therapeutic failure included narcotics, C1 inhibitor, fresh frozen plasma, analgesics, anti emetics, tranexamic acid, and Epsilon aminocaprioic acid.

Assessment Schedule. Time points at which the TEQ, VAS and IS were evaluated for each symptomatic anatomical location consisted of: 0 (baseline, just before study medication administration), 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, 2, 2½, 3, 3½, 4, 4½, 5, 5½, and 6 hours. Subjects remained under observation for at least 6 hours following treatment with study medication and were subsequently discharged at Investigator discretion. Following discharge, the subject was sent home with TEQ and VAS forms to complete at the 8, 12, and 24-hour time points. In addition, a diary was provided for the subject to record the time at which there was complete resolution of the angioedema attack symptoms, if resolution had not yet occurred at the time of discharge. The subject was also instructed to record any AEs and concomitant medications in the diary. Phone calls were scheduled at approximately 24 hours and at Day 4 to discuss subject status and provide reminders to complete the diary. Follow-up visits were planned for Day 7, Day 28, and Day 90. The VAS and TEQ forms and diary completed at home were collected at Day 7.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Randomization and Blinding. Randomization was stratified by gender (male or female) and by anatomical location of the attack (abdominal, peripheral, facial, or OPL). For subjects presenting with multiple symptomatic locations, the stratifying location was the most severe location based on OSV at the time of initial evaluation, or the most clinically serious location if the highest OSV was reported for more than one location. There was provision to randomize approximate equal numbers of subjects in the North American Region and the Rest of the World Region (ROW). The sponsor might limit randomization of subjects with certain primary attack locations if sufficient subjects with such attack locations had already been recruited in the study. Subjects, the Investigator, and study staff involved in the treatment and assessment of subjects were blinded to treatment allocation. The only un-blinded staff members were the pharmacists at each site who obtained the randomization instruction, prepared the medication, and dispensed it in opaque syringes that were identical for rhC1INH and saline. Both study products were clear and colorless solutions. These opaque syringes were labeled with identical labels that stated the subject number, protocol number, and date and time of preparation of the solution for injection. Post-exposure diagnostic laboratory results were not disclosed to any study personnel until the study had been un-blinded. Before discharge of the subject from clinical observation, all assessment forms were stored in the subject file and were not available for review by the subject or Investigator, to preserve non-biased assessment at each time point by both the subject and Investigator. The exception to this rule was VAS forms completed at initial Presentation and just prior to study medication administration (time = 0), to confirm eligibility of the attack and to ensure no regression of symptoms. There were no subjects for whom randomization was prematurely unblinded during the study.

Concomitant Medication. After recruitment, subjects continued their ongoing HAE maintenance therapy; changes in maintenance therapy were only allowed after consultation with the Investigator.

Disallowed Concomitant Medication (After Attack Onset). Subjects presenting with angioedema attacks for which they had already received narcotic or non-narcotic analgesia or other treatment (including pdC1INH, ecallantide, icatibant, anti-emetics, anti-spasmodics, supportive measures like oxygen, and IV fluids) were not eligible for treatment. Similarly, changes in current maintenance therapy (androgens and/or anti-fibrinolytics) from the time of the onset of the current attack were not allowed. The dosage of androgens and anti-fibrinolytics may not have been increased until complete resolution of the attack.

Rescue Medication (a single, open-label dose of rhC1INH) may have been provided to subjects who:

- Did not experience the beginning of relief within 4 hours
- Experienced beginning of relief at the 4-hour time point but who had still not achieved persistence of relief by 4.5 hours
- Was experiencing OPL symptoms or a significant degree of pain, discomfort, or disability due to their HAE symptoms.

Rescue medication may also have been provided prior to 4 hours in cases of life-threatening OPL symptoms.

Analysis Populations. The Intent-to-treat (ITT) Analysis Set was defined as the set of subjects who were randomized to a treatment group. Data were analyzed based on the treatment that the subject had been randomized to receive. The ITT Analysis Set was the primary analysis set for all efficacy endpoints. The Per-protocol (PP) Analysis Set was defined as the subset of subjects in the ITT Analysis Set without major protocol deviations. The following major protocol deviations were potential reasons for exclusion from the PP Analysis Set:

- Subject was excluded from either the ITT Analysis Set or the Safety Analysis Set
- Subject did not have any post baseline assessments of the TEQ
- Subject did not receive the full dose
- Subject failed an inclusion or exclusion criterion
- The subject's primary attack location was not an eligible attack location

A blinded review of study data was conducted to identify all major protocol violations.

Subgroup Analysis. Consistency of the primary analysis results across the following subgroups was to be assessed using the ITT Analysis Set, with summary statistics but without formal statistical analysis.

- Geographical region (USA, ROW)
- Gender (Male, Female)
- Race (Caucasian, Black/African American, Asian, or Other). The category Other consisted of the CRF categories American Indian, Alaska Native, Native Hawaiian / Other Pacific Islander, Other, or Unknown

- Age at screening (as a categorical variable, <18 years, 18 years to <65 years or ≥65 years)
- Primary anatomical location (Peripheral, Abdominal, Facial, OPL, Cutaneous (Facial or Peripheral), OFPL (Facial or OPL))
- Eligible anatomical location (Peripheral, Abdominal, Facial, OPL, Cutaneous (Facial or Peripheral), OFPL (Facial or OPL))
- Previous receipt of rhC1INH (naïve, non-naïve)

Sensitivity and Exploratory Analysis. An extensive list of exploratory and sensitivity analyses were proposed. Some of these analyses used alternative, exploratory definition of the efficacy endpoints based on the VAS, IS assessments instead of TEQ. These analyses and this reviewer's additional analyses using these alternative exploratory endpoints will be included in the review of study results when they play a contributory role to the conclusion.

Primary and secondary analysis. The null hypothesis for the primary efficacy analysis was that the two survival functions of the primary efficacy endpoint were identical between subjects receiving rhC1INH and subjects receiving saline. The alternative hypothesis was that the two survival functions were different. The primary efficacy analysis was an ITT log-rank test performed on the primary endpoint, stratified by primary attack location. Similar statistical test was planned for the secondary efficacy endpoint. There was no plan for interim analysis.

Sample size determination. Sample size was estimated based on results from study 1205RCT, where the median time to beginning of relief was 258 minutes with 95% confidence interval (CI) of (240, 495) for the saline arm, and was 122 minutes with 95% CI of (72, 136) for the rhC1INH 50IU/kg arm. The sample size was increased at the request of the FDA to increase information at specific anatomical locations. The applicant estimated that with 45 subjects in the rhC1INH arm and 30 in the saline arm planned for study 1310RCT, there was 99% power to detect a difference in the survival functions of the primary endpoint following the pattern observed in study 1205RCT. This power was calculated by simulation using a Weibull distribution with shape and scale parameters as estimated from the results of study 1205RCT (shape of 1.91 and 1.63, scale of 2.27 and 6.42 in the rhC1INH and saline arms, respectively). The use of rescue medication (which will be allowed from 4 hours) was incorporated into the power calculation. In particular, all simulated times greater than 4 hours were replaced with a censored value of 4 hour. The applicant stated that this might overestimate the proportion of censoring but should result in conservative estimates of power.

6.1.10 Study Population and Disposition

6.1.10.1   Populations Enrolled/Analyzed

The ITT analysis set consisted of a total of 75 randomized subjects, 44 to the rhC1INH arm and 31 to the saline arm, respectively. The PP analysis set consisted of 41 and 29 subjects in the two arms, excluding 3 and 2 subjects from the corresponding ITT arms.

6.1.10.1.1 Demographics

The demographic characteristics of the two treatment arms were in general similar when considering one factor at a time (Table 2). The majority of subjects were Caucasian (96%). There was a higher proportion of female than male subjects, 47 (63%) versus 28 (37%), with similar distributions in both the rhC1INH and saline arms. However, despite stratification by gender, due to the central randomization, an evaluation of gender by geographical location indicated an imbalance; within US, the rhC1INH arm had 11/22 (50%) females while the saline arm had 14/16 (88%) females; within ROW, the rhC1INH arm had 17/22 (77%) females while the saline arm had 5/15 (33%) females.

Table 2.
Demographic characteristics: ITT Analysis Set (Source: CSR p.76 Table 6).

	rhC1INH (N=44)	Saline (N=31)	Total (N=75)
Age at Screening, years			
Mean (SD)	39.4 (12.59)	41.4 (15.38)	40.2 (13.75)
Range	17-67	18-69	17-69
Age Subgroups, n (%)			
<18 years old	1 (2)	0	1 (1)
18 to 65 years old	42 (95)	29 (94)	71 (95)
>65 years old	1 (2)	2 (6)	3 (4)
Gender, n (%)			
Male	16 (36)	12 (39)	28 (37)
Female	28 (64)	19 (61)	47 (63)
Race, n (%)			
Caucasian	42 (95)	30 (97)	72 (96)
Asian	0	1 (3)	1 (1)
Black or African American	2 (5)	0	2 (3)
Hispanic/Latino Descent, n (%)			
Yes	0	2 (6)	2 (3)
Height, cm			
Mean (SD)	168.57 (7.498)	170.95 (10.065)	169.55 (8.667)
Range	155.0-185.0	155.0-190.0	155.0-190.0
Body weight at Screening, kg			
Mean (SD)	79.67 (19.876)	84.15 (24.888)	81.52 (22.037)
Range	46.5-153.0	53.6-158.0	46.5-158.0
BMI at Screening, kg/m^2			
Mean (SD)	27.963 (6.4510)	28.816 (8.6237)	28.316 (7.3831)
Range	18.02-51.12	17.43-58.03	17.43-58.03
Age at Admission, years			
Mean (SD)	39.7 (12.61)	41.9 (15.49)	40.6 (13.82)
Range	17-67	18-70	17-70
Age Subgroups, n (%)			
<18 years old	1 (2)	0	1 (1)
18 to 65 years old	42 (95)	29 (94)	71 (95)
>65 years old	1 (2)	2 (6)	3 (4)
Body Weight at Admission, kg			
Mean (SD)	79.65 (19.232)	84.77 (26.129)	81.77 (22.320)
Range	47.0-154.2	54.0-172.0	47.0-172.0

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline severity based on VAS at the primary attack location was comparable between the two treatment arms (Table 3). The most common primary attack locations in both arms were peripheral (45%) and abdominal (38%).

The CSR also summarized HAE medical history including usage of maintenance therapy for prophylaxis, impact of HAE, annual frequency of attacks, occurrence of prodromes before attack; urinalysis and stool hemoccult at baseline for abdominal attacks; concomitant medications including usage overall and of disallowed concomitant medications. Seven (18%) US subjects and 15 (40%) ROW subjects previously participated in other rhC1INH studies, studies 1203, 1205, 1207, and 1304.

Table 3.
Attack location and baseline severity: ITT Analysis Set (Source: CSR p.81 Table 9).

	rhC1INH (N=44)	Saline (N=31)	Total (N=75)
Overall VAS at baseline for the primary attack location, mm			
Mean (SD)	73.5 (14.13)	77.3 (12.61)	75.1 (13.56)
Range	50-100	49-100	49-100
n	43	31	74
Primary attack location,[a,b,c] n (%)			
Peripheral	19 (44)	14 (45)	33 (45)
Abdominal	16 (37)	12 (39)	28 (38)
Facial	6 (14)	2 (6)	8 (11)
OPL	2 (5)	3 (10)	5 (7)
Eligible anatomical locations,[c,d] n (%)			
Peripheral	16 (37)	11 (35)	27 (36)
Abdominal	15 (35)	11 (35)	26 (35)
Facial	6 (14)	1 (3)	7 (9)
OPL	2 (5)	2 (6)	4 (5)
Multiple	4 (9)	6 (19)	10 (14)
Abdominal, peripheral	0	2 (6)	2 (3)
Urogenital,[e] peripheral	2 (5)	0	2 (3)
Abdominal, peripheral, facial	1 (2)	0	1 (1)
Abdominal, urogenital[e]	1 (2)	0	1 (1)
Abdominal, urogenital,[e] peripheral	0	1 (3)	1 (1)
Facial, OPL	0	1 (3)	1 (1)
Peripheral, facial	0	1 (3)	1 (1)
Peripheral, OPL	0	1 (3)	1 (1)

Source: Table 14.1.9RCT.
RCT = randomized controlled trial; ITT = intent-to-treat; VAS = Visual Analog Scale; SD = standard deviation; OPL = oropharyngeal-laryngeal.
[a] For patients with multiple eligible attack locations, primary attack location defined as eligible location with highest overall VAS score at baseline; if overall VAS score was equal for two locations, most clinically serious location (clinically most important) was defined as the primary attack location.
[b] Patient (b)(6) (randomized to rhC1INH) did not receive study medication and is not included in the summary.
[c] Individual eligible anatomical locations percentages are based on non-missing N.
[d] Includes Patient (b)(6) (saline), with ineligible primary attack location (pre-dose VAS of 49 mm).
[e] Urogenital attacks were considered eligible as primary attack locations prior to implementation of Amendment 3.

6.1.10.1.3 Subject Disposition

A total of 227 subjects were screened and gave informed consent to enter the study. Of these, 190 (84%) subjects were eligible for entry into the RCT Phase of the study. The most common reason for ineligibility was a C1INH level >50%, or a diagnosis not consistent with HAE. Of the 190 eligible subjects, 75 subjects presented for treatment with an eligible acute angioedema attack in the RCT phase and 73 of those were treated and completed the required follow-up assessments for the RCT Phase. Subject -(b)(6)- was randomized to the rhC1INH arm, but was not treated and did not have any study measurements recorded after randomization. This subject was a male presented with peripheral attack at a Hungary center. The subject did not receive study medication as he "received another recombinant therapy on the same morning of the dosing day" (CSR p.157, Table 14.1.2RCT). Subject –(b)(6)- was treated with rhC1INH and withdrew consent 39 days later to participate in another investigational study. Efficacy endpoint assessment was not affected for this subject.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was the time to beginning of relief of symptoms (based on questions 1 and 2 of TEQ, with persistence) at the primary attack location. The primary efficacy analysis was pre-specified to be a log-rank test stratified by primary attack location, based on the ITT analysis set. This test yielded a p-value of 0.031. The median and 95% CI (in minutes) were 90.0 (61.0, 150.0) for the rhC1INH arm and 152.0 (93.0, -) for the saline arm, respectively. Figure 1 provides the Kaplan-Meier plot of the primary endpoint. The PP analysis yielded similar results.

6.1.11.2 Analyses of Secondary Endpoints

The secondary endpoint was time to minimal symptoms (based on question 3 of TEQ) at all locations. The analysis was pre-specified to be a log-rank test stratified by primary attack location, based on the ITT analysis set. This test yielded a p-value of 0.078. The median and 95% CI (in minutes) were 303.0 (240.0, 720.0) for the rhC1INH arm and 483.0 (300.0, 1440.0) for the saline arm, respectively. Figure 2 provides the Kaplan-Meier plot of the secondary endpoint. PP analysis was not conducted.

Figure 1.
Kaplan-Meier plot of the primary efficacy endpoint, time to beginning of relief of symptoms (based on questions 1 and 2 of the TEQ, with persistence) at the primary attack location: ITT Analysis Set (Source: CSR p.87 Figure 2)
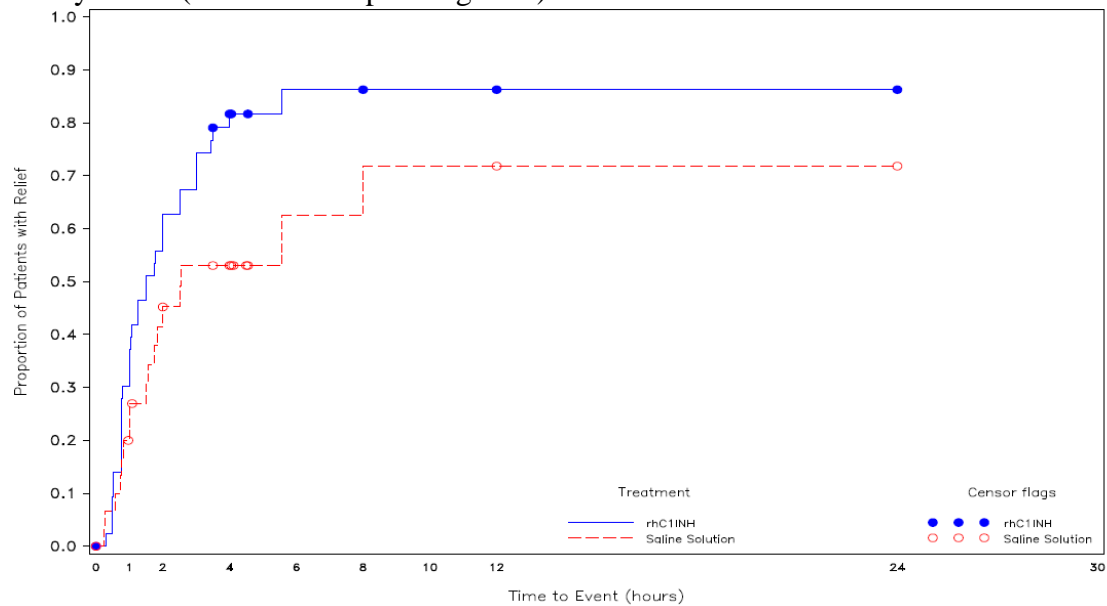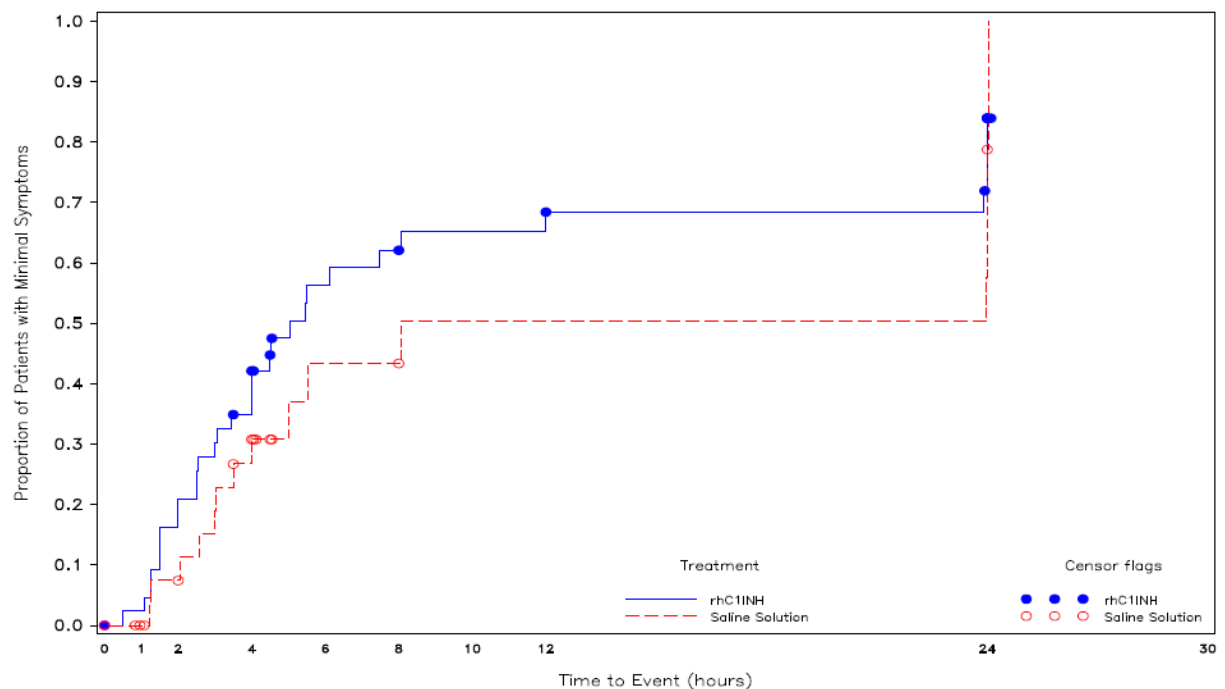

Figure 2.
Kaplan-Meier plot of time to minimal symptoms (based on question 3 of the TEQ) at all locations: ITT Analysis Set (Source: CSR p.96 Figure 3)

6.1.11.3 Subpopulation Analyses

Table 4 provides subgroup analysis on 25 categories planned on seven factors. Because almost 100% of the subjects were Caucasian and were between 18 and 65 years of age, the division of the factors of race or age at screening into categories were not meaningful. Categorization of the factor "eligible anatomical location" overlapped considerably with the factor "primary attack location" and therefore provided little additional information and would not be considered further. Several categories of the "primary attack location" included few subjects (≤ 5) in at least one of the two arms and therefore would not be considered further. The following subgroup categories remained after the above considerations and this reviewer evaluated their results.

- Primary attack location: Peripheral or Abdominal

- Gender: Male or Female

- Geographical location: USA or ROW

- Previous treatment with rhC1INH: Naïve or Non-naïve.

Reviewer Comment #3: *For the primary efficacy endpoint of time to beginning of relief of symptoms, numerically similar responses were observed between the rhC1INH and the saline arm, in the female and the US categories, out of the 8 subgroup categories. An inconsistent result was also observed in the US category in the secondary efficacy endpoint of time to minimal symptoms, with a median of 720.0 minutes in the rhC1INH arm and 331.0 minutes in the saline arm, respectively. The findings in the subgroup analysis will be discussed further below in Section 6.1.11.5, Exploratory and Post Hoc Analyses. However, the secondary efficacy endpoint will not be considered further because the ITT analysis of this endpoint was not statistically significant and this endpoint was measured with much less precision (wider interval in assessment schedule) compared to the primary efficacy endpoint.*

Table 4.
Subgroup analysis of the primary efficacy endpoint, time to beginning of relief of symptoms (based on questions 1 and 2 of the TEQ, with persistence): ITT Analysis Set (Source: CSR p.91 Table 15). Note that a "-" in the median or bounds of CI means that the quantity was not estimable, often times due to substantial amount of censoring.

	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=44)	Saline (N=31)
Primary Attack Location:		
Peripheral	105.0 (60.0, 150.0) [n=20]	- (93.0, -) [n=14]
Abdominal	60.5 (45.0, 107.0) [n=16]	130.0 (50.0, 480.0) [n=12]
Facial	- (180.0, -) [n=6]	- (- , -) [n=2]
Cutaneous (Facial or Peripheral)	120.0 (63.0, 180.0) [n=26]	- (93.0, -) [n=16]
OFPL (Facial or OPL)	286.5 (75.0, -) [n=8]	- (15.0, -) [n=5]
Oropharyngeal-Laryngeal	204.0 (75.0, 333.0) [n=2]	105.0 (15.0 -) [n=3]
Gender:		
Male	75.0 (45.0, 210.0) [n=16]	480.0 (150.0, -) [n=12]
Female	112.5 (63.0, 151.0) [n=28]	105.0 (60.0, 334.0) [n=19]
Race:		
Caucasian	90.0 (61.0, 150.0) [n=42]	152.0 (93.0, -) [n=30]
Asian	[n=0]	110.0 (- , -) [n=1]
Black/African American	128.5 (17.0, 240.0) [n=2]	[n=0]
Age at Screening:		
<18 Years Old	- (- , -) [n=1]	[n=0]
18-65 Years Old	90.0 (61.0, 150.0) [n=42]	152.0 (93.0, -) [n=29]
≥65 Years Old	47.0 (- , -) [n=1]	- (60.0, -) [n=2]
Geographical Location:		
USA	97.5 (45.0, 240.0) [n=22]	90.0 (50.0, -) [n=16]
Rest of World	90.0 (63.0, 120.0) [n=22]	334.0 (150.0, -) [n=15]
Previous Treatment with rhC1INH:		
Naive	97.5 (60.0, 180.0) [n=31]	334.0 (60.0, -) [n=22]
Non-naive	63.0 (45.0, 180.0) [n=13]	136.0 (105.0, -) [n=9]
Eligible Anatomical Location:		
Peripheral	105.0 (60.0, 150.0) [n=19]	- (90.0, -) [n=15]
Abdominal	61.0 (45.0, 120.0) [n=17]	130.0 (50.0, 480.0) [n=14]
Facial	210.0 (120.0, -) [n=6]	- (- , -) [n=3]
Cutaneous (Facial or Peripheral)	120.0 (63.0, 180.0) [n=24]	- (93.0, -) [n=17]
OFPL (Facial or OPL)	240.0 (120.0, -) [n=9]	- (105.0, -) [n=6]
Oropharyngeal-Laryngeal	204.0 (75.0, 333.0) [n=2]	105.0 (15.0, -) [n=4]

6.1.11.4 Dropouts and/or Discontinuations

The ITT analysis set contained a substantial amount of censoring for the primary efficacy endpoint, with 22 out of 75 observations being censored – 8 out of 44 (18%) in the rhC1INH arm and 14 out of 31 (45%) in the saline arm. The following three scenarios led to censoring.

- A randomized subject without any post-baseline efficacy data would have the time censored at 0 (e.g., subject -(b)(6)-).

- A subject who received rescue medication (open label rhC1INH) or disallowed concomitant medication prior to achieving the primary endpoint would have the time censored at the last time at which the TEQ was recorded for the location prior to their receipt of rescue medication or disallowed concomitant medication (anticipated to be the 4 Hour time point).

- A subject who did not receive rescue medication or disallowed concomitant medication, and who did not have beginning of relief of symptoms during the time that they were followed-up, would have the time censored at the last time at which the TEQ was recorded for the primary attack location.

Five and 13 subjects received rescue medication in the rhC1INH and the saline arm, respectively. Four and 2 subjects took disallowed medication in the rhC1INH and the saline arm, respectively. The censoring events were likely informative. A wide variety of sensitivity analyses were planned and presented by the applicant. They were considered of little value. The small sample size allows direct examination of the collection of the individual observations to discern potential trends and this exercise did not reveal anything of concern. In addition, treating receipt of rescue medication or disallowed medication as censoring events is likely conservative because there were more censoring events in the saline arm than in the rhC1INH arm.

6.1.11.5 Exploratory and Post Hoc Analyses

Reviewer Comment #4: *This section documents some of the post-hoc analyses with regard to the subgroup analysis findings, submitted by the applicant in the Efficacy Information Amendments (EIAs) in sequences 0005, 0013, 0016, and 0023, together with evaluation of this reviewer. It should be emphasized that these analyses were exploratory from a statistical perspective. These analyses may be useful to characterize the clinical performance of rhC1INH from a clinical perspective. Evaluation of the clinical significance of these analyses is deferred to the clinical review discipline.*

General considerations. In this section, we focus the exploratory analyses on the primary efficacy endpoint, the time to beginning of relief of symptoms at the primary attack location, based on TEQ Questions 1 and 2, with persistence, unless noted otherwise. The applicant had also explored several alternative definitions of time to beginning of relief, including using VAS decease $\geq$ 20mm as the definition of relief. This alternative definition of efficacy endpoint based on VAS decrease will be noted when we consider it below. The following considerations underlie the evaluation of the subgroup findings and analyses.

- For these post-hoc and exploratory analyses, p-values and confidence levels associated with confidence intervals, if provided, should be interpreted as an informal, convenient way to summarize qualitatively the extent of difference between two statistical distributions. They do not carry the usual probabilistic interpretation of statistical significance or lack thereof.

- The median and the attending confidence interval of the primary efficacy endpoint provide only a snapshot of a distribution at its 50th percentile. The Kaplan-Meier plot, on the other hand, captures the entire observed distribution. Thus in analyses intended for comparing two distributions, Kaplan-Meier plots were always examined, though often not included to save space. Instead, p-values from log-rank tests were reported to summarize comparisons of the entire distributions for the rhC1INH versus the saline arms. In some cases, the applicant presented the difference between the point estimates of medians of a time-to-event endpoint in the rhC1INH arm and the saline arm. The reported magnitude can be misleading, especially if the assessment schedule was sparse. For example, the time to minimal symptom was assessed at 8, 12, and 24 hours after study drug administration if the subject did not already achieve the endpoint by dismissal from the study center.

- The applicant's multiple amendments were extensive. We considered the following two types of analyses of no merit and did not consider them further in order to focus on issues that might be of comparatively more merit. The first type is subgroup analyses in select exploratory endpoints, such as the time to complete resolution of symptoms based on patient diary or time to the beginning of relief based on investigator scores. In addition to the major consideration of such analyses being post-hoc and exploratory, measurement of some of these endpoints were imprecise and prone to bias. The second type is subgroup analyses in studies 1205 and 1304, because study 1310 was considered to be the sole confirmatory trial. See Section 5.1, Review Strategy, for more information.

Subgroup analysis findings. For US subjects, the primary efficacy endpoint was similar between the two treatment arms (Table 4, Figure 3), with a median of 97.5 minutes [95% CI of (45.0, 240.0)] in the rhC1INH arm versus 90.0 minutes [95% CI of (50.0, -)] in the saline arm. For ROW subjects, the rhC1INH arm was similar to the two arms in US subjects, with a median of 90.0 minutes [95% CI of (63.0, 120.0)], while the ROW-saline arm responded much slower with a median of 334.0 minutes [95% CI of (150.0, -)] (Table 4, Figure 4). The finding in the females/males dichotomy was similar to that in the US/ROW dichotomy.

Figure 3.
Kaplan-Meier plot of the primary efficacy endpoint for US subjects in the ITT Analysis Set
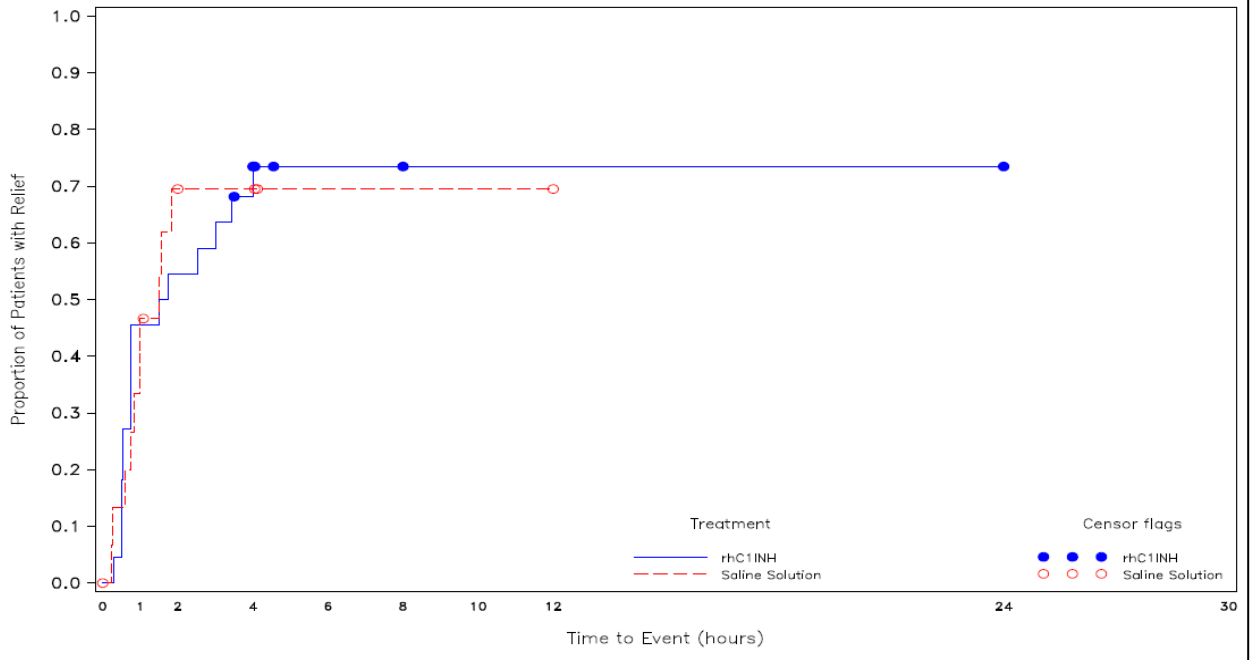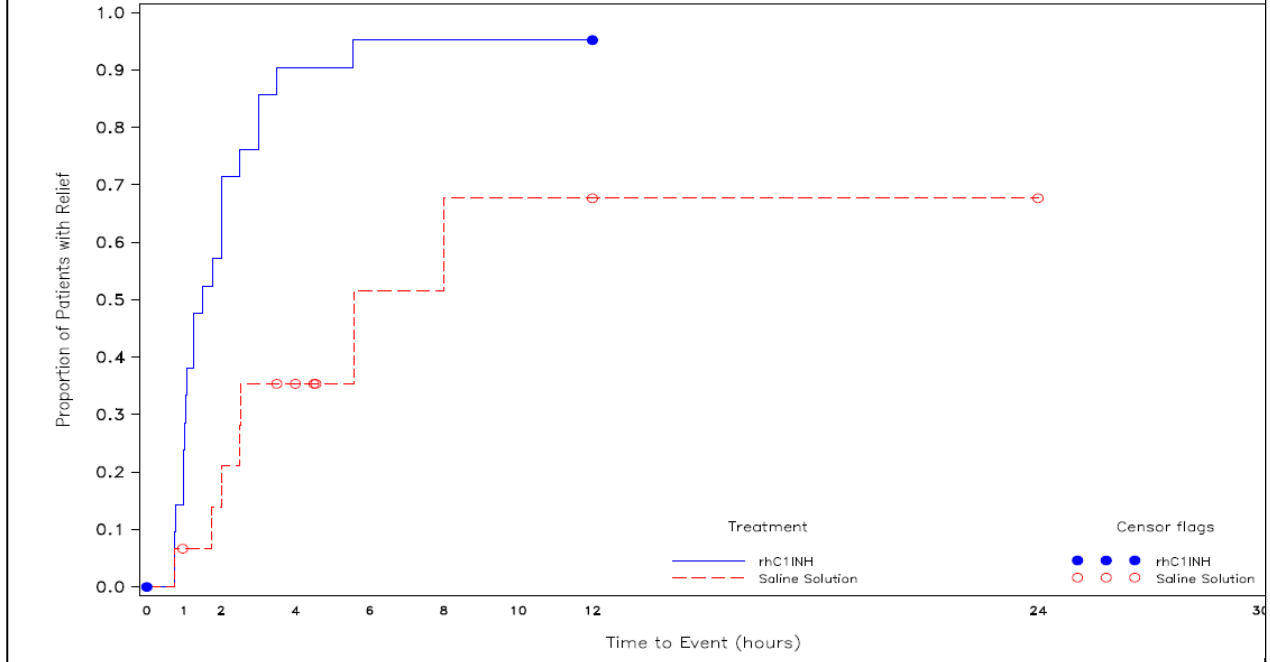(Source: CSR p.1001 Figure 14.2.1.11RCT p.1 of 2)

Figure 4.
Kaplan-Meier plot of the primary efficacy endpoint for ROW subjects in the ITT Analysis Set
(Source: CSR p.1002 Figure 14.2.1.11RCT p.2 of 2)

Imbalance in treatment assignment and focus on US subjects. Considering geographical region and gender together, there was an imbalance in treatment assignment (Section 6.1.10.1.1, Demographics). Table 5 examined the primary efficacy endpoint by the region-gender categories. Among the four categories, ROW-female and ROW-male showed trends favorable to rhC1INH compared with saline. There were only 2 US males in the saline arm so there was little information to compare the treatment arms in the US-male category. The US-female category was of substantial size, with 11 and 14 subjects in the rhC1INH and the saline arm, respectively. The Kaplan-Meier graph and the percentage of censoring (3/11 and 5/14) showed that there was no trend favoring rhC1INH in the US-female category. Considering the substantial interest in the literature in assessing consistency of efficacy results across regions in multi-regional trials and the imbalance of the combination of the two factors in treatment assignment, the rest of the review will focus on the US subjects and omit considerations in the females separately.

Table 5.
Exploratory analysis of the primary efficacy endpoint by geographical region and gender. P-values were computed with log-rank test. Note that p-values and confidence levels here do not carry usual probabilistic meaning (see "General considerations" above).

Region	Gender	rhC1INH		Saline		p-value
		N (censored)	Median (95% CI)	N (censored)	Median (95% CI)	
USA	Female	**11 (3)**	**151 (32, -)**	**14 (5)**	**90 (35, -)**	0.5552
USA	Male	**11 (3)**	**45 (30, -)**	**2 (1)**	**- (60, -)**	0.5045
ROW	Female	17 (1)	90 (60, 150)	5 (1)	152 (105, 334)	0.1990
ROW	Male	5 (1)	91 (45, 210)	10 (7)	- (44, -)	0.0065
USA		**22 (6)**	**98 (32, 240)**	**16 (6)**	**90 (35, -)**	0.9842
ROW		22 (2)	90 (61,120)	15 (8)	334 (120, -)	0.0011
Female		**28 (4)**	**113 (61, 151)**	**19 (6)**	**105 (50, 334)**	0.8139
Male		16 (4)	75 (30, 210)	12 (8)	480 (60, -)	0.0140

The applicant presented two potential explanations for the subgroup findings in the US subjects: (1) there was a relative delay in the saline arm subjects to present for evaluation from attack onset, compared to the rhC1INH arm subjects; (2) ROW subjects had more severe attacks compared to US subjects and rhC1INH was more efficacious in more severe attacks. These two considerations are discussed below.

"Delayed" presentation from attack onset in the US-saline arm. In Sequence 0005, the applicant presented that the time from attack onset to evaluation was longer in the US subjects versus in the ROW subjects; with averages of 220 and 289 minutes in the US-rhC1INH and US-saline arms versus 157 and 180 minutes in the ROW-rhC1INH and

ROW-saline arms, respectively. In the US, the saline arm subjects on average reported 69 minutes later than the rhC1INH subjects. The applicant suggested that this delayed reporting in the US-saline arm accounted for the efficacy observations in the US subjects. The Agency noted that three US female subjects had reporting times from attack onset that were more than four standard deviations away from the mean and termed them "outliers". These subjects reported to study centers 15.5h, 15.9h, and 18.2h after attack onset. Excluding these three "outliers", the average time from attack onset to reporting was similar between the two treatment arms in US subjects - 179 minutes for the US-rhC1INH subjects and 196 minutes for the US-saline subjects - and similar to that in the ROW subjects. The applicant, in response (Sequence 0013 and 0016), concluded that there was no delay in the US-saline arm subjects when the "outliers" were excluded and that this factor was not likely an explanation of the efficacy observation in the US subjects. The applicant explained that the three "outliers" had multiple locations experiencing HAE symptoms, and though the locations associated with the earliest symptoms were not eligible locations, these subjects all had other locations that were eligible. The Agency also performed analyses on the primary efficacy endpoint excluding the "outliers". The result in the US subjects was similar to that with the "outliers" included. The applicant, at the Agency's suggestion, performed an additional exploratory analysis by setting time 0 as the time of symptom onset at the primary attack location. This yielded a median of 356.5 minutes in time from attack onset to beginning of relief in the US-rhC1INH subjects versus 383 minutes in the US-saline subjects, a 26.5-minute difference. The Kaplan-Meier plot of this post-hoc exploratory efficacy endpoint still indicated similar responses between the two treatment arms in the US subjects. In addition, it is likely that the recorded time of attack onset (at the primary attack location) is inaccurate in that the subject might not have noted the precise time immediately, particularly if it had been months since the subject was enrolled and had study procedures explained. The difference in the medians of this exploratory endpoint between the two arms, 26.5 minutes, is very small relative to the respective median times to beginning of relief (356.5 versus 383 minutes). We note that most of the analyses involving the time from attack onset were added by the applicant after the finalization of the SAP (CSR p.72).

Baseline attack severity. In Sequence 0016, the applicant offered another explanation for the efficacy observation in the US subjects, that there were fewer US subjects who had severe attacks relative to ROW subjects. The applicant conducted analysis that included only subjects with baseline attack severity of VAS $\geq$ 75 mm and concluded that "This analysis showed generally shorter times to the beginning of relief of symptoms with rhC1INH compared with saline for the subgroup of US subjects." This explanation was not statistically convincing due to its post-hoc nature. In addition, "superiority" of rhC1INH among the VAS >=75mm US subjects was accompanied by corresponding "inferiority" of rhC1INH among the VAS < 75mm US subjects (Table 6).

Table 6.

The primary efficacy endpoint in the US subjects by baseline attack severity (Source: adapted from Sequence 0016 EIA Tables 26 and 27).

Baseline Attack Severity	Median (95% Confidence Interval), minutes [n]	
	rhC1INH (n=22)	Saline (n=16)
VAS ≥ 75mm	45 (32, 90) [n=9]	- (35, -) [n=8]
VAS < 75mm	240 (45, -) [n=13]	60 (45, 110) [n=8]

<u>Efficacy endpoint defined based on VAS.</u> In the study protocol, time to beginning of relief with persistence was also alternatively defined using VAS decrease ≥ 20mm as the criterion for relief. For US subjects, treatment arm comparison using this alternative definition yielded similar results as that using the primary efficacy endpoint.

<u>Rescue medication.</u> Efficacy Information Amendment (EIA) in sequence 0023 was a major amendment submitted based on communication between the applicant and the clinical review discipline, following the Late Cycle Meeting. Statistical evaluation of this amendment was not requested from the clinical review discipline and therefore a detailed statistical evaluation was not performed. The content of the amendment did not include new information from a statistical perspective; however, some information may be considered important from a clinical perspective. In particular, the applicant emphasized the differential usage of rescue medication between the two treatment arms in the US subjects as one aspect that favored the comparative efficacy of rhC1INH compared to saline. The applicant reported that there was more use of rescue medication in the rhC1INH arm compared with the saline arm in US subjects, 4/22 (18.2%) versus 6/16 (37.5%), respectively. This analysis was post-hoc. In addition, the following consideration may provide a more complete picture. Detailed evaluation and interpretation of the rescue medication usage and outcome are deferred to the clinical review discipline.

- In US subjects, there were six censoring events in each of the two treatment arms; the applicant attributed all six in the saline arm to receipt of rescue medication. However, the two additional censoring events in the rhC1INH arm occurred when the subject did not respond within the observation period, 480 minutes for subject -(b)(6)- and 1440 for subject -(b)(6)-.

- At the individual level, a subset of the US-saline subjects responded quickly, with 7 subjects responding within 60 minutes and all 10 non-censored subjects responding within 110 minutes.

- The censoring times for the for the rhC1INH group were 210, 240, 243, 273, 480, and 1440 minutes, and for the saline group were 0, 65, 120, 243, 247, and 720 minutes.

- Two of the censored US subjects in the saline arm were unusual. Subject -(b)(6)- was censored at time 0. Subject -(b)(6)- was missing essential records and the imputation does not appear to be meaningful; the clock time of baseline (time 0) was missing and imputed based on the clock time at the 5th hour post-baseline, when the first measurement of TEQ was taken (16.2 patient data listing, p.1468 of 9493, Listing 16.2.6.1.2RCT TEQ Results: RCT ITT Analysis Set, p.173 of 235). Only three TEQ assessments, at the assumed 5h, 5.5h, and 6h time points, were taken. It appears that subject -(b)(6)- should be listed as experiencing major protocol deviations in the CSR but was not.

Reviewer Comment #5: *Two subgroup categories, females and US subjects, showed numerically comparable responses between the two treatment arms in the primary efficacy endpoint, out of the eight categories that had a sufficient number of subjects per arm to discern a trend. This finding may reflect a chance observation of false negatives (Type II error) or confounding factors not considered in the study design, or it may reflect genuine lack of efficacy in the females, or US subjects, or both. It is not possible to discriminate between these two potential explanations with statistical reasoning based on the available data within the study, because the study was not powered for any subgroup analysis and the study size was small. Clinical judgment is required to assess which one of the two potential explanations is more plausible. The applicant had submitted various post-hoc analyses to explore the role of potential confounding factors in explaining the results in the US subjects and the females, and to explore re-analysis of the data, including attack severity at baseline and rescue medication usage, among others. It is impossible to assess the statistical strength of these additional analyses due to their post-hoc nature. Clinical judgment is required to assess the interpretation of these additional analyses.*

6.1.12 Safety Analyses

Study 1310 consisted of a RCT phase and an OLE phase. The RCT safety analysis set consisted of 74 subjects, 43 receiving an initial dose of 50 IU/kg rhC1INH and 31 receiving saline. Rescue medication, a dose of 50 IU/kg rhC1INH, was given to 5 subjects in the rhC1INH arm and 13 subjects in the saline arm.

Across both the RCT and OLE phases, among 74 subjects in the RCT Safety Analysis Set, 28 (38%) subjects were treated with rhC1INH for one attack, 18 (24%) subjects for 2-3 attacks, 12 (19%) subjects for 4-5 attacks, and 10 (14%) subjects were treated with rhC1INH for 6 or more attacks, with the maximum number of attacks treated being 15. Six (8%) subjects were not treated with rhC1INH (these subjects were treated in the RCT phase only, receiving saline). Four subjects received an additional dose of rhC1INH in the OLE phase. The total dose received by subjects had a median of 201 IU/kg and a maximum of 747 IU/kg.

6.1.12.3 Deaths
There were no deaths reported for subjects in study 1310.

6.1.12.4 Nonfatal Serious Adverse Events

Three subjects experienced a total of 5 Serious Adverse Events (SAE) during the RCT phase. Only 1 of these 5 events was treatment emergent adverse event (TEAE). Subject -(b)(6)- (rhC1INH arm) experienced a serious TEAE of severe abdominal hernia 79 days after administration of study medication. The subject was hospitalized and received concomitant medication (ciprofloxacin) and non-drug therapy. The event resolved with sequalae after 33 days, and was assessed as not related to study drug by the Investigator. The remaining 4 SAEs occurred prior to randomization and treatment and were therefore non-TEAEs. Subject -(b)(6)- (rhC1INH group) experienced two SAEs of moderate and severe HAE and an event of moderate suicide ideation. Subject -(b)(6)- (saline group) experienced an SAE of mild vaginal bleeding. All of these events resolved.

One subject experienced a treatment-emergent SAE during the OLE phase. Subject -(b)(6)- experienced a new moderate HAE attack that required hospitalization and administration of concomitant medication (iv fresh frozen plasma) approximately 25 days after the last administration of rhC1INH (for Attack 13). The event resolved without sequelae after 52.5 hours. The Investigator assessed the event as not related to the study drug.

6.2 Trial #2: Study 1205

Study 1205 was titled "A randomized, placebo-controlled, double-blind Phase II study of the safety and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in subjects with hereditary angioedema." Review of study 1205 was based mainly on the 1742-page CSR, dated July 15, 2009, with a 116-page main text. The first subject was enrolled on June 10, 2005 and the last subject completed on January 24, 2008. The last RCT subject (the 39th subject) was randomized on October 28, 2007 (28.5 months from first subject enrollment). The study consisted of a RCT and an OLE phase. Only the RCT phase is reviewed here.

The applicant and FDA both considered studies 1205 and 1304 as supportive studies and study 1310 as the sole confirmatory study. The design, conduct, and analysis of study 1205 rendered its efficacy results suitable only for hypothesis-generating purpose. This reviewer summarizes below some features of study 1205 and then includes the applicant's primary analysis of the primary endpoint. Please note that this is not intended to be a comprehensive, in-depth review of the study because of its hypothesis-generating nature for the efficacy endpoint.
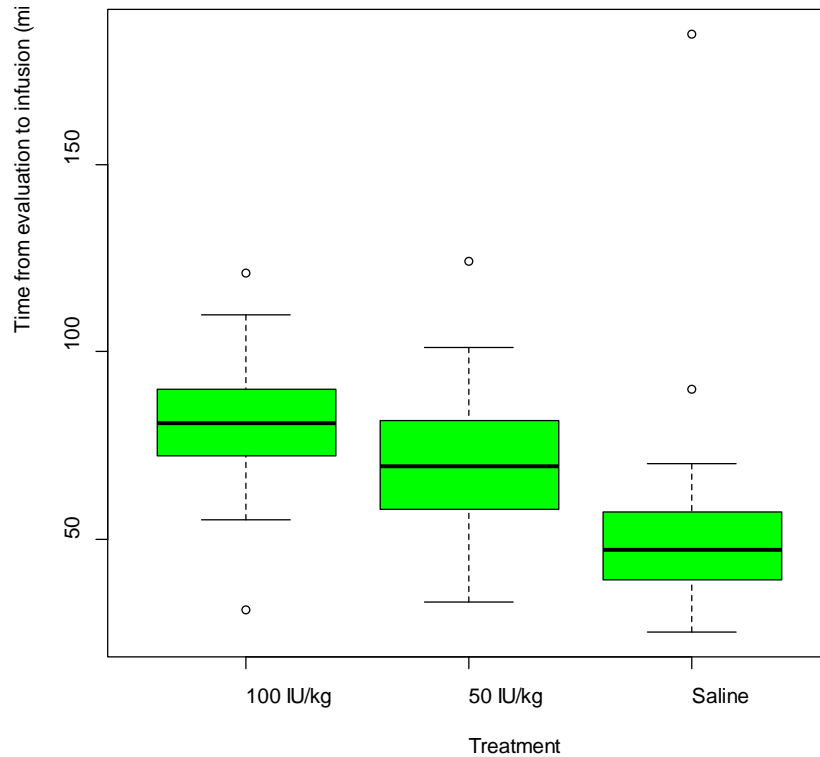
As in study 1310, eligibility consisted of HAE eligibility at the screening visit and attack eligibility at the randomization visit. The study was initially designed to perform an interim efficacy analysis of the first 39 subjects, and "if the safety analysis of this 39-subject study is acceptable, it would be the intention to amend the study to enroll an additional 36 subjects ..." Thirty nine subjects were randomized 1:1:1 to receive rhC1INH 100 U/kg, rhC1INH 50 U/kg, or saline. The 131 subjects eligible for treatment in the total set were from 4 centers in Canada (29 subjects) and 19 centers (102 subjects) in the US. Some apparent inadequacies of the study that precludes its post-hoc interpretation as a confirmatory study for efficacy claims are given below.

1. The study was planned as a Phase 2 study with the primary objective to assess safety and tolerability, and had been evaluated by the Agency as such. Substantial changes to the study protocol, statistical analysis plan (SAP), and study conduct that were not pre-specified had occurred after study initiation and also after conclusion of the RCT phase (for the SAP).

   a. Inclusion criteria were changed to allow peripheral angioedema attacks to be treated in the <u>November 1, 2006</u> version of the protocol, 16.5 months after enrollment of the first subject and more than half-way through the RCT phase till the randomization of the last subject. The same version of the protocol also changed the duration after treatment with which the subject would be closely monitored from 12 hours to 4 hours, along with other changes in the monitoring procedure.

   b. The <u>October 8, 2007</u> version of the protocol stated that "After the 39th subject has been randomized, sites will be notified in writing that the randomized phase of the trial has closed." This changed the plan of continuing the study until 75 subjects had been randomized. The version date is 20 days before the 39th subject was randomized. The SAP referred to, but did not provide a link to, a document titled "C1 1205-01 Interim Analysis SAP", dated <u>June 6, 2008</u>. The references in the study CSR to the interim analysis (IA) report and IA SAP linked to the study CSR itself and the overall SAP. This reviewer could not locate the IA report or the IA SAP. Given that the applicant closed the RCT phase before the interim analysis was performed, this reviewer decided not to pursue a review of the IA report or the IA SAP.

   c. The only version of the <u>SAP</u> enclosed in the BLA submission was dated <u>March 26, 2009</u>, more than a year after the conclusion of the RCT phase of the study and just 4 months before the study report date. This SAP changed the primary efficacy analysis population from Intent-to-Treat (ITT) in the usual sense to the Full Analysis Set (FAS) or MITT (modified Intent-to-Treat) that included randomized subject who took at least one dose of the study medication. This version also added methods for missing data handling. The p-value comparing the secondary endpoint, time to minimal symptoms, between the 100U/kg and the saline arms, changed from 0.0015 at the IA (no missing data imputation) to 0.04 at the final analysis (missing data imputed with Last Observation Carried Forward), due to change in imputation for a single subject, subject -(b)(6)-. Thus pre-specification of missing data handling was important. The same concern was expressed in an FDA letter dated May 29, 2009 regarding two amendments under IND 11785, "FDA notes that the results of the interim analyses of the primary and secondary efficacy endpoints for both studies C1 1205-01 and C1 1304-01 were known to you at the time you revised the SAPs for these studies. Consequently, there is no assurance that the revised SAPs are free from bias and, as such, they may not support the licensure of your product."

2. The design of study 1205 differs from study 1310, an adequate and well-controlled study, in important aspects. Below is an incomplete list of the differences and corresponding study outcomes.

   a. Randomization was not stratified. Imbalance with respect to gender was observed: 8:8:12 females randomized to the 100 U/kg, 50 U/kg, and placebo arms, respectively, and 5:4:1 males to the three arms, respectively.

   b. The primary efficacy endpoint was the time to beginning of relief of symptoms at the eligible location that shows the first response to treatment (OVS decrease of ≥20 mm from Baseline with persistence). The VAS appeared to be different from the VAS used for study 1310 as well. For example, there was a question of "How hungry are you?" for the abdominal and urogenital locations.

   c. VAS was assessed at a much sparser grid of time points compared to study 1310. The time points were -1 hour (subject reporting), 0 hour (start of infusion), 15 and 30 minutes, 1, 2, 4, 8, 12, 16, 24, and 48 hours, and Day 4 after the start of infusion. The assessment at 8 and 12 hours were only performed if the subject was still hospitalized. If the subject was discharged after 4 hours from the administration of study drug, the VAS score at 8 and 12 hours were not completed. In that case the 16 hours VAS score was completed and brought to the hospital at 24 hours post-infusion study visit.

   d. The Per Protocol population excluded 9 out of the 39 (23%) randomized subjects, compared to 5 out of 75 (7%) in study 1310. Six subjects were excluded because "the time between onset of symptoms at the location and Time -1 hours was > 5 hours." (CSR p.71).

   e. "Subjects must notify and discuss symptoms with the investigator or designee prior to traveling to the study center."

   f. The BL --(b)(4)-- refusal to file letter dated Feb 24, 2011 noted that "The protocols for the randomized, placebo-controlled trials lacked sufficient details concerning the handling of subjects in the analysis who were taking, prior to time of initial relief of symptoms, medications, such as C1-Inhibitor products, … which may potentially confound the efficacy analyses." This is in contrast to study 1310's explicit plan regarding rescue medication. Study 1205 in general lacks sufficient explicit details, not to be enumerated here, in the protocol compared with study 1310.

   g. It appears that it generally takes more time for the subjects in one of the two rhC1INH arms than those in the saline arm to start infusion after the start of evaluation (Figure 5). The Kruskal-Wallis test returns a p-value of 0.023. This systematic longer time for subjects in the rhC1INH arms to receive study drug, compared with the saline arm, may compromise efforts in blinding the investigators and the subjects to the assignment to arms.

Figure 5.

Time from start of evaluation to start of infusion by treatment arm for the mITT set (13 in the 100 U/kg, 12 in the 50 U/kg, and 13 in the saline arms, respectively). The medians were 81, 69.5, and 47 minutes, respectively. The numbers are calculated from the 27-page Listing 16.2.4.6 "Onset of HAE Symptoms and Time of Attack: Full Analysis Set (MITT)" (16.2 SUBJECT DATA LISTINGS, pp.699-725 of 4366), by subtracting "the time from attack onset to evaluation" from "the time from attack onset to start of infusion".

Because study 1205 were not adequately designed and conducted to prevent biases, statistical analyses of the study endpoints should be interpreted as exploratory and the corresponding p-values and confidence levels should not be interpreted to carry their usual probabilistic meaning. This reviewer does not perform additional analyses or verify the applicant's analyses. The results on the primary endpoint from the study report are included below for completeness (Figure 6, Table 7). Note that no subject was censored in the Kaplan-Meier plot.

Figure 6.
Kaplan-Meier plot of time to beginning of relief of symptoms (FAS, [mITT]) (Overall VAS Score) (Source: Original BLA 125495/0; study1205 CSR p.80)
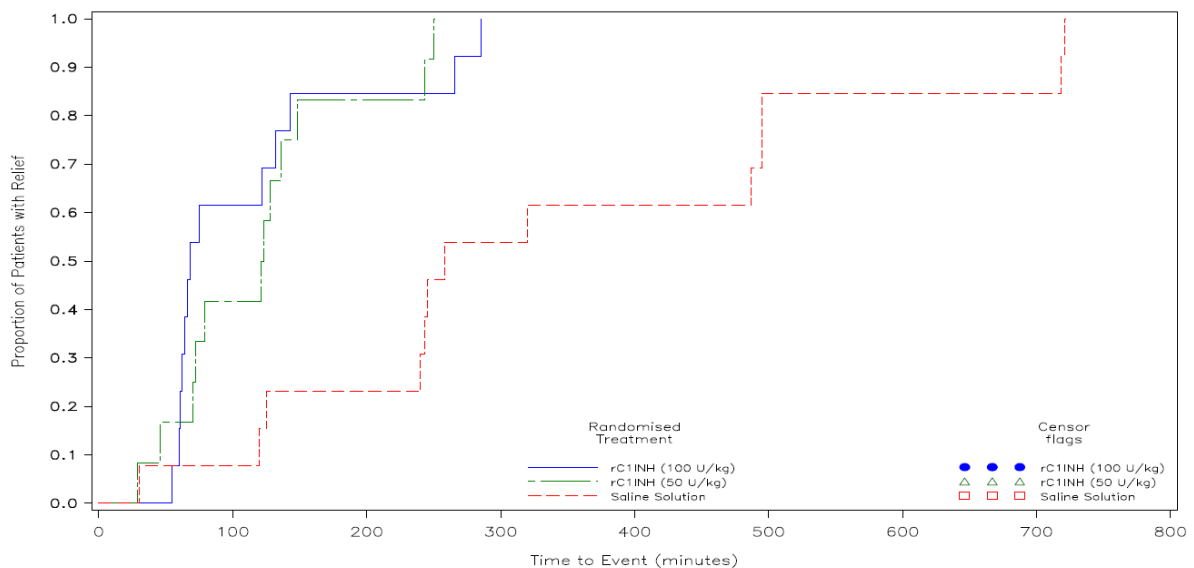

Table 7.
Median Time (Minutes) to beginning of relief of symptoms: Overall VAS Score Decrease of ≥20 mm with Persistence (FAS, [mITT]) (Source: Original BLA 125495/0; study1205 CSR p.79)

Table 16 Median Time (Minutes) to Beginning of Relief of Symptoms: Overall VAS Score Decrease of ≥20 mm with Persistence (FAS, [mITT])

Minutes	rhC1INH (100 U/kg) (N=13)	rhC1INH (50 U/kg) (N=12)	Saline Solution (N=13)
Median (95% CI)	68.0 (62.0, 132.0)	122.0 (72.0, 136.0)	258.0 (240.0, 495.0)
Log rank test p-value*	**0.001**	**<0.001**	

Source: *Table 14.2.1.1* CI=confidence interval, FAS=full analysis set, mITT=modified intention-to-treat,

8. INTEGRATED OVERVIEW OF SAFETY

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.3, Table of Studies/Clinical Trials, for the ten clinical trials used to evaluate safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The full safety database contained 236 subjects exposed to a total of 940 administrations of rhC1INH (Table 8, Figure 7). Data for subjects in these studies were pooled into three safety analysis sets as follows.

- The RCT Safety Analysis Set included pooled safety data from all subjects who received double-blind treatment (rhC1INH or saline) in study 1205RCT, study 1304RCT, and the RCT phase of Study 1310. In these studies, HAE subjects received a single treatment of rhC1INH or saline for an acute angioedema attack. The RCT Safety Analysis Set was a subset of the Safety Analysis Set (defined next) and included a total of 137 unique subjects who were treated for 144 angioedema attacks. The difference between the number of unique subjects and the number of treated attacks was due to participation of seven subjects in more than one study. Some subjects also received an additional dose of rhC1INH.

- The Safety Analysis Set included pooled safety data from seven studies, studies 1202, 1203, 1205RCT, 1205OLE, 1304RCT, 1304OLE, and 1310 (RCT and OLE phases), evaluating rhC1INH in subjects with symptomatic HAE. In the OLE studies/phase, subjects with HAE could receive repeated treatments for multiple separate acute angioedema attacks. This set consisted of 205 subjects with HAE treated for 650 acute angioedema attacks, including 4 subjects in study 1310RCT saline group that received rescue medication. The greatest number of treated attacks was counted for subjects who received rhC1INH 50 IU/kg single dose or 50 IU/kg single dose + additional dose (145 subjects treated for 393 attacks), the rhC1INH dose for which licensure is sought. Safety data for the saline group in the Safety Analysis Set are derived from the RCT studies as no subjects received saline in the OLE studies/phase.

- The Asymptomatic (Asymp)/HV Analysis Set consisted of all asymptomatic subjects with HAE (studies 1101 and 1207) and Healthy Volunteers (HVs) subjects (study 1106) treated in clinical trials of rhC1INH. This set included 51 subjects who received 290 doses of rhC1INH ranging from 6.25 to 100 IU/kg.

The demographic characteristics of subjects in the RCT Safety Analysis Set were similar to those in the Safety Analysis Set at the time they were treated for Attack 1. Note that Table 9 in ISS p.54 listed 222 as the total number of subjects in the Safety Analysis Set,

which is inconsistent with the 205 given elsewhere in the text. Most subjects were of Caucasian race (95%). More subjects were female (63%). Subjects aged between 14 and 71 years, with a median of 37 years, 87% between 18 and 65 years, 19 adolescent subjects (<18 years of age), and 9 subjects over age 65 years. Subjects weighted between 44 and 172 kg, with a median of 75.2 kg.

Figure 7.
Studies contributing to the Safety Analysis Set (Source: ISS p.35, Figure 1).
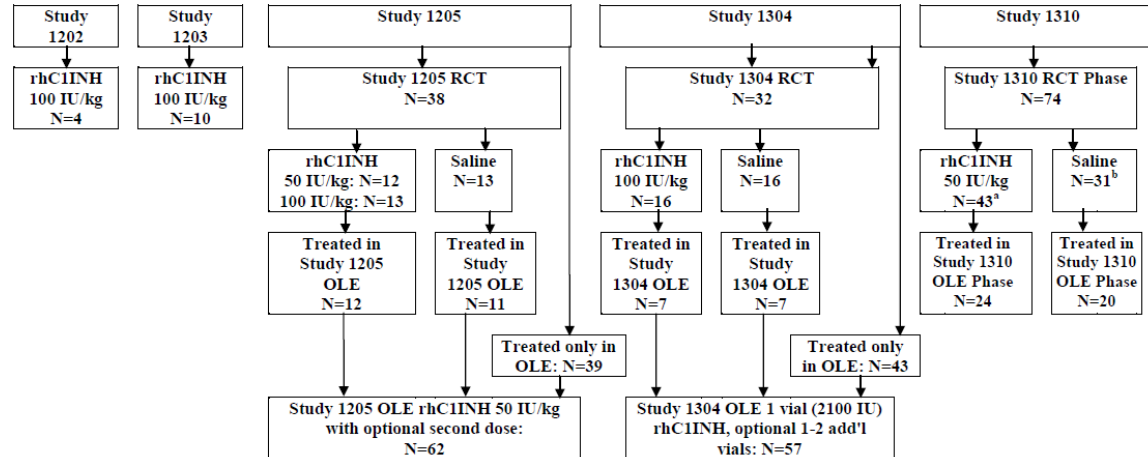
Table 8.
Number of HAE subjects and HV subjects who received rhC1INH, and number of treated attacks or administrations by study for all clinical studies. (Source: ISS p.32, Table 2)

Study	Study Population	Number of Participants	Number of Attacks
1202/1203	Symptomatic HAE patients	14	21
1205 RCT	Symptomatic HAE patients	25	25
1205 OLE	Symptomatic HAE patients	62	168
1304 RCT	Symptomatic HAE patients	16	16
1304 OLE	Symptomatic HAE patients	57	194
1310 RCT Phase	Symptomatic HAE patients	56[a]	56
1310 OLE Phase[b]		44	170
Subtotal	**Symptomatic HAE patients**	**205[c]**	**650**

Study	Study Population	Number of Participants	Number of Administrations
1106	HV subjects	14	59
1101	Asymptomatic HAE patients	12	24
1207	Asymptomatic HAE patients	25	207
Subtotal	**Asymptomatic HAE patients/HV subjects**	**51**	**290**

All studies	**All populations**	**236**	**940**

HAE: hereditary angioedema; HV: healthy volunteer; OLE: open-label extension; RCT: randomized, controlled trial; rhC1INH: recombinant human complement component 1 esterase inhibitor.

Notes: Table does not include patients who only received saline.

[a] In the RCT Phase of Study 1310, thirteen patients randomized to saline treatment also received rhC1INH as rescue medication; these 13 patients are included in the total 56 patients.
[b] Interim data collected through 14 September 2012 are included for the OLE Phase of Study 1310.
[c] Because some patients participated in more than one study, the total count only considers unique patients.

8.4 Safety Results

8.4.1 Deaths

One death was reported for an asymptomatic HAE subject treated in a prophylaxis study, study 1207. Subject -----(b)(6)------ experienced a fatal laryngeal angioedema attack 25 days after receiving the final dose of rhC1INH in the study. This subject was a 50-year-old female in Romania with a past medical history of more than 50 acute angioedema attacks per year. In study 1207, the subject received eight weekly slow iv injections of rhC1INH 50 IU/kg between --------(b)(6)------ and ------(b)(6)------. The subject experienced a total of seven breakthrough attacks during the study period; two of these attacks were treated with rhC1INH on February 12, 2010 and March 05, 2010. On --(b)(6)---, 25 days after the last administration of rhC1INH, the subject telephoned the Investigator around 1430 h (2:30pm) to report dysphonia, malaise, and progressive swelling of the neck. The subject was taken to the local hospital by ambulance and was admitted around 1700 h. The Investigator was informed at 2030 h (8:30pm) that the subject had died an hour before. The subject was not given any rhC1INH or any other medications. No laboratory data were provided. Autopsy was performed on ----(b)(6)---------. The cause of death was reported as laryngeal edema. The Investigator assessed this event as not related to treatment with rhC1INH.

8.4.2 Nonfatal Serious Adverse Events

Acute angioedema attacks commencing >24 h after rhC1INH administration (coded to MedDRA PT Hereditary angioedema) assessed as serious are included.

Table 11 summarizes the frequency of subjects experiencing at least one SAE for both the RCT Safety Analysis Set and the Safety Analysis Set, and the types of SAE in MedDRA Preferred Term. Only the hypersensitivity experienced by one subject in the rhC1INH 50 IU/kg single dose group in study 1205 was rated as "possible" in its relationship to study drug. All the other SAEs were rated as "Definitely not", "Unlikely", or "Not related". Notably, all 4 SAEs reported in the saline dose group were from study 1304RCT.

Table 12 summarizes SAEs by dose group for the Asymp/HV Analysis Set. Four of 51 rhC1INH-treated participants (8%) experiences at least one SAE. All SAEs were assessed by the Investigator as severe. The three SAEs, excluding the death reported previously, are summarized below.

- One HV subject in study 1106 experienced severe allergic reaction commencing three minutes after start of iv injection of rhC1INH. This subject had previously-undisclosed history of allergy to rabbit dander/hair. This SAE was assessed as probably related to study drug.

- One asymptomatic HAE subject that was treated in study 1101 experienced severe abdominal HAE attack 71 days after receiving rhC1INH 6.25 IU/kg. This SAE was assessed as unlikely related to study drug.

- One asymptomatic HAE subject that was treated in study 1207 experienced appendicitis 4 days after the subject's last dose of rhC1INH. This SAE was assessed as definitely not related to study drug.

Table 9.

Frequency of subjects experiencing at least one SAE and the types of SAE in MedDRA Preferred Term, by dose group, for both RCT Safety Analysis Set and Safety Analysis Set (Source: summarized based on ISS pp.83-86, Table 20)

Dose Group	RCT Safety Analysis Set	Safety Analysis Set	MedDRA Preferred Term
rhC1INH 100 IU/kg single dose	2/29	3/43	Abdominal Pain Colitis Laryngeal oedema
rhC1INH 50 IU/kg single dose	2/61	11/129	Vertigo Hereditary Angioedema Colitis Laryngeal edema Oedema Peripheral Pneumonia Abdominal pain Hypersensitivity *Escherichia* sepsis Sepsis Urinary tract Infection Abdominal hernia
rhC1INH 50 IU/kg + additional dose	0/5	2/21	Hereditary Angioedema Abdominal pain Angioedema
rhC1INH 2100 IU single dose	-	1/43	Acute myocardial infarction
rhC1INH 2100 IU + additional dose	-	1/34	Tonsillitis
Saline	3/47	3/47	Prostate examination (biopsy) Biliary colic Calculus ureteric Ureteric calculus Removal

Table 10.
SAEs by MedDRA SOC and Preferred Term, all Administrations – Asymp/HV Analysis Set
(Source: ISS p.118, Table 29)

	rhC1INH 100 IU/kg Single dose (N=20) n (%)	rhC1INH 50 IU/kg + Add'l dose (N=1) n (%)	rhC1INH 50 IU/kg Single dose (N=31) n (%)	rhC1INH ≤25 IU/kg Single dose (N=9) n (%)	rhC1INH Total (N=51) n (%)
Total number of administrations	65	1	212	12	290
Number of participants with ≥1 SAE	1 (5)	0	2 (6)	1 (11)[a]	4 (8)[a]
MedDRA SOC Preferred Term					
Immune system disorders	1 (5)	0	0	0	1 (2)
Hypersensitivity	1 (5)	0	0	0	1 (2)
Infections and infestations	0	0	1 (3)	0	1 (2)
Appendicitis	0	0	1 (3)	0	1 (2)
Respiratory, thoracic and mediastinal disorders	0	0	1 (3)	0	1 (2)
Laryngeal edema	0	0	1 (3)	0	1 (2)
Congenital, familial and genetic disorders	0	0	0	1 (11)	1 (2)
Hereditary angioedema[a]	0	0	0	1 (11)	1 (2)

8.6 Safety Conclusions

There does not appear to be a safety signal from a statistical perspective.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Original BLA 125495/0 proposed the treatment of acute angioedema attacks in HAE subjects with a single dose of 50 IU/kg of rhC1INH. The supporting clinical database comprised eight clinical studies. Study 1310 was the sole adequate, well-controlled confirmatory study, out of the three randomized, double-blind, and saline-controlled studies that treated single acute attacks in HAE subjects, to support efficacy claims.

Study 1310 randomized 75 HAE subjects reporting with eligible acute attacks, at a 3:2 ratio, stratified by gender and the anatomical location of the angioedema attack, to receive 50 IU/kg rhC1INH or saline in a double-blind manner to treat the acute attacks. The study aimed to ensure roughly 50% of the subjects treated were from US. The primary efficacy endpoint was the time to beginning of relief of symptoms with persistence at the primary attack location, based on TEQ, a patient reported outcome.

The primary efficacy endpoint was significantly shorter in the rhC1INH arm compared to the saline arm, with a median of 90 minutes versus 152 minutes, and a p-value of 0.031 from the primary analysis of log-rank test stratified by the primary attack location.

Findings in subgroup analysis in study 1310 received further statistical consideration. Only 8 out of the 25 planned subgroup categories in the protocol had sample sizes in the treatment arms not close to 0 or 100%. Among these, for the primary efficacy endpoint, numerically similar response times between the rhC1INH arm and the saline arm were observed in two categories, female subjects and US subjects. Due to interest in evaluating consistency across regions in multi-regional trials and the imbalance in treatment assignment when geographical region and gender were considered at the same time, further statistical consideration was focused on the US subjects. For US subjects, the median times were 97.5 and 90.0 minutes in the rhC1INH versus the saline arm, respectively.

The observed similarity in response time between the two arms in US subjects may reflect Type II error or confounding factors not considered in the study design, or it may reflect genuine lack of efficacy in the US subjects. It was not possible to discriminate between these two potential explanations with statistical reasoning based on the available data within the study, because the study was not powered for any subgroup analysis and the study size was small. Clinical judgment is required to assess which one of the two potential explanations is more plausible.

The applicant had submitted various post-hoc analyses to explore the role of potential confounding factors in explaining the results in the US subjects and to explore re-analysis of the data, including attack severity at baseline and rescue medication usage, among others. Statistical reasoning is of limited value due to the post-hoc nature of these additional analyses. Clinical judgment is required to assess the interpretation of these additional analyses.

The full safety database contained 236 subjects, including healthy volunteers (HV), asymptomatic HAE subjects, and HAE subjects experiencing acute attacks, exposed to a total of 940 administrations of rhC1INH at various doses, single or repeated. The rhC1INH 50 IU/kg single dose or 50 IU/kg single dose plus additional doses, the proposed rhC1INH dose in the application, were given to 145 subjects for 393 attacks.

One death was reported for a Romania HAE subject under rhC1INH prophylaxis treatment in study 1207, after experiencing a fatal laryngeal angioedema attack 25 days after the final dose of rhC1INH. Two nonfatal serious adverse events (SAE) were assessed as probably or possibly related to rhC1INH. One HV subject in study 1106 experienced severe allergic reaction commencing three minutes after start of iv injection of rhC1INH. This subject had previously-undisclosed history of allergy to rabbit dander/hair. One HAE subject receiving a single dose of 50 IU/kg rhC1INH in study 1205OLE experienced hypersensitivity. The remaining nonfatal SAEs were assessed as "unlikely", "definitely not", or "not related" in their relationship to study drug by the applicant.

10.2 Conclusions and Recommendations

Overall the sole confirmatory study showed statistically significant reduction in time to beginning of relief of symptoms with persistence, from a median of 152 minutes in the saline arm to 90 minutes in the rhC1INH arm (p=0.031). Approximately half of the subjects were treated at US sites. These subjects showed similar time to beginning of

relief in the two arms, with a median of 97.5 minutes in the rhC1INH arm and of 90 minutes in the saline arm. The degree of concern over this observation and the likelihood that this observation reflects Type II errors instead of genuine lack of efficacy in the US subjects cannot be determined statistically with available data and is therefore deferred to clinical judgment. The product rhC1INH does not produce a safety signal from a statistical perspective.