

Application Type	Original Application
STN	125495/0
CBER Received Date	April 16, 2013
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Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Pharming Group NV
Established Name	Recombinant C1 Esterase Inhibitor (Human)
(Proposed) Trade Name	RUCONEST
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	<No Formulations>
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	50 IU/kg
Indication(s) and Intended Population(s)	Treatment of acute attacks of hereditary angioedema in adult and adolescent patients, Adult, Young Adult

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Glossary

C1INH	C1 esterase inhibitor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
(b)(4)	----- (b)(4) -----
FAS	Full Analysis Set
HAE	Hereditary Angioedema
HV	healthy volunteer
ITT Analysis Set	intent-to-treat analysis set
---(b)(4)---	----- (b)(4) -----
mITT	modified intent-to-treat
OLE	Open label extension
pd-C1INH	plasma-derived C1INH
PP Analysis Set	per protocol analysis set
PRO	patient-reported outcome
RCT	Randomized controlled trial
rhC1INH	recombinant C1INH (Ruconest)
RTF	Refuse-to-File
SAE	serious adverse event
---(b)(4)---	----- (b)(4) -----
TEAE	Treatment-emergent adverse event
TEQ	Treatment effect questionnaire
VAS	Visual analog scale

1. Executive Summary

Hereditary angioedema (HAE) is an autosomal dominant genetic disease resulting from reduced plasma levels of C1 esterase inhibitor (C1INH). Episodic edema can occur at subcutaneous or submucosal anatomical sites, which varies greatly in location, frequency and duration among affected patients. Laryngeal/pharyngeal edema can be life-threatening. Currently licensed or approved products to treat HAE include plasma-derived C1INH (Berinert[®], Cinryze[®]), a synthetic polypeptide inhibitor of activated kallikrein (Kalbitor[®]), and a low-molecular weight inhibitor of bradykinin receptor 2 (Firazyr[®]).

Pharming Group NV has submitted STN 125495 for licensure of their recombinant human C1 esterase inhibitor (rhC1INH) product Ruconest[®], which is purified from transgenic rabbit milk, for the following indication:

RUCONEST is a recombinant human C1 esterase inhibitor (rhC1INH) indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients.

The two phase 2 studies [1304](#) and [1205](#), the results of which are generally supportive for the claim of efficacy and which were the basis for the European Medicines Agency (EMA) approval, will be discussed; followed by a discussion of the phase 3 [pivotal study 1310](#). The results for the pre-specified analysis subgroups ‘female’ and ‘geographic region – U.S.’ in the pivotal study 1310 suggested lack of efficacy in these subgroups, and required discussions with the applicant.

1.1 Product.

Ruconest has the -----(b)(4)-----; however, the attached oligosaccharide structures are -----(b)(4)----- . The product is purified from (b)(4) rabbit milk using three chromatography steps, with a solvent/detergent virus inactivation step, a nanofiltration step for virus removal, -----(b)(4)----- for the final formulation, followed by vialing and lyophilization.

After reconstitution, the final vialled product contains rhC1-INH 150 IU/mL in an excipient containing sucrose 67 mg/mL, sodium citrate 6 mg/mL, and citric acid 72 micrograms/mL.

Potency is assigned by measurement in a C1 esterase inhibition assay using an international standard that was established in 2010. The clinical trials 1205, 1304, and 1310 were completed or ongoing when the international standard was established, so all used products labeled in “U/kg”, not “IU/kg”. This review uses the dosing terminology used in the trials, “U/kg”, because this terminology was used in the clinical trial protocols. The final labeling will refer to “IU/kg”. (see section [5.3](#))

1.2 Regulatory Background.

IND 11785 was submitted in June 2004 to CDER. The IND was transferred to CBER in October 2008. STN-(b)(4)- (precursor BLA to STN125495) received a refuse-to-file letter from CBER on February 24, 2011 (see [Appendix 2](#)). STN125495 was submitted on April 16, 2013,

and refuse-to-file recommendations were made by the BLA chair and the clinical reviewer, which were overruled by supervisors (see section 2.5 for a more detailed regulatory chronology).

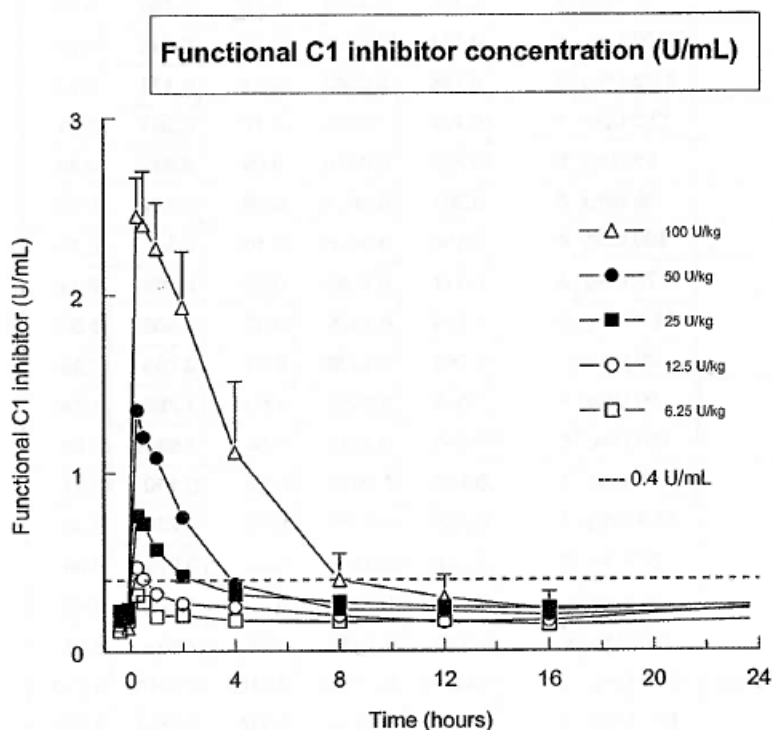
1.3 Clinical Studies.

1.3.1 Dose Justification for Clinical Studies of Ruconest

There were no clinical dose-finding studies. The applicant based the dose for clinical studies on assumptions made from the pharmacokinetics of Ruconest.

Study 1101 was a phase 1 exploratory study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ascending intravenous doses of recombinant C1 inhibitor in asymptomatic patients with hereditary angioedema.

The following graph shows the levels of functional C1 inhibitor activity (U/mL) that were observed in plasma samples over time:



Source: STN125495 Module 5.3.3.2 clinical report for study C1 1101-01 page 39 of 96

The applicant made the assumption that C1-INH levels above 70% of the normal level, maintained for several hours after dosing, would be effective in treating a HAE attack.

Based on these results, the applicant chose doses of 50 U/kg and 100 U/kg to be tested in efficacy studies.

1.3.2 Study 1205 RCT

[Study 1205 RCT](#) was a randomized (1:1:1), double-blind, saline-controlled, parallel group (rhC1INH 100 units/kilogram vs. 50 units/kilogram vs. saline), multi-center clinical study, with an open-label extension study upon completion of study 1205 RCT. The study was conducted in the U.S. and Canada.

The primary efficacy endpoint was the time to the beginning of relief, assessed using overall severity VAS scores, where beginning of relief was defined as a decrease in VAS score ≥ 20 mm (with persistence of the decrease at the next assessment time) at an eligible anatomical location, compared to Baseline (Time 0, just prior to study medication infusion). If a patient had an attack at more than 1 (eligible) location, the earliest relief/resolution of these locations was considered.

The applicant's summary of the efficacy results for study 1205 is given in the following table:

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: STN125495, Study 1205 Clinical Report, p.79

CI=confidence interval, FAS=full analysis set, mITT=modified intention-to-treat, SD=Standard deviation, VAS=visual analog scale 95% CI's are displayed as conventional estimates of CI, statistical tests are performed at 1% level.

* Comparing against Saline Solution.

The interpretation of Study 1205 outcomes is complicated by an imbalance in subjects for the important baseline covariates gender and anatomical site (abdominal vs. non-abdominal) (see [6.1.11.1](#)). The small study size and the imbalance in the number of subjects in the gender, anatomical site, and dose cohorts makes study 1205 difficult to interpret for a definitive analysis of dose effect.

1.3.3 Study 1304 RCT

[Study 1304 RCT](#) was a randomized (1:1), saline-controlled, double-blind, parallel group (rhC1INH 100 units/kilogram i.v. vs. saline i.v.), multi-center clinical study. The study was conducted in Italy (26 subjects at 7 sites), Spain (2 subjects at 1 site), UK (1 subject at 1 site), Israel (1 subject at 1 site), and Romania (2 subjects at 1 site). The study was followed by an open-label extension (OLE).

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

infusion). If a patient had an attack at more than one (eligible) location, the earliest relief/resolution of these locations was considered.

The applicant's summary of the efficacy results for study 1304 is given in the following table:

Time to Beginning of Relief of Symptoms: Overall VAS Score Decrease of ≥ 20 mm

	rhC1INH (100 U/kg)	Saline Solution	Log rank test P= value
FAS (mITT)	61.5 (40.0, 75.0) [N = 16]	508.0 (70.0,720.0) [N = 16]	0.003
PP Analysis Set	63.0 (20.0, 123.0) [N = 11]	520.0 (480.0,720.0) [N = 15]	<0.001

95% CIs are displayed as conventional estimates of CI, statistical test are performed at 2.941% level

It should be noted that study 1304 was small compared to other marketing authorization studies for this indication, and the dose studied was not the dose sought for labeling, which is 50 units/kg.

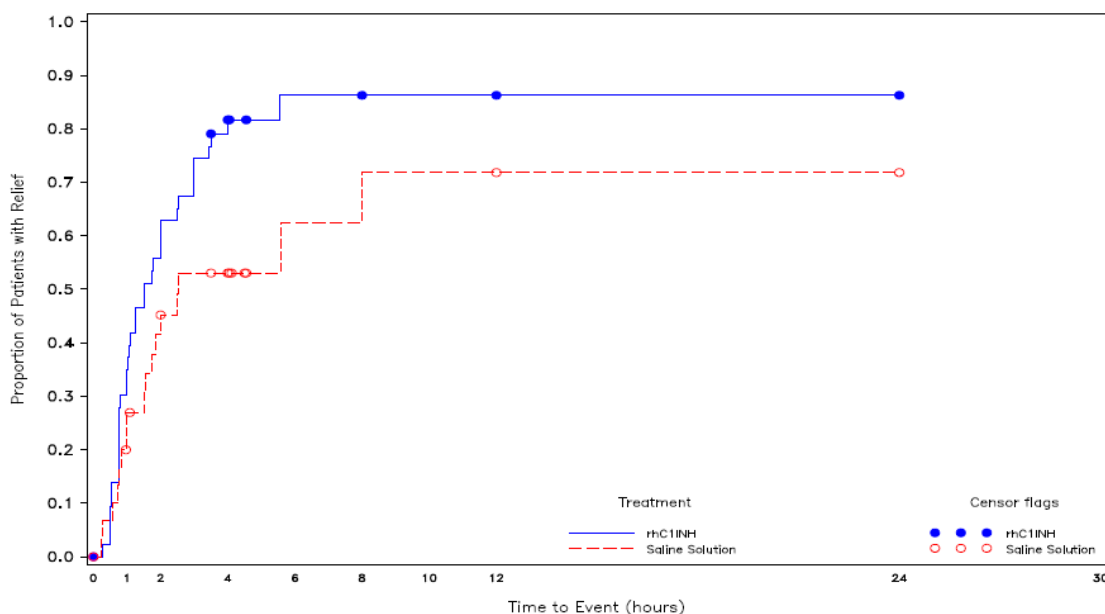
1.3.4 Study 1310 RCT

The pivotal study 1310 RCT was a randomized (3:2) placebo-controlled controlled trial in 73 HAE subjects (42 rhC1INH; 31 saline) experiencing a HAE attack (37 subjects at US sites; 36 at European sites). The rhC1INH dose was 50 units/kg, the placebo was saline. The primary endpoint was time-to-initial-relief-of-symptoms as measured by a Treatment Effect Questionnaire (TEQ), with a secondary endpoint being outcome evaluation by a visual analog scale (VAS).

The primary efficacy endpoint was the time to beginning of relief of symptoms at the primary attack location (based on Questions 1 and 2 of the TEQ, with persistent improvement at the next assessment time).

The study 1310 RCT results for the primary endpoint time-to-beginning-of-relief-of-symptoms are shown in the following Kaplan-Meier plot:

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms with Persistence (Based on Questions 1 and 2 of the TEQ, with Persistence) in the RCT Phase: RCT ITT Analysis Set



Source: STN125495 Study 1310 Clinical Report page 87 of 2609

The applicant's summary of the efficacy results for study 1310 is given in the following table

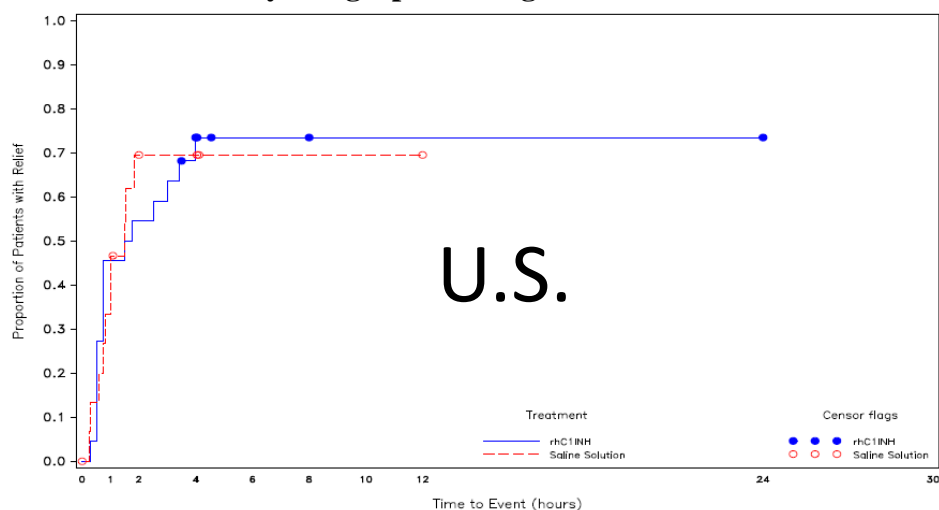
Study 1310 RCT: Time (minutes) to Beginning of Relief of Symptoms based on questionnaire

Time to Beginning of Relief of Symptoms, minutes	RUCONEST 50 Units/kg (N=44)	Placebo (N=31)
Median	90	152
95% CI	(61, 150)	(93, -)
p-value	0.031	

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

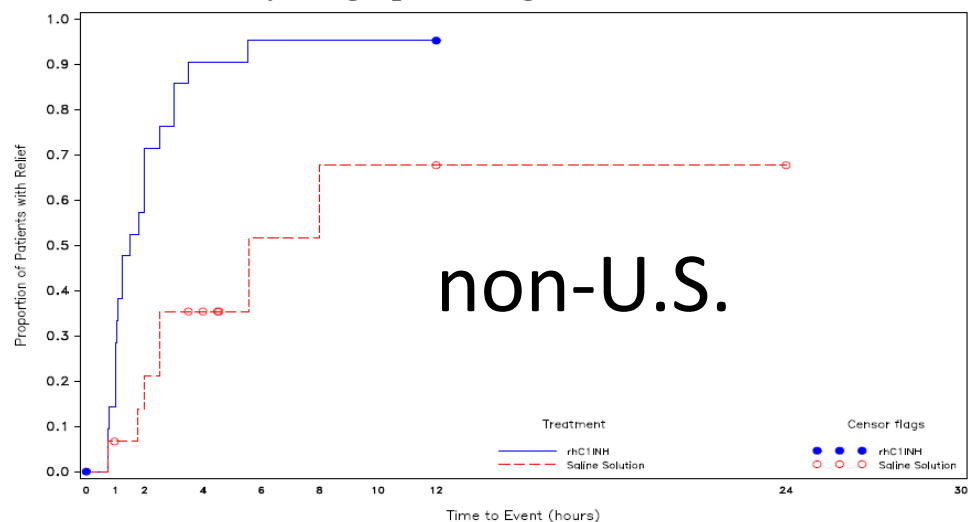
Taken as a whole, study 1310 RCT showed statistical significance for treatment effect, although this outcome was driven by the non-U.S. results, which differed from the U.S. results, as shown in the following two charts:

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence) at the primary attack location by Geographical Region - USA



Source: STN125495 Study 1310 Clinical Report, Page 1001 of 2609

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence) at the primary attack location by Geographical Region – Rest of the World



Source: STN125495 Study 1310 Clinical Report, Page 1002 of 2609

The applicant identified the rapid response in the U.S. female placebo subgroup as being responsible for this outcome, as shown in the following table:

Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence), Subgroup Analyses: RCT ITT Analysis Set		
	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=44)	Saline (N=31)
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]
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]
Source: Table 14.2.1.15RCT to Table 14.2.1.21RCT. TEQ = Treatment Effect Questionnaire; CI = confidence interval; RCT = randomized controlled trial; ITT = intent-to-treat; Notes: In the saline treatment group 11 (35%) patients received rescue medication or disallowed concomitant medication prior to beginning of relief of symptoms, and were therefore censored, resulting in inestimable medians for some of the subgroups; values that are not estimable are displayed as '-'. Source: STN125495/0 Clinical Report		

The anomalous results in the pre-specified analysis subgroups 'gender' and 'geographic region' were not included in the pre-BLA meeting package because the applicant said the results for pre-specified subgroups were not available at that time. Upon submission of STN125495, the review team made a Refuse-to-File (RTF) recommendation for scientific incompleteness based on these anomalous gender and geographic region results; however, this recommendation was overruled by CBER supervisors who said this RTF provision does not apply to this situation. These anomalous results are also not presented in the publication of study 1310.¹

In the File-with-Deficiencies letter (see [Appendix 3](#)) FDA referred to the failure to demonstrate efficacy in these two subgroups. The applicant replied (see [Appendix 4](#)) that both outcomes could be explained by one observation: the long average time interval for U.S. females in the placebo arm from time of HAE attack onset to the time of presentation at the clinical site. The applicant argued that a longer time to treatment would tend to favor a quicker response because HAE attacks are self-limiting.

FDA reviewers have identified systematic differences in the databases for the U.S. and non-U.S. components of study 1310 that led to the conclusion that, even though the same protocol was used, the U.S. and non-U.S. components were conducted as if they were separate clinical trials (see section [6.3.11.5](#) Exploratory and Post Hoc Analyses).

¹ *Ann Allergy Asthma Immunol* **112**:163-169 (2014)

The FDA review team discussed these results with the applicant, and the applicant responded with four post-hoc analyses to address these concerns (see [6.3.11.1](#)).

1.4 Immunogenicity

Most studies used single-dose administration of Ruconest, with some subjects receiving additional doses for subsequent HAE attacks that were treated in open-label extension studies. Therefore, the safety database is not designed to provide detailed information on Ruconest immunogenicity over long-term use. The submitted safety database shows that at least 10% of subjects formed a specific antibody response to Ruconest after five treated HAE attacks; however, these antibodies did not neutralize Ruconest activity in an in vitro C1 esterase inhibition assay (see [6.3.12.5](#)). At least 50% of subjects formed antibodies against rabbit host cell proteins after five treated HAE attacks. There were no adverse events attributable to post-exposure antibody formation; however, one normal volunteer in study 1106 who had an undisclosed pre-existing rabbit allergy developed anaphylaxis during Ruconest administration, with complete recovery. The Ruconest label includes a contraindication in subjects with a history of allergy to rabbits or rabbit-derived products and a warning about the possibility for a hypersensitivity reaction after treatment with Ruconest.

1.5 Thrombogenicity

There were no reported thromboembolic adverse events in the Ruconest studies.

1.6 Laryngeal HAE Attacks

There were too few subjects with laryngeal HAE attacks to evaluate efficacy for this anatomical location. In study 1205, one subject who was treated with 50 Units/kg for a facial attack subsequently developed two reported episodes of laryngeal edema on the same day. In study 1310, one subject developed laryngeal edema symptoms after saline treatment and was rescued with Ruconest, but did not report initial relief until 4 hours later. These cases are not supportive for a claim of efficacy for the use of Ruconest to treat laryngeal HAE attacks.

There is a safety concern based on the lack of efficacy information on the use of Ruconest to treat laryngeal HAE attacks. Therefore, a Limitation of Use regarding the effectiveness of Ruconest for laryngeal attacks is included in the labeling (see [6.1.12.5](#)).

1.7 Deaths

There were no deaths during the clinical trials. However, one Romanian female subject died from HAE laryngeal edema 25 days after completing the routine prophylaxis exploratory study 1207. The applicant stated no C1INH containing product was available to the patient at the time of the laryngeal HAE attack (see [8.4.1](#))

1.8 Recommendation

1. The totality of the efficacy data shows that Ruconest is effective for treating HAE attacks.
2. The anomalous gender and geographic results from study 1310 appear to arise from the rapid placebo response in the U.S. female subgroup, which remains unexplained and can only be addressed through additional clinical studies, if clarification is needed. The Ruconest label provides the option for an additional dose if there is an inadequate response after the first dose.
3. The safety database has not demonstrated a safety concern.
4. Labeling should be limited to the treatment of abdominal and facial acute HAE attacks until additional information is available on the efficacy for treatment of laryngeal HAE attacks.
5. Labeling should be strengthened with more information on product immunogenicity.
6. Pharmacovigilance for adverse events that may be related to immunogenicity is warranted. This will be done through monitoring passive reports to the CBER adverse events reporting system. There is an ongoing IND study of the use of Ruconest for routine prophylaxis in subjects with HAE which should provide additional information. A patient registry has been required by the European Medicines Agency, and FDA is adding this patient registry as a post-marketing commitment.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hereditary angioedema (HAE) is an autosomal dominant genetic disease resulting from reduced plasma levels of C1 esterase inhibitor (C1INH). Episodic edema can occur at subcutaneous or submucosal anatomical sites, which varies greatly in location, frequency and duration among affected patients. Laryngeal/pharyngeal edema can be life-threatening.

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

Currently licensed or approved products to treat HAE attacks include plasma-derived C1INH (Berinert[®]), a synthetic polypeptide inhibitor of kallikrein (Kalbitor[®]), and a low-molecular weight inhibitor of bradykinin receptor 2 (Firazyr[®]).

2.3 Safety and Efficacy of Pharmacologically Related Products

The following table contrasts the licensure or approval endpoints, study size, and safety findings for Berinert, Kalbitor, and Firazyr:

Product	Efficacy Endpoint	Number of Subject Studied in Efficacy Studies	Safety Observations
Berinert [®]	Time of onset of relief of symptoms (standardized question at time intervals) for abdominal or facial symptoms	124 subjects in pivotal study; 28 subjects with laryngeal attacks in post-licensure study	Nausea, dysgeusia, headache “Thromboembolic events including basilar artery thrombosis, multiple pulmonary microemboli, and thrombosis have been reported with the use of Berinert at the recommended dose following treatment of HAE.”

Product	Efficacy Endpoint	Number of Subject Studied in Efficacy Studies	Safety Observations
Kalbitor [®]	Outcome score at a defined time [Mean Symptom Complex Severity (MSCS) score or the Treatment Outcome Score (TOS)]	143 subjects in 2 studies	Anaphylaxis (boxed warning)
Firazyr [®]	Time of onset of relief (VAS at time intervals) for abdominal or cutaneous symptoms	223 subjects in 3 studies; 60 subjects with laryngeal attacks	Injection site reactions, pyrexia, transaminase increased, dizziness

Source: adapted from Full Prescribing Information for the products

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

Ruconest was approved in the European Union in October 2010 based on the efficacy results from studies 1205 and 1304; study 1310 had not been initiated at that time.

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

The main items in the regulatory background are as follows:

- February 5, 2004, pre-IND meeting with CBER
- June 4, 2004, IND 11785 submitted to CDER
- July 29, 2004, IND 11785 placed on clinical hold by CDER
 - December 15, 2004, clinical hold lifted on IND 11785
- November 10, 2008, IND 11785 transferred to CBER
- June 24, 2010, European Medicines Agency (EMA) granted market authorization for Ruconest for treatment of HAE attacks
 - based on efficacy data from studies 1205 & 1304
- February 24, 2011, Refuse-to-File letter issued for STN-(b)(4)- (see [Appendix 2](#))
- June 15, 2011, CBER issued Special Protocol Assessment (SPA) letter (see [Appendix 1](#)) for study 1310
- December 21, 2012, FDA (CBER) fax responding to November 30, 2012, pre-BLA meeting package

- CBER said BLA can be submitted
 - sponsor did not present the pre-specified geographic or gender analysis in the pre-BLA meeting package
- April 16, 2013, STN125495 submitted, containing results for pivotal study 1310 and supporting data from previous studies
 - Refuse-to-File (RTF) recommendation memos recorded from the clinical reviewer (Dr. Maplethorpe) and the BLA chairperson (Elena Karnaukhova, Ph.D.) based on scientific incompleteness [i.e. failure to demonstrate efficacy in study 1310 for female subjects (63% of enrollment) and failure to demonstrate efficacy in study 1310 for U.S. subjects (50% of enrollment)]
 - RTF recommendation was overruled by Nisha Jain, M.D. (supervisor of Dr. Maplethorpe), Abdu Alayash, Ph.D. (supervisor of Dr. Karnaukhova), and Basil Golding, M.D. (Division Director) because they said the scientific incompleteness RTF provision does not apply in this situation
- July 26, 2013, the applicant responded (see [Appendix 4](#)) to comments in the June 14, 2013, File-with-Deficiencies letter (see [Appendix 3](#))
- October 10, 2013, Mid-cycle meeting
- January 16, 2014, Late-Cycle meeting (LCM)
 - FDA informed the applicant of a major review issue: results of pivotal study 1310 suggest a lack of efficacy among female subjects and subjects enrolled at U.S. sites
 - The applicant presented additional analyses of previously submitted data
- April 29, 2014, Dr. Basil Golding informed the review team that OBRR management decided on March 19, 2014, that STN125495 would be approved
- May 30, 2014, the applicant submitted a final report for requested analysis for neutralizing antibodies among anti-Ruconest positive samples

2.6 Other Relevant Background Information

A Brief Note on Primary Endpoint Justification for Clinical Trials in HAE

The measurement of treatment response in clinical trials of drugs intended to treat HAE attacks is imprecise and highly variable between different clinical trials, “making it extremely difficult to compare results across studies.” (Dr. T. Caballero)

The reasons for the difficulty in HAE attack outcome assessment are summarized by Dr. Teresa Caballero² as follows:

- Extensive heterogeneity with respect to attack location, involvement of single or multiple locations, severity of edema and pain, and attack course and resolution. Importantly, this heterogeneity is observed not only among different HAE patients, but also in comparing different attacks in the same patient.

² *J Clin Immunol* **32**:1204-1212 (2012)

- Symptomatology varies depending on attack location. Although most or all attacks involve substantial edema and pain, abdominal attacks may also involve nausea and/or vomiting, and facial attacks may result in airway compromise and/or facial disfigurement.
- Attacks occur without warning (although some patients may experience prodromal symptoms such as fatigue, erythema marginatum, or paresthesias), and the temporal pattern of attacks varies significantly among patients and within the same patient over time.
- Many symptoms of attacks resist objective evaluation by the physician, and can be experienced and reported by the patient only; these symptoms include pain and sensations of internal swelling.
- Attacks are generally self-limiting, with symptoms increasing in severity over the initial 24 h after symptom onset and then resolving over the following 2 to 5 days. This feature introduces an important element of time sensitivity into efficacy considerations, as an effective acute therapy is expected to resolve symptoms significantly more rapidly than the typical course of an attack.

Plasma-derived C1INH concentrates were approved for marketing in Europe in the 1970-1980's based on replacement dosing, without formal efficacy studies. U.S. licensure required a measurement of efficacy that could be used in adequate and well-controlled clinical trials. In developing an instrument to measure efficacy for treatment of HAE attacks, investigators emphasized two principles:

1. C1INH replacement products affect the earliest part of a proteolytic activation cascade that causes the symptoms of a HAE attack, and do not affect the physiological processes involved in the resolution of a HAE attack; and
2. The patient is the most appropriate evaluator of the primary endpoint, because the investigator cannot observe these early effects, and there is no objective measurement that can register these early effects.

Most protocols for the treatment of HAE attacks use a patient-reported outcome (PRO) measure for the primary endpoint time-to-initial-relief of HAE symptoms. Protocols use one or both of the following two PRO types:

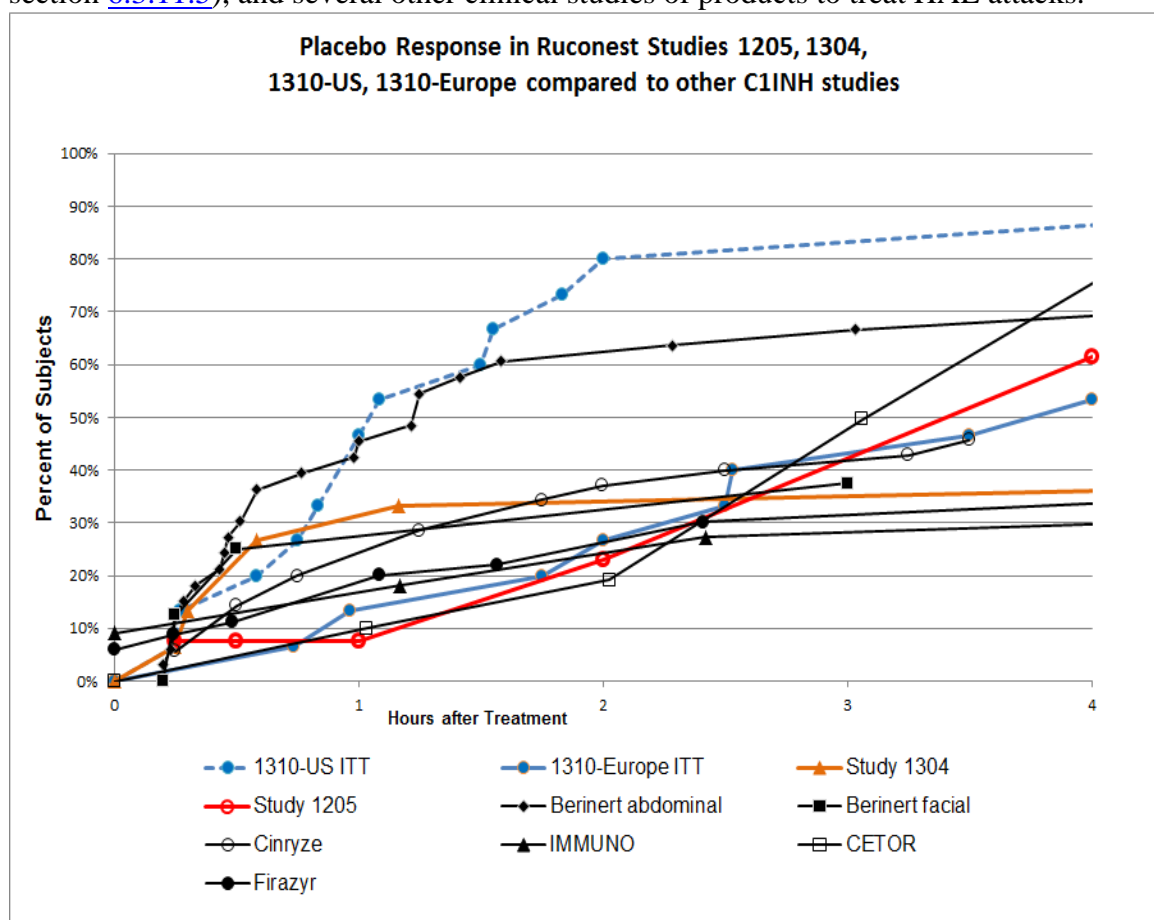
1. Visual Analog Scale (VAS) recording of symptom severity on a 100 millimeter scale in response to a standardized question at specified time intervals, and
2. Categorical recording of symptom severity (worse, no change, better, etc.) in response to a standardized question at specified time intervals.

The choice of methodology appears to influence the timing of response parameters across studies. In addition there appear to be inherent differences in response kinetics based on

anatomical site of the HAE attack (submucosal sites respond sooner than subcutaneous sites); and there appear to be differences related to gender.³

Ruconest phase 2 studies 1205 RCT (U.S. and Canada) and 1304 RCT (Europe) used VAS measurements to assess HAE attack outcomes. Ruconest pivotal study 1310 RCT used categorical outcomes in response to a standardized question at specified time intervals to assess HAE attack outcomes; study 1310 also used a VAS measurement as a secondary endpoint.

The variability of the endpoint time-to-initial-relief of HAE symptoms can be seen in the following chart. This chart shows the time course of the response in the placebo arm for the three Ruconest studies 1304, 1205, and 1310 (separated into the U.S. and European subgroups because these were conducted as if they were two separate studies – see section 6.3.11.5), and several other clinical studies of products to treat HAE attacks.



Study	Source of Data and Primary Endpoint
Ruconest study 1304	STN125495 Listing 16.2.6.3

³ For example, see page 77 of the August 16, 2011, FDA Clinical Review Addendum for NDA 22-150 (Firazyr), or see the European Medicines Agency CHMP ASSESSMENT REPORT FOR Firazyr, which states “Thus, there appears to be a gender effect on the efficacy endpoints irrespective of the treatment arms. This may be related to how females and males perceive their symptom severity.”

Study	Source of Data and Primary Endpoint
	The endpoint was a decrease in VAS score ≥ 20 mm (with persistence of the decrease at the next assessment time).
Ruconest study 1205	STN125495 Listing 16.2.6.3 The endpoint was a decrease in VAS score ≥ 20 mm (with persistence of the decrease at the next assessment time).
Ruconest study 1310	STN125495 Listing 16.2.6.4RCT The endpoint was the time to beginning of relief of symptoms at the primary attack location based on a categorical outcome Treatment Effect Questionnaire [TEQ] (with persistent improvement at the next assessment time).
Berinert (plasma-derived C1INH) abdominal attacks vs. facial attacks	STN125287 Summary Basis of Regulatory Approval (SBRA) The primary efficacy end point was a self-reported time period from the start of treatment to the onset of symptom relief.
IMMUNO (plasma-derived C1INH)	<i>Transfusion</i> 36 :540-549 (1998)
Cinryze (plasma-derived C1INH)	<i>NE JM</i> 363:513–522(2010) The endpoint was improvement with no worsening by a categorical symptom score for 3 successive 15 minute periods.
CETOR (European pre-cursor of Cinryze)	<i>J Allergy Clin Immunol</i> 117 (4):904-908(2006) Figure 1 The primary efficacy end point was a self-reported time period from the start of treatment to the onset of symptom relief.
Firazyr (bradykinin receptor 2 antagonist)	Study 2102 Source: NDA 22-150 clinical review memo Figure 3 The endpoint was a 50% reduction in a 3-item symptom VAS

Among the reasons for this study-to-study variability in outcomes are the following:

- Small sample sizes
- Differences in the proportion of enrolled subjects with subcutaneous or submucosal symptoms
- Differences in the proportion of male or female subjects enrolled
- Differences in baseline HAE attack severity
- Differences in the time from HAE attack onset to the time of HAE attack treatment
- Differences in data censoring procedures based on the use of concomitant medications that could affect the primary endpoint, and
- Psychological factors that could affect this subjective PRO primary endpoint.

Although this variability is seen easiest in the outcomes from the placebo arms of these studies, the factors causing this variability are expected to hold for the active treatment arms, as well. In the ideal study design, randomization and sufficient sample size would be expected to address most of these factors; however, HAE studies enroll only several

subjects at any given study site, and the total sample size is limited by the availability of subjects. Nevertheless, within these limitations, the Berinert[®] licensure study 3001 (IMPACT)⁴ was successful in demonstrating improved outcomes from using a dose of 20 U/kg over the use of 10 U/kg, marking the first time⁵ that a dose-response had been demonstrated in an adequate and well-controlled study of C1INH replacement therapy.

One consequence of the study-to-study variability for treatment of HAE attack studies is that quantitative comparisons across studies (i.e. response rates) cannot be made reliably. This should be kept in mind when reviewing the anomalous results for the pivotal study 1310 RCT for the pre-specified analysis subgroups “geographic region – U.S. and Rest of World (ROW),” and the finding that study 1310 was conducted as if it were two separate clinical trials (U.S. or Europe), based on an analysis of database structure for these subgroups (see section [6.3.11.5](#)). Viewed from this perspective, one can ask if it is valid to pool the results for these two geographic regions; however, this is a study design issue which can be addressed for future clinical studies, not this one.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The applicant did not submit the pre-specified analysis subgroups ‘female’ and ‘geographic region – U.S.’ in the pre-BLA package. This caused difficulties at the time of BLA filing. If the applicant had informed FDA of the lack of demonstration of efficacy in these important subgroups, in this reviewer’s opinion, it is likely that the sponsor would have been encouraged to perform additional clinical studies, rather than to file the BLA.

The applicant did not conduct analyses on serum samples from subjects who formed antibodies against Ruconest to see if the antibodies inhibited the activity of Ruconest. FDA requested that these studies be done during the review period.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant did not reveal the anomalous results in study 1310 for the pre-specified analysis subgroups ‘female’ and ‘geographic region – U.S.’ at the pre-BLA meeting or in the publication of this study.¹ The applicant has urged FDA not to require disclosure of these results in the labeling because the applicant said this information would not be useful to physicians or patients.

3.3 Financial Disclosures

Dr. S. de Vries, Chief Executive Officer of Pharming Group NV, signed form FDA 3454 with checked box stating:

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (list of names of

⁴ *J Allergy Clin Immunol* **124**:801-808 (2009)

⁵ *Allergy Asthma Proc* **34**(4):312-327 (2013)

clinical investigators for all studies, attached) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

21 CFR 54.2(f) describes unacceptable payments to investigators as follows:

(f) *Significant payments of other sorts* means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than \$25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.

The published report¹ of study 1310 states as follows:

Disclosures: Dr Riedl has been a scientific consultant to Santarus Biocryst, CSL Behring, Dyax, Isis, Shire, and ViroPharma and received funding from Pharming, CSL Behring, Dyax, Shire, and ViroPharma. Dr Baker has received funding from ViroPharma and Shire. Dr Rashef received grants from Shire HGT, Pharming BV, and Teva, Inc, research funding from Pharming BV and consulted for Shire HGT. Dr Moldovan received research fees from Pharming Technologies and CSL Behring. Dr Li received research fees from Pharming. Dr Farkas received consulting, speaking, and travel fees from CSL Behring, Shire, and SOBI. Dr Cicardi received research and educational grants from Shire and CSL Behring; served as speaker and on the advisory board of ViroPharma, SOBI, and Dyax and on the advisory board of BioCryst; and received a grant from Pharming. Dr Bernstein has served as speaker and consultant for Shire, Dyax, ViroPharma, and CSL Behring; received grants from Pharming, Dyax, Shire, ViroPharma, and CSL Behring; served on the board of directors for the American Academy of Allergy, Asthma, and Immunology, chair of Allergists for Israel, and editor in chief for the *Journal of Asthma*. Dr Lumry received consulting fees from BioCryst, CSL Behring, Shire HGT, and ViroPharma; served on the speaker's bureau of Shire HGT and ViroPharma; received grants from CSL Behring, Dyax, Shire HGT, and ViroPharma; and served on the medical advisory board of Hereditary Angioedema Association.

Reviewer's Comment: The amounts and details of the payments listed in the published report are not available for review. The financial disclosure appears to be in line with other pharmaceutical company-sponsored investigations. Evaluating a higher dose or

multiple doses in the pivotal trial 1310. may have aided in the efficacy analysis of the results of that trial.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

There were no significant safety or efficacy issues related to the other review disciplines

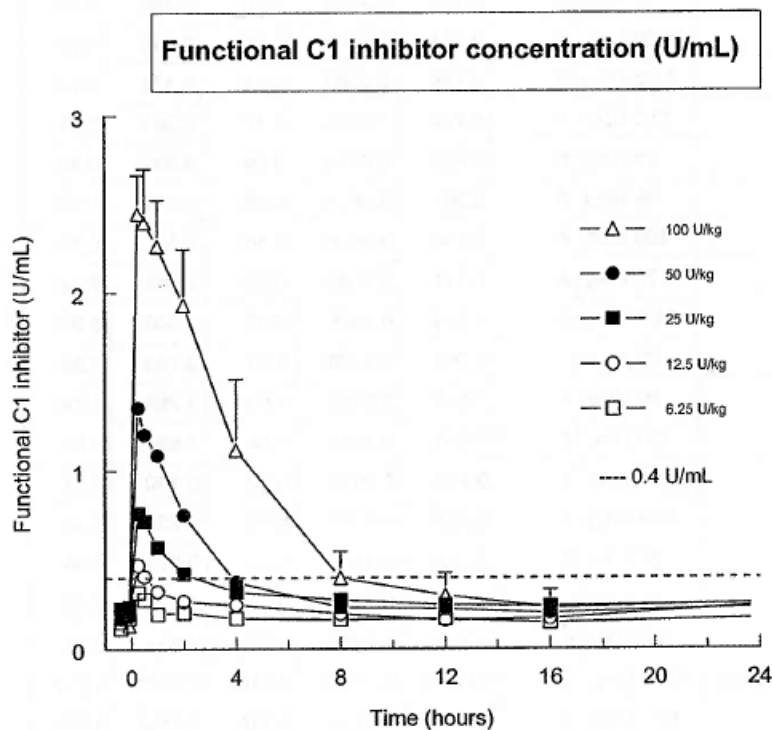
4.3 Nonclinical Pharmacology/Toxicology

Nonclinical toxicology studies have not demonstrated a risk for thrombosis at the labeled dose.

4.4 Clinical Pharmacology

Study 1101 was a phase 1 exploratory study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ascending intravenous doses of recombinant C1 inhibitor in asymptomatic patients with hereditary angioedema.

The following graph shows the levels of functional C1 inhibitor activity (U/mL) that were observed in plasma samples over time:



Source: STN125495 Module 5.3.3.2 clinical report for study C1 1101-01 page 39 of 96

The applicant made the assumption that C1-INH levels above 70% of the normal level, maintained for several hours after dosing, would be effective in treating a HAE attack.

Based on these results, the applicant chose doses of 50 U/kg and 100 U/kg to be tested in efficacy studies.

Reviewer's Comment: The most appropriate drug development plan would have been justify the dose based on clinical dose-finding studies, not on theoretical considerations. The licensure study for Berinert shows that this is possible.

4.4.1 Mechanism of Action

Plasma C1 esterase inhibitor (C1INH) is a 71.1 kD plasma glycoprotein (26% carbohydrate)⁶ that was first described⁷ in 1957 as the plasma activity that inhibits the C1 proteinase activity of the complement cascade. (Its apparent molecular weight of 104 kD by SDS-PAGE analysis, which is often cited in the medical literature, appears to be artifactually large.)⁷ It is the only inhibitor of C1 esterase. Subsequent research demonstrated that it is a more general proteinase inhibitor of the serpin class, having inhibitory activity against C1r, C1s, kallikrein, tissue plasminogen activator, plasmin, and coagulation factors XIa and XIIa, among others. In vitro, C1INH inhibits plasmin; however, it does not appear to be a significant inhibitor of plasmin in vivo.⁸

C1 esterase inhibitor has the following activities:

- inhibition of the classical complement cascade,
- inhibition of coagulation factors XIa and XIIa
- inhibition of the conversion of plasminogen to plasmin, and
- inhibition of activated kallikrein in the kallikrein-bradykinin pathway.

Ruconest (rhC1INH) has an apparent molecular weight of -----(b)(4)-----, however this molecular weight is also artifactually large, as shown by -----(b)(4)----- analysis that assigns a molecular weight of (b)(4) kD; the difference in molecular weight from plasma C1INH is accounted for by Ruconest having only (b)(4) carbohydrate content.⁹

The in vitro proteinase inhibitory activity of Ruconest, as compared to plasma-derived C1-INH, is shown by the measured on-rate kinetic parameter in the following table:

Second-Order Rate Constants for Inhibition of Target Proteases by rhC1INH and Human Plasma Derived (pd) C1INH

	$k_{on} (M^{-1}.s^{-1})$			
	C1s	Factor XIa	Factor XIIa	Kallikrein
rhC1INH ^a	$6.1 \pm 0.3 \times 10^4$	$9.8 \pm 0.5 \times 10^2$	$6.9 \pm 0.5 \times 10^3$	$9.1 \pm 0.1 \times 10^3$
pdC1INH ^a	$5.1 \pm 0.3 \times 10^4$	$9.0 \pm 0.2 \times 10^2$	$5.7 \pm 0.4 \times 10^3$	$7.6 \pm 0.3 \times 10^3$
pdC1INH ^b	6.3×10^4	-	5.7×10^3	8.2×10^3

⁶ *J Mol Biol* **214** 751-763 (1990)

⁷ *J Exp Med* **106**:327-343 (1957)

⁸ *Mol Immunol* **45**(16):4057-4063 (2008)

⁹ *J Biotechnology* **162** :319- 326 (2012)

	$k_{on} (M^{-1}.s^{-1})$			
	C1s	Factor XIa	Factor XIIa	Kallikrein
pdC1INH ^b	$6.2 \pm 0.4 \times 10^4$	$3.9 \pm 0.3 \times 10^2$	$4.5 \pm 0.3 \times 10^3$	$7.8 \pm 0.4 \times 10^3$

^a Data generated at Pharming Technologies B.V. The data are the mean \pm SD of 3 experiments. The values for k_{off} were virtually zero. rhC1INH: batch 04I00013; pdC1INH: Ceter

^b Data reported in literature

Source: STN125495 module 2.3.S.1, page 10

Reviewer's Comment: These product characterization data support the idea that Ruconest should be effective at some dose; however, the structural differences between Ruconest and plasma-derived C1INH imply that the dose should be determined from clinical outcomes, and not from theoretical considerations.

4.4.2 Human Pharmacodynamics (PD)

Study 1101 demonstrated an increase in plasma C4 levels at 12 hours after dosing in asymptomatic HAE subjects. This is consistent with the expected pharmacodynamic effect.

4.4.3 Human Pharmacokinetics (PK)

Ruconest is eliminated from the plasma approximately 20-fold faster than plasma-derived C1INH products (see the clinical pharmacology review for more details regarding human PK).

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review briefly discusses the two small phase 2 studies (study 1205 RCT and study 1304 RCT) which provided the data for approval in the European Union, and focuses on the pivotal phase 3 study 1310 RCT that was required by FDA. Special attention is given to the anomalous results for the pre-specified analysis subgroups 'female' and 'geographic region – U.S'. Studies are discussed individually, and not as pooled safety or efficacy study results, for the reasons cited in section [2.6](#).

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

1. STN 125495 Ruconest, Pharming NV Group
2. IND 11785 rhC1INH, Pharming NV Group

5.3 Table of Studies/Clinical Trials

Please note that the terms Units (U) and International Units (IU) are used interchangeably. For the accuracy of this review, the terminology used in discussing the three efficacy RCTs (1205, 1304 and 1310) are consistent with their protocols where Units/kg or U/kg were used. For the final label, dosing of the product is referred to by International Units or IU/kg.

TABULAR LISTING OF ALL CLINICAL STUDIES

Type of Study	Protocol Number	Study Report Location	Objective(s)	Study Design	Test Product; Dose* and Regimen	Sample Size; Subjects (administrations)	Population	Study Status
PK	C1 1106-02	Module 5.3.3.1.1	PK, Safety, Tolerability, Immunogenicity	Open-label	rhC1INH 100 U/kg 5 doses at 3-week intervals	14 (59 administrations)	Healthy Volunteers	Completed
PK	C1 1101-01	Module 5.3.3.2.1	PK/PD, Safety, Tolerability	Open-label	rhC1INH 6.25, 12.5, 25, 50, 100 U/kg 2 ascending doses, at least 5 week intervals	12 (24 administrations)	Asymptomatic HAE patients	Completed
Efficacy	C1 1205-01 RCT	Module 5.3.5.1.1	Efficacy, Safety, Tolerability, PK/PD	Randomized, double-blind placebo-controlled	rhC1INH 50 or 100 U/kg or Saline	38 (25 rhC1INH and 13 placebo administrations)	Symptomatic HAE patients	Completed
Efficacy	C1 1304-01 RCT	Module 5.3.5.1.2	Efficacy, Safety, Tolerability	Randomized, double-blind placebo-controlled	rhC1INH 100 U/kg or Saline	32 (16 rhC1INH and 16 placebo administrations)	Symptomatic HAE patients	Completed

Type of Study	Protocol Number	Study Report Location	Objective(s)	Study Design	Test Product; Dose* and Regimen	Sample Size; Subjects (administrations)	Population	Study Status
Efficacy	C1 1310 RCT + OLE	Module 5.3.5.1.3	Efficacy, Safety	Randomized, double-blind, placebo-controlled with open-label extension	rhC1INH 50 U/kg (max 4200 IU) or saline OLE: rhC1INH 50 U/kg (max 4200 IU) based upon clinical response, a second dose may be given	RCT: 74 (56 rhC1INH [including rescue] and 31 placebo administrations) OLE: 44 (170 administrations)	Symptomatic HAE patients	RCT Phase completed OLE Phase ongoing#
Exploratory	C1 1202-01	Module 5.3.5.2.1	Efficacy, Safety, Tolerability, PK/PD	Open-label	rhC1INH 100 U/kg One dose per acute attack.	4 (6 administrations)	Symptomatic HAE patients	Completed
Exploratory	C1 1203-01	Module 5.3.5.2.1	Efficacy, Safety, Tolerability, PK/PD	Open-label	rhC1INH 100 U/kg One dose per acute attack.	10 (15 administrations)	Symptomatic HAE patients	Completed
Efficacy	C1 1205-01 OLE	Module 5.3.5.2.2	Efficacy, Safety, Tolerability,	Open-label extension	rhC1INH 50 U/kg initial dose; based upon clinical response, a second dose may be given	62 (168 administrations)	Symptomatic HAE patients	Completed
Efficacy	C1 1304-01 OLE	Module 5.3.5.2.3	Efficacy, Safety, Tolerability, PK/PD	Open-label extension	rhC1INH 2100 U initial dose; based upon clinical response, a second dose may be given	57 (194 administrations)	Symptomatic HAE patients	Completed
Exploratory	C1 1207	Module 5.3.5.2.4	Efficacy, Safety, Tolerability & PK/PD,	Open-label	rhC1INH 50 U/kg once weekly for 8 weeks, with 50 U/kg for acute attacks	25 (207 administrations)	Asymptomatic HAE patients	Completed

Source: STN125495, Module 5.2 , page 2

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

STN125495 was not presented to an Advisory Committee.

5.4.2 External Consults/Collaborations

There were no formal consultations. CBER reviewers have discussed general aspects of study design for drugs to treat HAE attacks with CDER reviewers of these drugs.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 Study 1205 RCT (first subject enrolled 10 June 2005, last patient completed 24 January 2008)

Study 1205 RCT was a phase 2 randomized (1:1:1) placebo-controlled trial in 38 HAE subjects experiencing a HAE attack (US & Canada). The primary endpoint was time-to-initial-relief-of-symptoms as measured by a VAS. Enrollment required a baseline VAS of at least 50 millimeters, and a response required repeated demonstration of at least a 20 millimeter decrease from the baseline VAS.

6.1.1 Objectives (Primary, Secondary, etc)

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

6.1.2 Design Overview

Double-blind, multi-center, saline-controlled, randomized (1:1:1) study of rhC1INH (100 U/kg or 50 U/kg) with an OLE phase

6.1.3 Population

Subjects were males or females ≥ 12 years of age with a clinically-suspected or laboratory confirmed diagnosis of HAE type I or II (C1INH activity $< 50\%$ of normal, with normal C1q and absence of anti-C1INH antibodies).

6.1.4 Study Treatments or Agents Mandated by the Protocol

The Ruconest dose was 100 Units/kg or 50 Units/kg, the placebo was saline. Study agents were prepared in opaque syringes, for intravenous administration, to product the blind.

6.1.6 Sites and Centers

This was an in-clinic study at centers in the U.S. (26 sites) and Canada (4 sites).

United States of America		Canada	
Site		Site	
01	BL Zuraw	10	G Sussman
08	T Craig	17	W Yang
11	RF Lockey	20	J Hebert
12	A Shad	22	B Ritchie
16	C Kirkpatrick		
18	MA Park		
19	JA Grant		
23	D Suez		
24	L Schwartz		
27	M Riedl		
28	RJ Levy		
29	HH Li		
31	L Edara		
32	VR Bonagura		
33	JA Bernstein		
36	JN Moy		
38	M Koleilat		
39	J Offenberger		
40	A Szema		
41	MA Michelis		
43	AC Engler		
44	M Richheimer		
46	SM Maseehur Rehman		
48	TC Marbury		
49	O Alpan		
50	SL Bahna		

6.1.7 Surveillance/Monitoring

The primary endpoint time-to-initial-relief-of-symptoms was measured by VAS at times -1 hour, -45 minutes, 0 (start of treatment), 15 minutes, 30 minutes, 1 hour, 2, hours, 4 hours, 8 hours, 12, hours, 16 hours, 24 hours, and 48 hours. Adverse events and concomitant medications were monitored at all time points.

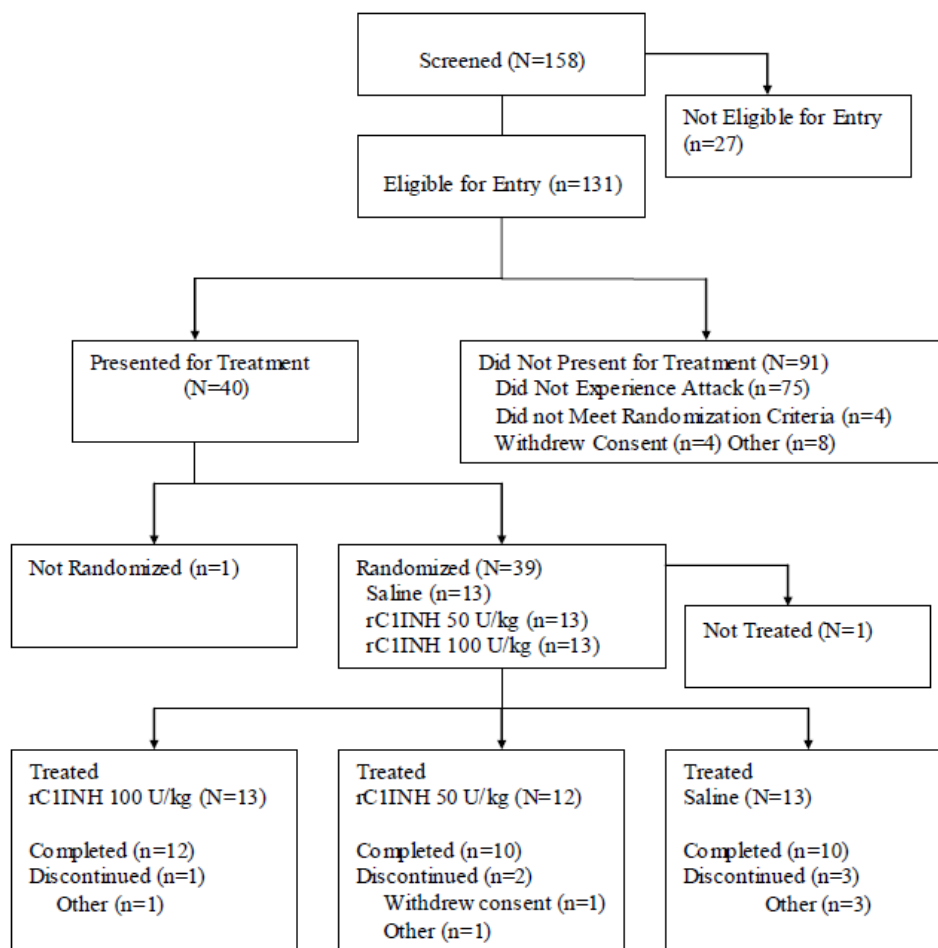
6.1.8 Endpoints and Criteria for Study Success

To be eligible, subjects were required to have a VAS ≥ 50 mm at baseline. Success was defined as a 20mm decrease in the VAS from baseline, with persistence at following time points.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary endpoint time-to-beginning-of-relief-of-symptoms was captured by a VAS at scheduled time points. Statistical analyses for success were pre-specified.

6.1.10 Study Population and Disposition



Source: STN125495 Study 1205 Clinical Report page 70

^aSubject -(b)(6)-: had a HAE attack and was treated in the OLE phase of the study.

^bSubject -(b)(6)-: retreated and did not complete Day 90

^cSubject -(b)(6)-: PI discretion, Subject -(b)(6)-: approved by sponsor for open-label dosing, Subject -(b)(6)-: Treatment 1

6.1.10.1 Populations Enrolled/Analyzed

Subjects were males or females > 12 years of age with a clinically-suspected or laboratory confirmed diagnosis of HAE type I or II (C1INH activity < 50% of normal, with normal C1q and absence of anti-C1INH antibodies).

6.1.10.1.1 Demographics

Study 1205: Demographics

	rhC1INH 100 U/kg (N=13)	rhC1INH 50 U/kg (N=12)	Saline Solution (N=13)	Total (N=38)

	rhC1INH 100 U/kg (N=13)	rhC1INH 50 U/kg (N=12)	Saline Solution (N=13)	Total (N=38)
Age on day of treatment visit (years)				
Mean	34.2	40.7	32.4	35.6
SD	15.68	12.18	11.30	13.34
Median	28.0	40.0	34.0	34.5
Range	17-66	20-59	17-55	17-66
Age on day of treatment visit (years)				
<18 years	1	0	1	2
18-65 years	11	12	12	35
>65 years	1	0	0	1
Sex				
Male	5	4	1	10
Female	8	8	12	28
Race				
Caucasian	12	12	11	35
African American	0	0	1	1
Asian	1	0	1	2
Mean height (cm) (at Screening)	168.78	170.17	164.82	167.87
Mean body weight (kg) (on date of treatment)	75.05	86.59	69.95	76.95
Mean BMI (kg/m ²) (on date of treatment)	26.13	29.78	25.63	27.11
Mean number of cigarettes and cigars smoked per day	0.4	0.1	2.3	0.9
Mean number of alcohol units per week	1.69	3.58	2.54	2.58

Source: STN125496 study 1205 Clinical Report page 73

BMI = body mass index, FAS=full analysis set, mITT = modified intent to treat, SD = standard deviation

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

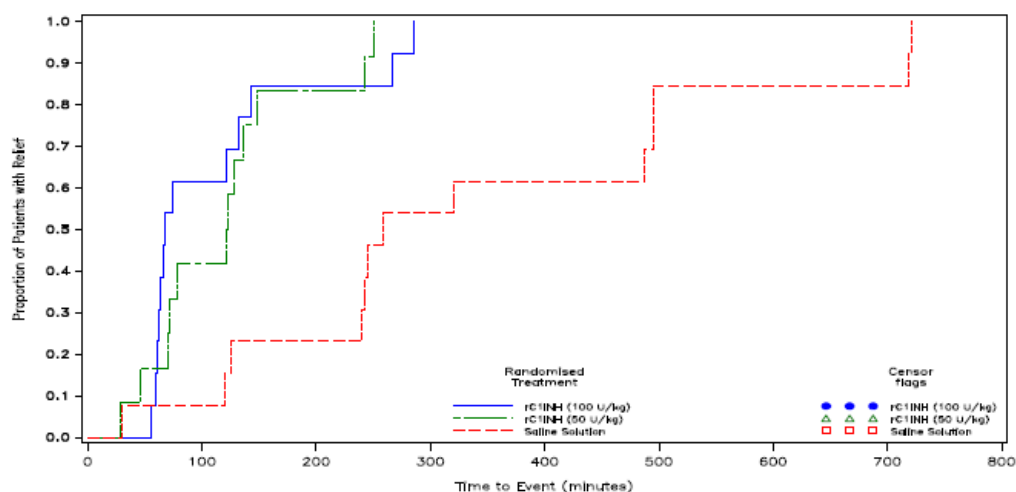
Patients with life-threatening laryngeal HAE attacks were ineligible.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The following Kaplan-Meier graph shows the results for study 1205:

Figure 2 Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms (FAS, [mITT]) (Overall VAS Score)



Source: [Figure 14.2.1.1](#)

Source: STN125495 study 1205 Clinical Report

The interpretation of Study 1205 outcomes is complicated by an imbalance in subjects for the important baseline covariates gender and anatomical site (abdominal vs. non-abdominal), as shown in the following table:

Study 1205: Subject Disposition by Gender and Anatomical Site

	Male		Female	
	Abdominal	Non-Abdominal	Abdominal	Non-Abdominal
rhC1INH 100 U/kg	4	1	4	4
rhC1INH 50 U/kg	2	2	3	5
Saline	1	0	2	10

The placebo arm was 12:1 female, and 10 of the 12 females in the placebo arm were scored for non-abdominal symptoms. It is a consistent finding in studies for treatment of HAE attacks that abdominal symptoms respond more quickly than do non-abdominal symptoms.

The applicant's summary of the efficacy results for study 1205 is given in the following table:

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

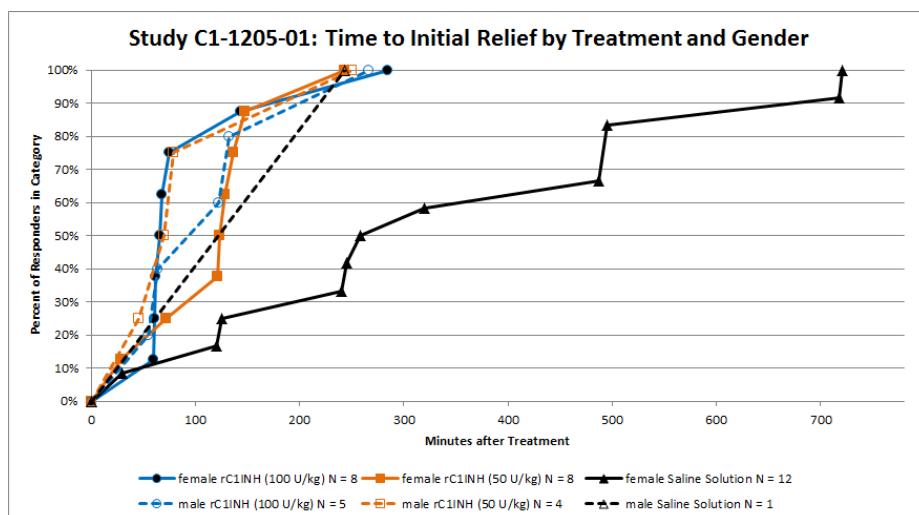
	rhC1INH (100 U/kg) (N=13)	rhC1INH (50 U/kg) (N=12)	Saline Solution (N=13)
Median (95% CI)	68.0 (62.0, 132.0)	122.0 (72.0, 136.0)	258.0 (240.0, 495.0)
Log rank test p-value*	0.001	<0.001	

Source: STN125495, Study 1205 Clinical Report, p.79

CI=confidence interval, FAS=full analysis set, mITT=modified intention-to-treat, SD=Standard deviation, VAS=visual analog scale 95% CI's are displayed as conventional estimates of CI, statistical tests are performed at 1% level.

* Comparing against Saline Solution.

The following graph shows the time to initial relief of HAE symptoms by treatment and by gender for study 1205:

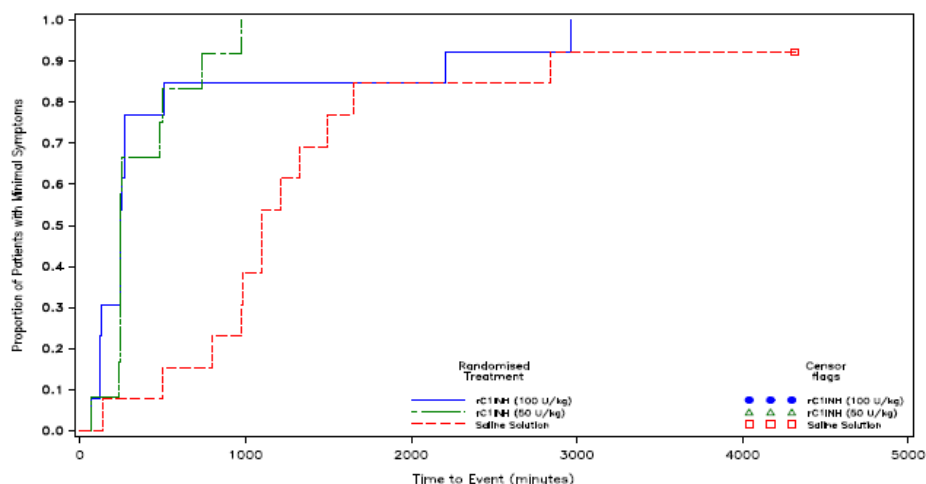


It can be seen that in study 1205 the response was driven by the 12 female placebo subjects, 10 of whom had subcutaneous HAE symptoms, and the other 2 had submucosal (abdominal) symptoms. The small study size and the imbalance in the number of subjects in the gender, anatomical site, and dose cohorts makes study 1205 difficult to interpret for a definitive analysis of dose effect.

6.1.11.2 Analyses of Secondary Endpoints

The secondary efficacy endpoint was the time to minimal symptoms, where 'minimal symptoms' was defined as an overall severity VAS score of <20 mm in severity of symptoms for all anatomical locations of an attack. The following Kaplan-Meier graph shows the results for this secondary endpoint for study 1205:

Figure 3 Kaplan-Meier Plot of Time to Minimal Symptoms (Overall VAS Score) (FAS, [mITT])



Source: [Figure 14.2.2.1](#)

FAS=full analysis set, mITT=modified intention-to-treat, VAS=visual analog scale

Table 22 Sensitivity Analyses: Median Time (Minutes) to Minimal Symptoms (FAS, [mITT] and PP) and 95% CI (Overall VAS Score)

	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	Saline Solution
Per Protocol			
Log rank test p-value			
Modified ITT			
VAS score < 20mm: Using date and time of study drug administration Log rank test p-value	240.0 (120.0, 255.0) [n=13] p=0.044	242.0 (235.0, 482.0) [n=12]	1096.0 (967.0, 1492.0) [n=13]
Excluding peripheral locations Log rank test p-value	252.0 (240.0, 450.0) [n=9] p=0.024	245.0 (237.0, 500.0) [n=7]	1270.0 (495.0, 1650.0) [n=10]

Source: STN125496 Study 1205, Clinical Report p. 86

CI=confidence interval, FAS=full analysis set, mITT=modified intention-to-treat, VAS=visual analog scale
p-values are for the comparison against Saline solution. If rhC1INH (100 U/kg) versus Saline solution is not significant at 1% then following the closed test procedure no hypothesis test is carried out for the comparison of 50 U/kg rhC1INH and Saline solution (see *Section 13.1*).

6.1.11.3 Subpopulation Analyses

The following table shows the outcomes for the primary endpoint by anatomical site, gender, race, and age:

Study 1205 Subgroup Analyses: Median Time (Minutes) to Beginning of Relief of Symptoms: Overall VAS Score Decrease of ≥ 20 mm with Persistence (FAS, [mITT]) and 95% CI

	rhC1INH (100 U/kg)	rhC1INH (50 U/kg)	Saline Solution
Eligible anatomical location:			
Orofacial-pharyngeal and/or Laryngeal	67.5 (60.0, 75.0) [n=2]	- [n=0]	306.0 (120.0, 495.0) [n=6]
Laryngeal	- [n=0]	- [n=0]	495.0 (487.0, 495.0) [n=3]
Orofacial	67.5 (60.0, 75.0) [n=2]	- [n=0]	120.0 (30.0, 125.0) [n=3]
Pharyngeal	- [n=0]	- [n=0]	- [n=0]
Abdominal	68.0 (55.0, 285.0) [n=5]	70.0 (29.0, 148.0) [n=5]	243.0 (240.0, 245.0) [n=3]
Genitourinary	- [n=0]	250.0 (-, -) [n=1]	320.0 (-, -) [n=1]
Other (peripheral)	93.0 (62.0, 132.0) [n=6]	124.5 (79.0, 136.0) [n=6]	560.0 (30.0, 721.0) [n=5]
Sex:			
Male	122.0 (55.0, 266.0) [n=5]	74.5 (46.0, 250.0) [n=4]	243.0 (-, -) [n=1]
Female	67.0 (61.0, 143.0) [n=8]	125.5 (72.0, 148.0) [n=8]	289.0 (240.0, 495.0) [n=12]
Race:			
White	70.5 (62.0, 132.0) [n=12]	122.0 (72.0, 136.0) [n=12]	245.0 (125.0, 495.0) [n=11]
Non-White	68.0 (-, -) [n=1]	- [n=0]	488.0 (258.0, 718.0) [n=2]
Age:			
Age < 65 years at Screening	71.5 (62.0, 132.0) [n=12]	122.0 (72.0, 136.0) [n=12]	258.0 (240.0, 495.0) [n=13]
Age \geq 65 years at Screening	66.0 (-, -) [n=1]	- [n=0]	- [n=0]

Source: STN125495 Study 1205 Clinical Report, page 82

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

Reviewer's Comment: The disproportionate number of females with non-abdominal symptoms in the placebo arm was shown in section [6.1.11.1](#), above. The small sample size for these

subgroups, and the influence of the baseline covariates ‘gender’ and ‘anatomical site’ on the variability of primary endpoint outcomes complicates the interpretation of study 1205 results.

6.1.12 Safety Analyses

Study 1205: Treatment Emergent Adverse Events

		rC1INH (100 U/kg)		rC1INH (50 U/kg)		Saline Solution	
Body System	Preferred Term	Events	Subjects	Events	Subjects	Events	Subjects
	Any Adverse Event	13	5	7	4	10	6
	Gastrointestinal disorders						
	Colitis	1	1				
	Vomiting					1	1
	General disorders and administration site conditions						
	Injection site swelling					1	1
	Mucosal hyperaemia					1	1
	Immune system disorders						
	Hereditary angioedema	1	1	1	1		
	Infections and infestations						
	Cystitis					1	1
	Fungal infection					1	1
	Sinusitis	1	1				
	Tooth abscess			1	1		
	Urinary tract infection			1	1		
	Investigations						
	C-reactive protein increased			1	1		
	Haematocrit increased	1	1				
	Haemoglobin increased	1	1				
	Musculoskeletal and connective tissue disorders						
	Back pain			1	1		
	Myalgia					1	1
	Nervous system disorders						
	Headache	3	2			1	1
	Vertigo	2	1				
	Psychiatric disorders						
	Insomnia					1	1
	Renal and urinary disorders	1	1				
	Renal failure acute	1	1				
	Respiratory, thoracic and mediastinal disorders						

		rC1INH (100 U/kg)		rC1INH (50 U/kg)		Saline Solution	
Body System	Preferred Term	Events	Subjects	Events	Subjects	Events	Subjects
	Nasal congestion	1	1				
	Pharyngeal inflammation	1	1				
	Throat irritation					1	1
Skin and subcutaneous tissue disorders							
	Erythema			1	1		
	Pruritis			1	1		
	Rash erythematous					1	1

Source: STN125495 study 1205; derived from Analysis Dataset ADAE

Reviewer's Comment: Most of the TEAEs in the above table are representative for patients undergoing HAE attacks, or who are receiving intravenous administration of a biologic. Subject -(b)(6)-, a 66 year old female, experienced moderate acute renal failure 31 days after treatment with Ruconest 100 U/kg, with complete recovery. It is difficult to attribute this adverse event to the study agent because of the time interval after treatment. Subject -(b)(6)-, experienced an elevated blood C-reactive protein [6.7 mg/dL; normal range: 0-0.8 mg/dL] 24 hours after treatment with Ruconest 50 U/kg. No further explanation has been submitted. This appears to be an isolated event, not related to treatment.

6.1.12.3 Deaths

There were no deaths,

6.1.12.4 Nonfatal Serious Adverse Events

There were two treatment-emergent serious adverse events in study 1205 RCT:

- Subject -(b)(6)- in the rhC1INH 100 U/kg treatment group had severe colitis of 3 days duration, which was classified as a treatment-emergent SAE, on a single occasion on Day 31.
- Subject -(b)(6)- in the rhC1INH 50 U/kg had a new HAE attack on day 7, classified as severe, following treatment.

There were two serious adverse events in study 1205 OLE:

Hypersensitivity. Subject ----(b)(6)---- was a 33-year-old female subject in Study 1205 OLE. First single dose of rhC1INH 50 U/kg on 22 August 2008.

- On the day of the second administration of rhC1INH 50 U/kg single dose, the subject experienced pruritus.
- On the day of the third administration of rhC1INH 50 U/kg single dose, the subject reported dizziness.

- On 20 January 2009, the subject received her fourth administration of rhC1INH 50 U/kg single dose.
- Approximately 10 minutes after the start of the injection, the subject reported itching of the lips and soft palate. Five minutes later, she reported a “lump” sensation on the left side of the throat. An oral examination revealed a red, swollen area on the left side of the soft palate, with deviation of the subject’s uvula to the right.
- The event was treated with diphenhydramine.
- The subject’s symptoms resolved within 20 minutes of treatment.
- This subject did not have positive anti-C1INH or anti-HRI antibodies at any time point during the study. Subsequent testing of pre- and postexposure samples did not reveal the presence of anti-rabbit dander IgE antibodies.
- The subject did not receive any further rhC1INH treatments after this event.

Reviewer’s Comment: This serious adverse event appears to be a hypersensitivity reaction directly related to Ruconest administration.

Laryngeal Edema. Subject ----(b)(6)---- was a 28-year-old male subject in Study 1205 OLE.

- He received rhC1INH 100 U/kg single dose in Study 1205 RCT.
- On 23.Nov.2007 at 22:30, the subject developed swelling above the nasal bridge which progressed to swelling of both eyes by the morning of 24.Nov.2007.
- In the morning of 24.Nov.2007 around 8:30, he was presented to the emergency department.
- He was treated with Amicar (aminocaproic acid) 4 gram intravenously (IV) x 1 and then 1 gram/hour for 2 hours and one unit of fresh frozen plasma (FFP).
- The subject had been admitted to the intensive care unit because of this attack, which was progressing and was accompanied by hoarseness and decreased oxygen saturation during sleep.
- The subject received rhC1INH 50 U/kg single dose on 24 November 2007 at 14:20.
- Following treatment with rhC1INH, the subject’s angioedema attack progressed further, involving the tongue and soft palate.
- The subject was intubated for protection of the airway.
- On the same day, the subject experienced tense right hand and arm edema.
 - Danazol was administered; however, the event continued to worsen.
 - The right arm and hand swelling decreased spontaneously over a period of approximately 24 h and fully resolved by 30 November 2007. However, the subject experienced the sequelae numbness, tingling, and weakness until 18 January 2008.
- There was no change in study treatment due to this event.

Reviewer’s Comment: This event appears to show lack of efficacy of Ruconest in both preventing laryngeal edema symptoms from developing in this subject, who originally only had facial symptoms, and lack of efficacy in this patient after being treated with Ruconest during the attack at the 50 U/kg dose.

6.1.12.5 Adverse Events of Special Interest (AESI)

Laryngeal Edema

(see the narrative is for subject ----(b)(6)---- at [6.1.12.4](#))

6.1.12.7 Dropouts and/or Discontinuations

Study 1205 RCT - Study Completion: Safety Analysis Set

	rC1INH (100 U/kg) (N=13)	rC1INH (50 U/kg) (N=12)	Saline Solution (N=13)	Total (N=38)
Number of subjects who completed the study	12 (92%)	10 (83%)	10 (77%)	32 (84%)
Number of subjects who discontinued prematurely	1 (8%)	2 (17%)	3 (23%)	6 (16%)
Primary reason for premature discontinuation*				
Adverse event	0	0	0	0
Lost to Follow-up	0	0	0	0
Withdrew consent	0	1 (50%)	0	1 (17%)
Protocol violation	0	0	0	0
Other**	1 (100%)	1 (50%)	3 (100%)	5 (83%)

Source: STN125495 study 1205 Clinical Report page 4 of 1547

* Percentages are based on the number of subjects who prematurely discontinued.

** Subject withdrew for another reason than those specified on the CRF and are detailed on the listing.

Reviewer's Comment: There are no concerns based on subject discontinuations.

6.2 Trial #2 Study 1304 (first subject enrolled 27 July 2004, last subject completed 13 November 2007)

Study 1304 RCT was a phase 2 randomized (1:1) placebo-controlled trial in 32 HAE subjects experiencing a HAE attack (26 subjects at 7 sites in Italy; 6 subjects at 5 other European sites). The Ruconest dose was 100 Units/kg, the placebo was saline. The primary endpoint was time-to-initial-relief-of-symptoms as measured by a VAS. Enrollment required a baseline VAS of at least 50 millimeters, and a response required repeated demonstration of at least a 20 millimeter decrease from the baseline VAS.

6.2.1 Objectives (Primary, Secondary, etc)

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

6.2.2 Design Overview

Double-blind, multi-center, saline-controlled, randomized study of rhC1INH with an OLE phase

6.2.3 Population

Subjects were males or females ≥ 16 years old with a clinical and laboratory diagnosis of HAE with baseline plasma level of functional C1INH $< 50\%$ of normal. For randomization into the study, the patient had to have evidence for exacerbation or development of an abdominal angioedema and/or of facial-oropharyngeal angioedema and/or laryngeal angioedema and/or of genitourinary angioedema and/or peripheral angioedema attack, with onset of eligible symptoms not longer than 5 hours before evaluation of eligibility for randomization.

Subjects were required to have a VAS score of overall severity of angioedema symptoms of ≥ 50 mm at least 1 anatomical location at the time of evaluation (Time -1 hours), with no clear improvement (improvement defined as a decrease in VAS score of overall severity of angioedema symptoms ≥ 20 mm) in angioedema signs between determination of eligibility, (Time -1 hour) and baseline (Time 0 hours).

Subjects could not have rabbit allergies, or could not be presenting or developing a life-threatening attack (an attack requiring immediate emergency procedures to prevent death, hypoxemia related injuries or other unfavorable outcomes).

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study agents were required to be administered within 6 hours of the attack onset.

- rhC1INH: 125 milligrams/vial (lyophilized) reconstituted with 5 mL Water for Injection (WFI)

- Placebo: 0.9% NaCl in WFI

Study agents were administered in opaque syringes through an i.v. cannula using an infusion pump.

From page 33 of the study report:

“Method of Assigning Patients to Treatment Groups

The central randomization was carried out when the patient presented with an acute angioedema attack. After the eligibility of the patient was confirmed, an Interactive Voice Response System (IVRS) was used to obtain the treatment allocation. Treatment allocation was stratified by attack type (‘submucosal’ and ‘peripheral’) at the discretion of the Investigator. The block size was 2 with an allocation ratio of 1:1.”

Reviewer Comment: It is not customary to allow investigator discretion in an important study design feature, such as stratification procedures.

6.2.6 Sites and Centers

Italy: 01 M Cicardi, Milan 02 R Perricone, Rome 03 E Cillari, Palermo 04 S Neri, Catania 05 G Realdi; M Cancian, Padova 06 M Triggiani, Naples 07 V Montinaro, Bari	Spain: 11 T González-Quevedo, Sevilla 12 M Guilarte Clavero, Barcelona 13 A Campos, Valencia 14 M Rubio Sotés, Madrid United Kingdom: 21 H Longhurst, London 22 P L Yap, Edinburgh Israel: 32 Y Graif, Tel Aviv 34 M Schlesinger, Ashkelon Romania: 71 D Moldovan, Tirgi Mures
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6.2.8 Endpoints and Criteria for Study Success

To be eligible, subjects were required to have a VAS ≥ 50 mm at baseline. Success was defined as a 20mm decrease in the VAS from baseline, with persistence at additional time points.

6.2.9 Statistical Considerations & Statistical Analysis Plan

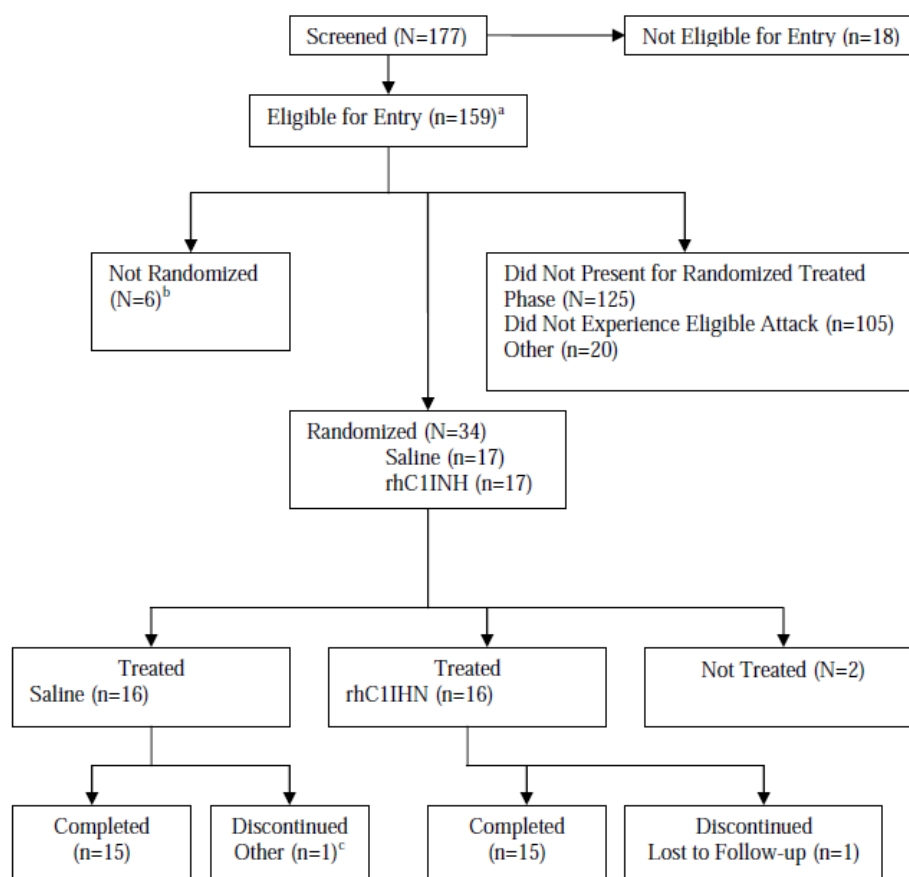
Primary Endpoint: Time to Beginning of Relief of Symptoms (VAS decrease of ≥ 20 mm)

The primary efficacy is the time to beginning of relief of symptoms at the location that shows the first response to treatment (VAS decrease of ≥ 20 mm).

Reviewer's Comment: It is a design flaw to base a data analysis decision on a study outcome. By defining the primary endpoint as the time of the earliest symptom relief, the study design introduces a source of bias. The symptom to be used for the primary endpoint should be specified before treatment is started.

6.2.10 Study Population and Disposition

Subject Disposition



Source: STN125495 study 1304 Clinical Report page 62

6.2.10.1 Populations Enrolled/Analyzed

Subjects were males or females > 16 years of age with a clinically-suspected or laboratory confirmed diagnosis of HAE type I or II (C1INH activity < 50% of normal, with normal C1q and absence of anti-C1INH antibodies).

6.2.10.1.1 Demographics

Study 1304: Demography, Smoking and Alcohol Use (FAS, [mITT])

	rhC1INH (N=16)	Saline (N=16)	Total (N=32)
Age on day of treatment visit (years)			
Mean	46.1	44.5	45.3
SD	14.51	16.77	15.44
Median	42.0	40.0	40.5
Range	19-67	17-71	17-71
Age on day of treatment visit (years)			
< 65 years	14	14	28
≥ 65 years	2	2	4
Sex			
Male	8	7	15
Female	8	9	17
Race			
Caucasian	16	16	32
Mean height (cm) (at Screening)	171.2	170.6	170.9
Mean body weight (kg) (on date of treatment)	84.16	77.25	80.70
Mean BMI (kg/m ²) (on date of treatment)	28.86	26.17	27.52
Mean number of cigarettes and cigars smoked per day	6.6	5.4	6.0
Mean number of alcohol units per week	3.19	1.12	2.15

Source: STN125495 study 1304 Clinical Report page 64

BMI = Body mass index, SD = Standard deviation,

FAS = Full Analysis Set, mITT = Modified Intention-To-Treat

6.2.10.1.3 Subject Disposition

Study 1304: Subject Disposition

	All Subjects (N=177)
HAE subjects screened	177
Subjects Not Eligible for Entry Into the Treated Phase	18
Subjects Eligible for Entry Into the Treated Phase ^a	159
Presented for Randomized Treated Phase ^b	34
Randomized	34
Treated (Included in FAS [mITT])	32

	All Subjects (N=177)
Subjects Who Did Not Present for Randomized Treated Phase	125
Main Reason for Not Entering the Treatment Phase	
Subject Did Not Experience an Eligible Attack	105
Subject Withdrew Consent	0
Other	20

Source: STN125495 study 1304 Clinical Report page 60

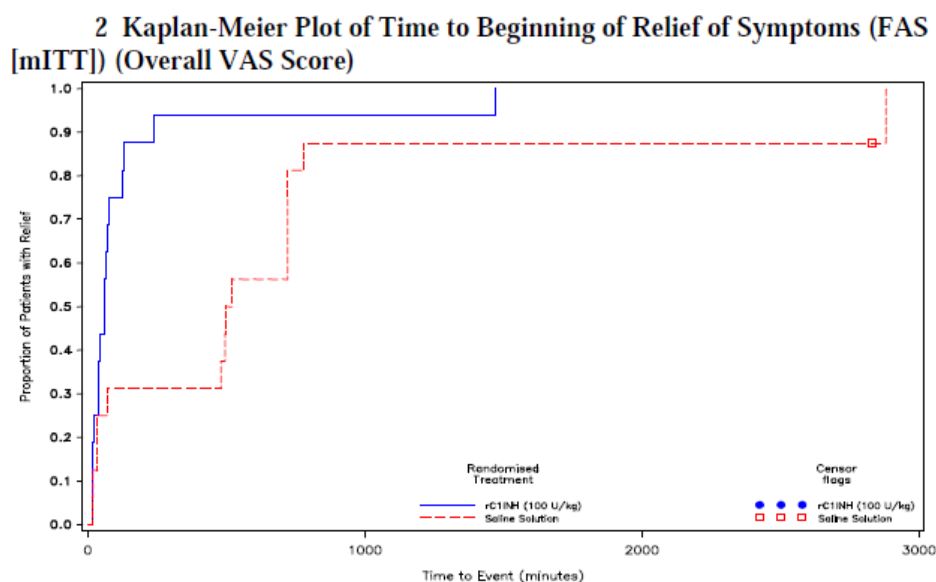
^a Includes 77 subjects who did not have the final screening CRF page completed but were eligible for entry into the randomized treatment phase

^b 6 subjects who were screened during the randomized phase who did not present for treatment until the open label phase.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The results are shown in the applicant's Kaplan-Meier plot below:



Source: [Figure 14.2.1.1](#) FAS = Full Analysis Set, mITT = Modified Intention-To-Treat, VAS=visual analog scale

The applicant's summary of the efficacy results for study 1304 is given in the following table:

Time (minutes) to Beginning of Relief of Symptoms: Overall VAS Score Decrease of ≥ 20 mm

	rC1INH (100 U/kg)	Saline Solution	Log rank test P=value
Full Analysis Set (mITT)	61.5 (40.0, 75.0) [N = 16]	508.0 (70.0,720.0) [N = 16]	0.003

	rC1INH (100 U/kg)	Saline Solution	Log rank test P= value
Per Protocol Analysis Set	63.0 (20.0, 123.0) [N = 11]	520.0 (480.0, 720.0) [N = 15]	<0.001

95% CIs are displayed as conventional estimates of CI, statistical test are performed at 2.941% level
The Full Analysis Set (FAS or Modified Intention-To-Treat [mITT] Set) was defined as the set of subjects who provided informed consent, were randomized to one of the treatment groups and who took at least one dose of the study drug.

Reviewer's Comment: Study 1304 was a small study where the dose studied was not the dose sought for labeling, which is 50 Units/kg. Nevertheless, study 1304 provides supportive evidence of the efficacy of Ruconest to treat HAE attacks.

6.2.12 Safety Analyses

The following table shows the treatment-emergent adverse events in study 1304 RCT:

Study 1304: Treatment-Emergent Adverse Events

		rC1INH (100 U/kg)		Saline Solution	
Body System	Preferred Term	Events	Subjects	Events	Subjects
Congenital, familial and genetic disorders					
	Hereditary angioedema	21	5	16	4
Gastrointestinal disorders					
	Abdominal pain	5	1	4	2
	Abdominal pain upper			1	1
	Diarrhoea	1	1		
General disorders and administration site conditions					
	Condition aggravated	1	1		
	Pain			2	2
	Pyrexia			1	1
Hepatobiliary disorders					
	Biliary colic			1	1
Infections and infestations					
	Herpes simplex	1	1		
	Tonsillitis	1	1		
Investigations					
	Prostate examination			1	1
Musculoskeletal and connective tissue disorders					

		rC1INH (100 U/kg)		Saline Solution	
Body System	Preferred Term	Events	Subjects	Events	Subjects
	Pain in extremity			1	1
Nervous system disorders					
	Headache	3	1	5	3
Renal and urinary disorders					
	Calculus ureteric			1	1
Reproductive system and breast disorders					
	Menstrual disorder	1	1		
	Scrotal swelling	2	1		
Respiratory, thoracic and mediastinal disorders					
	Epistaxis			2	1
Surgical and medical procedures					
	Ureteric calculus removal			1	1
Vascular disorders					
	Hypotension			1	1

Source: STN125495 study 1304 Analysis Dataset ADAE

Twelve of the 15 TEAEs in the Ruconest study arm occurred in one subject [abdominal pain (5 events), headache (3 events), scrotal swelling (2 events), tonsillitis (1 event), and herpes simplex (1 event). One subject in the Ruconest arm experienced the remaining 3 TEAEs (diarrhea, condition aggravated, and menstrual disorder).

6.2.12.3 Deaths

There were no deaths.

6.2.12.4 Nonfatal Serious Adverse Events

Three subjects (all in the saline arm) had serious adverse events (biliary colic, diagnostic prostate examination, ureteric calculus with removal). One Ruconest subject experienced laryngeal edema on days 2 and 95 after treatment.

Reviewer's Comment: The TEAEs do not indicate a safety concern for Ruconest. However, the occurrence of laryngeal edema on day 2 after treatment with 100 U/kg may indicate limitations on the duration of effect if used for routine prophylaxis of HAE attacks.

There were no subject discontinuations for adverse events.

6.3 Trial #3 Study 1310 RCT (first subject enrolled Jan 30 2011, last subject completed Sep 26 2012)

The pivotal study 1310 RCT was a randomized (3:2) placebo-controlled controlled trial in 73 HAE subjects (42 Ruconest; 31 saline) experiencing an attack (37 subjects at US sites; 36 at European sites) with an open-label extension (OLE). The Ruconest dose was 50 U/kg, the placebo was saline. Enrollment required a baseline VAS of at least 50 millimeters. The primary endpoint was time-to-initial-relief-of-symptoms as measured by a Treatment Effect Questionnaire (TEQ), with a secondary endpoint being outcome evaluation by a VAS. Success for the primary endpoint required repeated demonstration of symptom improvement based on timed responses to questions 1 and 2 of the TEQ, which are given below:

Question 1: To what extent has the overall severity of your [relevant attack location] HAE attack changed since you received the infusion?

Much Worse	Worse	A Little Worse	Not Changed	A Little Better	Better	Much Better
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Question 2: Overall, has the intensity of your [relevant attack location] HAE attack begun to decrease noticeably since you received the infusion?

Yes	No
-----	----

A success for the secondary endpoint, VAS response, required repeated demonstration of at least a 20 millimeter decrease from the baseline VAS.

6.3.1 Objectives (Primary, Secondary, etc)

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

6.3.2 Design Overview

- Randomized, double-blind placebo-controlled, multicenter and multinational, with an open-label extension
- Subjects with a baseline symptom severity score greater than 50mm, as measured by a VAS, were randomized 3:2 to Ruconest (50 U/kg) or saline
- Primary endpoint: time-to-beginning-of-relief-of-symptoms, as measured by a decrease of 20mm in the VAS compared to baseline, with persistence
- Rescue treatment with Ruconest was permitted at 4 hours, or earlier if subjects experienced life-threatening oropharyngeal-laryngeal angioedema symptoms

Reviewer's comment: The use of an investigational treatment to 'rescue' a subject after the same investigational treatment has been found to be inadequate is not advisable in a clinical trial if there are approved or licensed medicines that can serve this purpose. This is a safety concern, but it is also a study analysis concern in that it complicates that attribution of outcomes to doses.

6.3.3 Population

Subjects were males or females > 18 years of age with a clinically-suspected or laboratory confirmed diagnosis of HAE type I or II (C1INH activity < 50% of normal, with normal C1q and absence of anti-C1INH antibodies).

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to Ruconest received 50 U/kg intravenously in one injection, not to exceed a total dose of 4200 Units for subjects weighing more than 84 kg. Subjects randomized to saline received a volume-match intravenous injection.

The protocol contained a list of ‘disallowed medications’ that could confound evaluation of the primary endpoint. The list included, analgesics, narcotics, anti-emetics, anti-spasmodics, and supportive measures. The use of these disallowed medications immediately prior to study entry was an exclusion criterion.

6.3.6 Sites and Centers

Site	Investigator	No. Subjects C1=C1INH Pl=Placebo
Baker Allergy, Asthma & Dermatology Research Center, LLC 3975 SW Mercantile Drive, Suite 165, Lake	Dr. James W. Baker Holly Morrison, FNP	9 4 C1 5 Pl
Medical Research of Arizona 7514 E. Monterey Way, Suite 1A, Scottsdale AZ85251	Dr. Aaron J. Davis Michael E. Manning, MD Thomas F. Hartley, MD Jean A. Nelson, FNP-C	2 2 C1
Family Allergy and Asthma Center, PC 5555 Peachtree Dunwoody #340 Atlanta GA 30342	Dr. Robyn J. Levy	9 5 C1 4 Pl
Institute for Asthma and Allergy, PC 5454 Wisconsin Avenue, Suite 700 Chevy Chase MD 20815	Dr. Huamin Henry Li Martha White, MD, CPI Michael Kaliner, MD Athena Economides, MD Mark Scarupa, MD Davis Jeong, MD	3 2 C1 1 Pl

Site	Investigator	No. Subjects C1=C1INH Pl=Placebo
University of South Florida Asthma, Allergy Immunology, Clinical Research Unit 13801 Bruce B. Downs Blvd, Suite 505 Tampa, FL 33613	Dr. Richard F. Lockey Dennis K. Ledford, MD Roger Fox, MD Mark Glaum, MD Robert Pesek, MD Ahmed Butt, MD David Fitzhugh, MD James Parkerson, MD Michel Alkhalil, MD Neetu Talreja, MD Salman Aljubran, MD Susan Culverhouse, MD	2 1 C1 1 Pl
Pennsylvania State Milton S. Hershey Medical Center 500 University Drive HO 41, C5860 Hershey, Pennsylvania 17033	Dr. Timothy Craig Faoud Ishmael, MD Thomas Mertz, DO Gisoo Ghaffari, MD Neil Baman, MD Efren Rael, MD Maria Gutierrez, MD Pooja Jhaveri, MD Puneet Bajaj, MD Neeti Bhardwaj, MD Neelu Kalra, MD Natalia Vernon, MD	1 1 C1
Optimed Research, LTD 8080 Ravines Edge Court, Suite 200 Columbus OH 43235	Dr. Don McNeil Elden L. Apling, MD Philip Neil Rancitelli, MD Ann Urbank, MS, CNP	5 3 C1 2 Pl
AARA Research Center 10100 N. Central Expy. Stes. 125 & 200 Dallas TX 75231	Dr. William Lumry Kimberly Poarch, PA-C	2 2 C1

Site	Investigator	No. Subjects C1=C1INH PI=Placebo
University of Cincinnati Physicians INC. Department of Internal Medicine Division of Immunology/Allergy 3255 Eden Avenue, Suite 250 ML 0563 Cincinnati, OH 45267-0563	Dr. Jonathan A. Bernstein David Bernstein, MD Benjamin Davis, MD Andrew Smith, MD Haejin Kim, MD Tolly Epstein, MD Chris McNight, MD James Wesley Sublett, MD Gang Cheng, MD Priyal Amin, DO	2 1 C1 1 PI
Marycliff Allergy Specialists 823 West 7th Avenue Spokane, WA 99204	Dr. Richard G. Gower E. Suzanne Levitch, ARNP	1 1 PI
Asthma and Allergy Center Washington University School of Medicine 10 Barnes West Drive, Suite 200 St. Louis MO 63141	Dr. James Wedner Anthony Kulczycki Jr, MD Andrew L. Kau, MD, PhD James Tarbox, MD Jennifer Welch, MD Natalie Beaven Miller, MD Sarena S. Sawlani, MD Kathryn Lindsey Batte McMullan, MD	2 1 C1 1 PI
Clinical Center Serbia Clinic for Immunology and Allergology Koste Todorovica 2 11000 Belgrade Serbia	Dr. Sladjana Andrejevic Dr. Radovan Mijanovic Dr. Dimitrije Dimitrijevic	4 1 C1 3 PI
Ospedale Luigi Sacco Azienda Ospedaliera – Polo Universitariolo Divisione di Medicina Interna Via G.B.Grassi 74 20157 Milano Italy	Prof. Dr. Marco Cicardi Dr. Andrea Zanichelli Dr. Anna Coerezza	3 1 C1 2 PI
Semmelweis Egyetem III. sZ Belgyogyaszati Klinika Kutvolgyi ut 4 1125 Budapest Hungary	Prof. Dr. Henriette Farkas Dr. Györgi Temesszentandrás Dr. László Jakab Dr. Lászlóné Egri	3 3 C1

Site	Investigator	No. Subjects C1=C1INH PI=Placebo
PHI University Clinical Centre Skopje Unit of Allergology and Clinical Immunology Department of Dermatology Vodnjanska 17, 1000 Skopje Macedonia	Prof Dr. Vesna Grivcheva-Panovska Dr. Veronica Davceva Bitoljanu	7 6 C1 1 PI
Spitalul Clinic Judetean Mures Sectia Clinica Medicina Interna Compartimentul de Alergologie si Imunologie Str. Gh. Marinescu nr. 1 540103 Targu-Mures Romania	Dr. Dumitru Moldovan Dr. Enikő Mihály Dr. Noemi Anna Bara Cristian Podoleanu	9 6 C1 3 PI
Szpital Uniwersytecki w Krakowie Oddziel Kliniczny Chorob Wewnetrznych Poradnia Alergologiczna ul. Sniadeckich 10 31-531 Krakow Poland	Prof. Dr. Krystyna Obtulowicz Dr. Marcin Stobiecki Dr. Grzegorz Porebski	7 3 C1 4 PI
UMHAT Tsaritsa Yoanna – ISUL EAD Clinic of Ear-Nose-Throat Diseases 8 Bialo More street 1527 Sofia Bulgaria	Dr. Todor Shirov Prof. Dr. Ivan Tchalakov	1 1 PI
Allergy Immunology & Angioedema Center Sheba Medical Center Tel Hashomer Ramat Gan Israel 62621	Dr. Avner Reshef Mona Iancovici Kidon, MD Avner Goren, MD	3 2 C1 1 PI

6.3.7 Surveillance/Monitoring

For the primary endpoint, the TEQ was measured in-clinic at baseline, then every 15 minutes to 60 minutes, then every 30 minutes to 8 hours. The secondary endpoint VAS was also measured at these time points.

Adverse events were monitored throughout the in-clinic stage, and at day 28 and day 90. Antibody response was measure at baseline, day 28 and day 90.

Concomitant medication use was monitored throughout the study to capture use of medications that could affect outcomes.

6.3.8 Endpoints and Criteria for Study Success

The TEQ consisted of the following 3 questions:

Question 1: To what extent has the overall severity of your [fill in anatomical site] HAE attack changed since you received the infusion?						
Much worse	Worse	A little worse	Not changed	A little better	Better	Much better
Question 2: Overall, has the intensity of your [fill in anatomical site] HAE attack symptoms begun to decrease noticeably since you received the infusion?						
Yes	No					
Question 3: At this moment, are your [fill in anatomical site] HAE attack symptoms minimal (barely noticeable)?						
Yes	No					

Answering “Yes” to TEQ question 2 for two consecutive time points defined success. The resulting database of TEQ question 2 outcomes was used to define the minimally-important difference as measured by the VAS (secondary endpoint).

6.3.10 Study Population and Disposition

Subject Disposition: RCT ITT Analysis Set (N = 75)

	rhC1INH (N=44) n (%)	Saline (N=31) n (%)	All Subjects (N=75) n (%)
RCT ITT Analysis Set (Presented for Treatment with Eligible Attack)	44 (100)	31 (100)	75 (100)
RCT Safety Analysis Set (Treated)	43 ^a (98)	31 (100)	74 (99)
Completed the RCT Phase^b			
Yes	42 (95)	31 (100)	73 (97)
No	2 ^c (5)	0	2 (3)
Reason for Discontinuation During RCT Phase			
Withdrew Consent	1 ^d (2)	0	1 (1)

Source: STN125495 study 1310 Clinical Report page 73 of 2609

RCT = randomized controlled trial; HAE = hereditary angioedema; ITT = intent-to treat.

Note: Percentages are based on the number of subjects in the RCT ITT Analysis Set.

^aSubject -(b)(6)- was randomized to rhC1INH, but did not receive study medication.

^bCompleted up to Day 90 visit of RCT Phase or received an open-label administration of rhC1INH prior to Day 90 visit of the RCT Phase.

^cSubjects -(b)(6)- (did not receive study medication) and -(b)(6)- (withdrew consent to participate in another investigational study) did not complete the RCT Phase.

^dSubject -(b)(6)- received randomized treatment with rhC1INH and subsequently withdrew consent to participate in another investigational study.

6.3.10.1 Populations Enrolled/Analyzed

Subjects were males or females ≥ 13 years of age (≥ 18 years of age outside the U.S. or Canada) with a clinically-suspected or laboratory confirmed diagnosis of HAE type I or II (C1INH activity $< 50\%$ of normal, with normal C1q and absence of anti-C1INH antibodies).

6.3.10.1.1 Demographics

Demographic Characteristics: RCT ITT Analysis Set

	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)

	rhC1INH (N=44)	Saline (N=31)	Total (N=75)
Range	47.0-154.2	54.0-172.0	47.0-172.0

Source: STN125495 Study 1310 Clinical Report page 76 of 2609

RCT = randomized controlled trial; ITT = intent-to-treat; SD = standard deviation; BMI = body mass index.

Notes: Age at Screening was calculated as the integer part of (Date of screening visit – Date of birth)/365.25;

Age at Date of Admission was calculated as the integer part of (Date of admission visit – Date of birth)/365.2.

BMI was calculated as Weight (kg) / Height (m)².

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The following table shows the distribution of subjects who received disallowed medication during the study:

Concomitant Medications that may have Interfered with the Assessment of the Impact of rhC1INH on Efficacy: RCT ITT Analysis Set

ATC Text Preferred Term	rhC1INH (N=44)	Saline Solution (N=31)	Total (N=75)
Number of subjects taking at least one concomitant medication	4 (9%)	2 (6%)	6 (8%)
Anilides	2 (5%)		2 (3%)
Medinite	1 (2%)		1 (1%)
Paracetamol	1 (2%)		1 (1%)
Androstan derivatives		1 (3%)	1 (1%)
Stanozolol		1 (3%)	1 (1%)
Propionic acid derivatives	1 (2%)		1 (1%)
Naproxen sodium	1 (2%)		1 (1%)
Salicylic acid and derivatives	1 (2%)		1 (1%)
Acetylsalicylic acid	1 (2%)		1 (1%)
Serotonin (5ht3) antagonists		1 (3%)	1 (1%)
Ondansetron		1 (3%)	1 (1%)

Source: STN125495 Study 1310 Clinical Report Table 14.1.7.2RCT page 228 of 2609

The following table shows the distribution of subjects who received rescue medication or disallowed medication during the study:

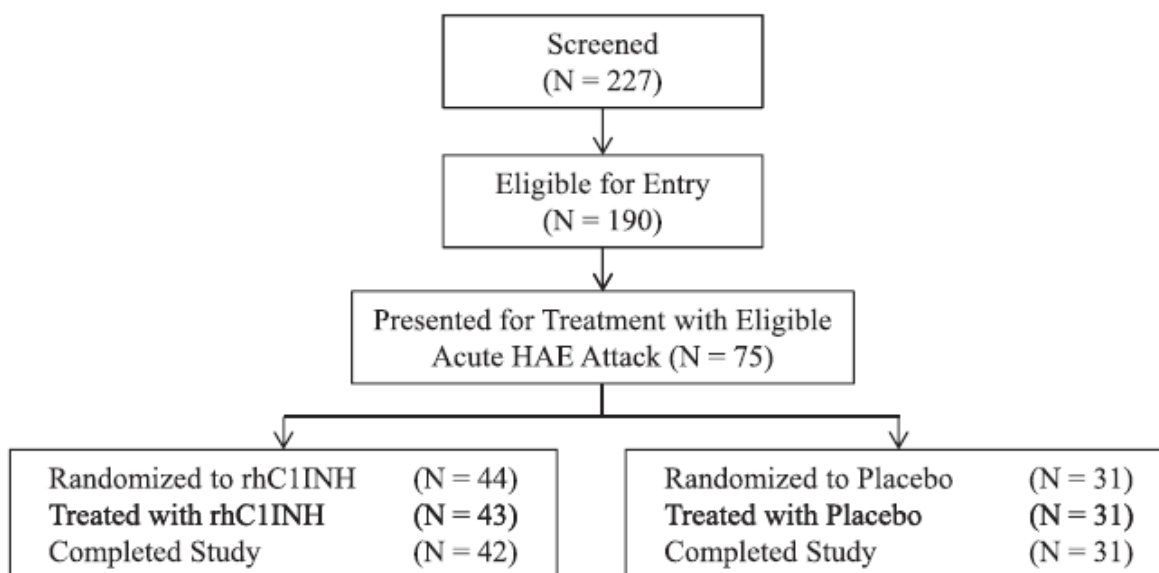
Number of Subjects Receiving Rescue Medication or Disallowed Concomitant Medication: RCT ITT Analysis Set

	rhC1INH (N=44)	Saline Solution (N=31)
Did the patient receive rescue medication?		
Yes	5 (13%)	13 (43%)

	rhC1INH (N=44)	Saline Solution (N=31)
No	35 (88%)	17 (57%)
Did the patient receive disallowed concomitant medication?		
Yes	4 (9%)	2 (3%)
No	40 (91%)	29 (94%)

Source: adapted from STN125495 Study 1310 Clinical Report Table 14.2.12RCT
page 548 of 2609

6.3.10.1.3 Subject Disposition



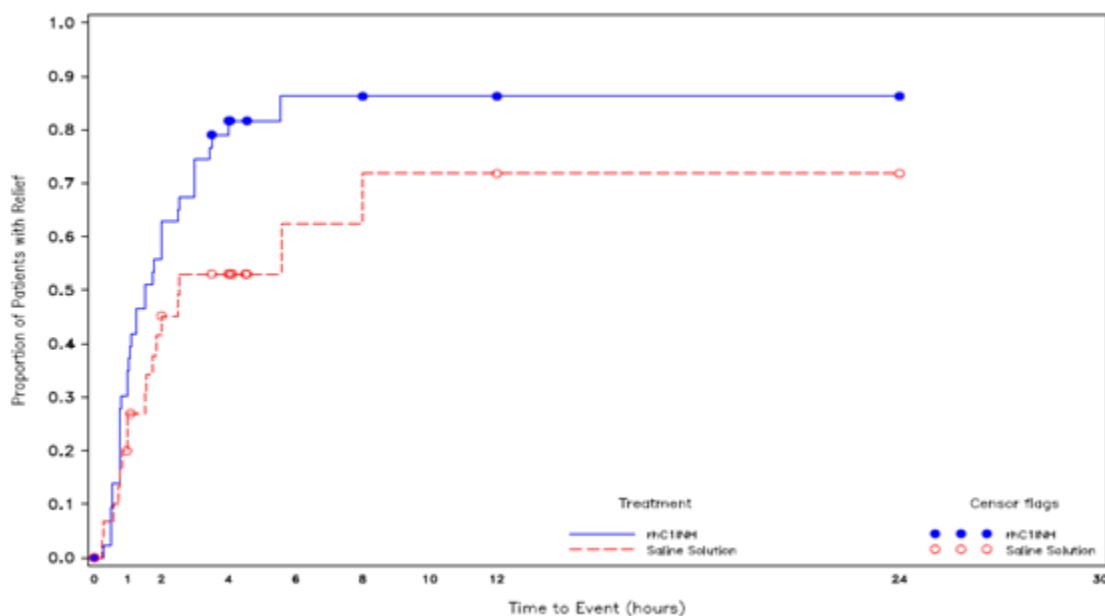
Source: *Ann Allergy Asthma Immunol* **112**: 163-169 (2014)

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The following Kaplan-Meier plot and table show the applicant's presentation of the results for the primary endpoint time-to-beginning-of-relief-of-symptoms for study 1310 RCT:

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms with Persistence (Based on Questions 1 and 2 of the TEQ, with Persistence) in the RCT Phase: RCT ITT Analysis Set



Source: STN125495 Study 1310 Clinical Report page 87 of 2609

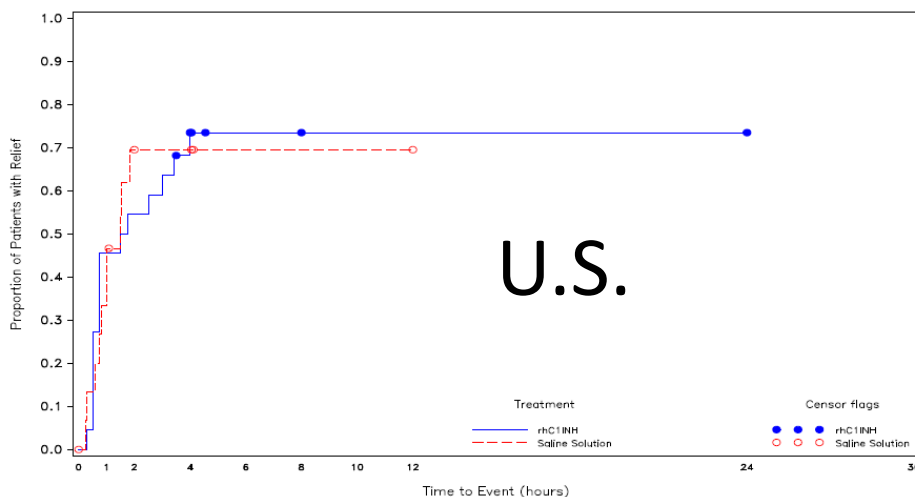
Study 1310 RCT: Time (minutes) to Beginning of Relief of Symptoms based on questionnaire

Time to Beginning of Relief of Symptoms, minutes	RUCONEST 50 Units/kg (N=44)	Placebo (N=31)
Median	90	152
95% CI	(61, 150)	(93, -)
p-value	0.031	

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

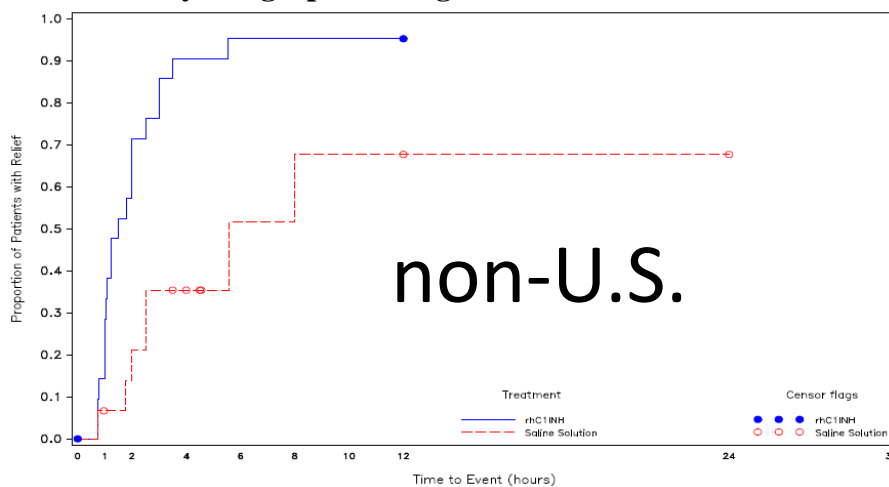
Taken as a whole, study 1310 RCT showed statistical significance for treatment effect, although this outcome was driven by the non-U.S. results, which differed from the U.S. results, as shown in the following two charts:

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence) at the primary attack location by Geographical Region - USA



Source: STN125495 Study 1310 Clinical Report, Page 1001 of 2609

Study 1310: Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence) at the primary attack location by Geographical Region – Rest of the World



Source: STN125495 Study 1310 Clinical Report, Page 1002 of 2609

The applicant identified the rapid response in the U.S. female placebo subgroup as being responsible for this outcome, as shown in the following table:

Time (minutes) to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence), Subgroup Analyses: RCT ITT Analysis Set		
	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=44)	Saline (N=31)
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]
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]

Source: Table 14.2.1.15RCT to Table 14.2.1.21RCT.
TEQ = Treatment Effect Questionnaire; CI = confidence interval; RCT = randomized controlled trial; ITT = intent-to-treat;
Notes: In the saline treatment group 11 (35%) patients received rescue medication or disallowed concomitant medication prior to beginning of relief of symptoms, and were therefore censored, resulting in inestimable medians for some of the subgroups; values that are not estimable are displayed as ‘-’.

Source: STN125495/0 Clinical Report

The anomalous results in the pre-specified analysis subgroups ‘gender’ and ‘geographic region’ were not included in the pre-BLA meeting package because the applicant said the results for pre-specified subgroups were not available at that time. Upon submission of STN125495, the review team made a refuse-to-file (RTF) recommendation for scientific incompleteness based on the anomalous gender and geographic region results; however, this recommendation was overruled by CBER supervisors who said this RTF provision does not apply to this situation. These anomalous results are also not presented in the publication¹⁰ of study 1310. When FDA proposed addition of this information to the physician’s insert (PI), the applicant questioned the relevance of this information to physicians or patients; FDA responded that such information could assist physicians and patients in assessment of lack of therapeutic effect, as has been reported¹¹ in a small case study from the United Kingdom, in which 6 of 11 HAE patients with moderate to severe HAE attack symptoms declined continued treatment with Ruconest because of the perception of an inadequate response (rapid HAE attack recurrence, suboptimal response compared to plasma-derived C1INH products) at the Ruconest labeled dose (50 Units/kg).

FDA reviewers have identified systematic differences in the databases for the U.S. and non-U.S. components of study 1310 (see [6.3.11.5](#)) that led to the conclusion that, even though the same protocol was used, the U.S. and non-U.S. components were conducted as if they were separate clinical trials. Among the identified differences in the database structures are the following:

¹⁰ *Ann Allergy Asthma Immunol* **112**:163-169 (2014)].

¹¹ *Eur J Dermatol* **24**(1):28-34 (2014)

- Differences in the extent of adverse event monitoring (more intense and longer in the U.S.)
- Differences in the amount of concomitant medications (more medication use over longer periods in the U.S.)
- Differences in the degree of use of medications to treat HAE (greater in the U.S.)
- Differences in the baseline HAE attack severity (more severe in Europe)
- Differences in the relationship between the time of achieving the primary endpoint as measured by TEQ or by VAS (greater difference in these time points in Europe than in the U.S.)
- Two separate clinical trial monitoring organizations used (one for Europe, another for the U.S and a few European sites)

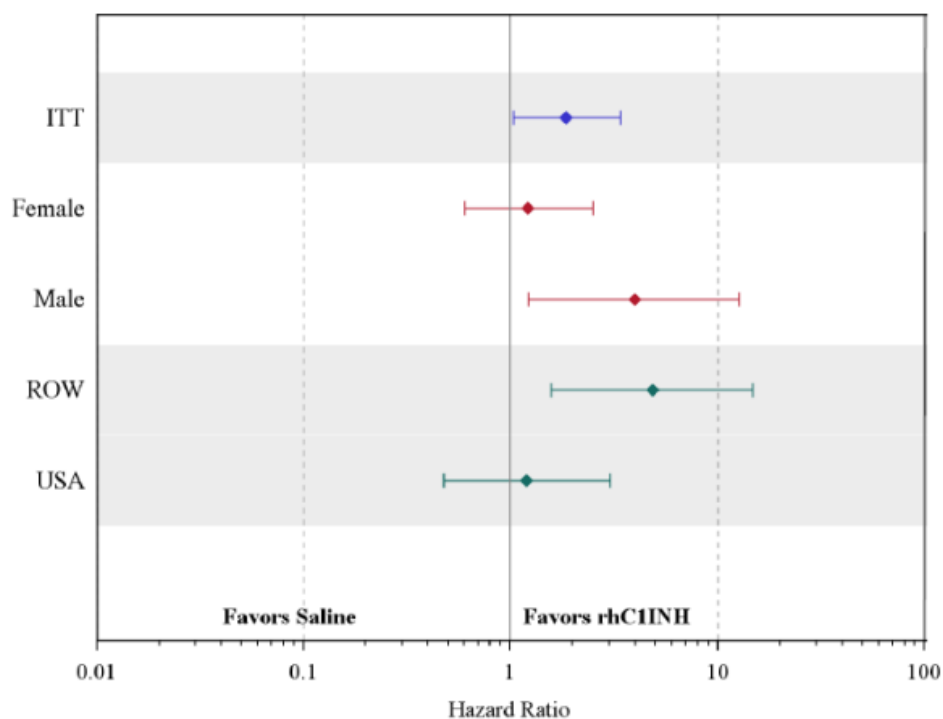
These differences may contribute to the overall differences in outcomes between the geographic regions – U.S. and Rest of World (ROW).

The FDA review team discussed these results with the applicant, and the applicant responded with the following four post-hoc analyses to address these concerns:

I. Applicant Response: Represent Study 1310 Results as Hazard Ratios

Representation of the data as hazard ratios removes the time element from the data and results in ratios greater than 1.0 if a response curve precedes the placebo response curve by any amount of time. Using this approach, the applicant states that the hazard ratios for gender and geographic region are greater than 1.0, as is the hazard ratio for the entire study 1310 (ITT).

Hazard Ratio for Time to Beginning of Relief of Symptoms with Persistence at the Primary Attack Location (Based on TEQ) - 1310 RCT ITT Analysis Set (N=75)



Source: Table 14.2.1.1RCT, Table 14.2.1.13RCT, Table 14.2.1.16RCT, Table 14.2.1.19RCT, Study 1310 CSR (Sequence 0000).

This analysis is problematic because it ignores statistical significance, and it focuses attention instead on whether a Kaplan-Meier response curve for Ruconest precedes that of the control by any amount of time (i.e. the hazard ratio is greater than 1.0).

Clinical trial methodology for treatment of HAE attacks was motivated by licensure requirements for plasma-derived C1INH products that were intended for replacement therapy to treat HAE attacks. The methodology was accepted -- even though there was minimal justification of the clinical benefit associated with the primary endpoint time-to-initial-relief of HAE symptoms -- because of the urgency for finding a measurable endpoint that could be used to evaluate dose-related outcomes, and permit product licensure. The licensure standard required a demonstration of statistical significance for a pre-defined difference in the primary endpoint outcomes between test agent and control.

The hazard ratio analysis that the applicant presents is most often used for outcomes that represent clinically important outcomes (morbidity, mortality), and not for a comparison of outcomes between the study agent response and the placebo response for a partially-validated¹², surrogate outcome for clinical benefit, such as the endpoint time-to-initial-relief of HAE symptoms.

¹² *Patient 5*(2):113-126 (2012); this paper evaluated content validity of the VAS for HAE attacks, but did not establish validity of VAS for measuring clinical benefit. There is no “gold standard” against which the VAS or any other outcome measure of the primary endpoint time-to-beginning-of-relief could be compared.

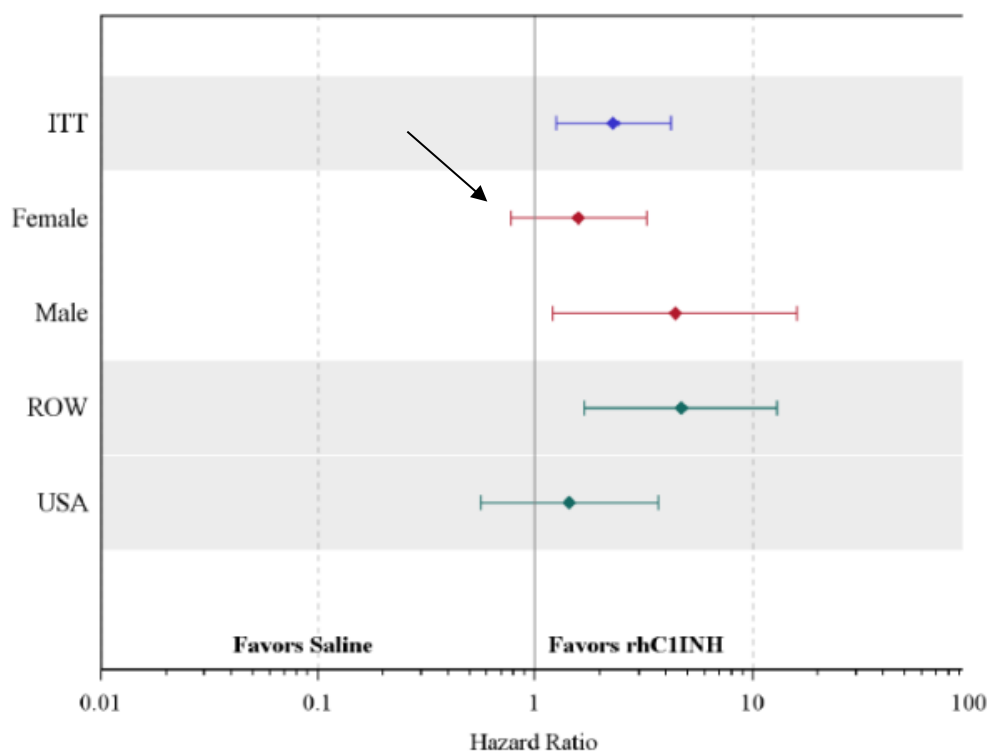
II. Applicant Response: Sensitivity Analyses

i. Sensitivity Analysis by time-from-attack-onset to time-of-initial-relief

This analysis is based on an unproven assumption that subjects who took longer to present for treatment would respond sooner than subjects who presented immediately, other factors being equal.

This analysis shifts the hazard ratio for the female subgroup in the favorable direction (see arrow), as shown below:

Hazard Ratio for Time to Beginning of Relief of Symptoms with Persistence at the Primary Attack Location (Based on TEQ) Measured from Time of Attack Onset - 1310 RCT ITT Analysis Set (N=75)



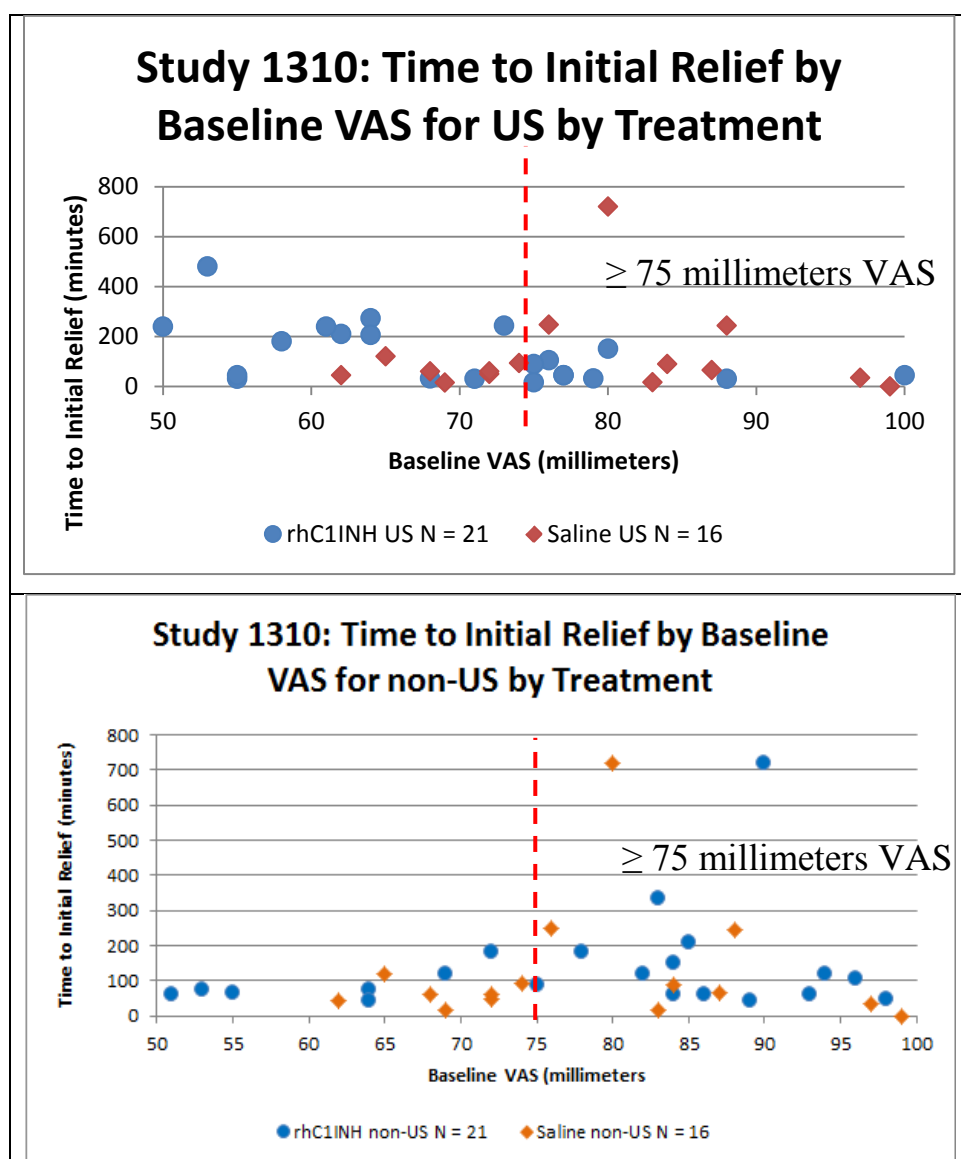
Source: Figure 1, Figure 2, Table 2 and Appendix 3, Table 16, Figure 1 through Figure 4, 1.11.3 Efficacy Information Amendment, Sequence 0016).

This post hoc analysis rests on an unproven assumption (i.e. a difference in a few hours from attack onset to treatment will result in measureable differences in outcomes), and may never be subjected to testing for ethical reasons. For this reason, in this reviewer's opinion, this analysis is not useful for understanding the results of study 1310.

ii. Sensitivity Analysis by HAE attack severity at baseline

This analysis is inspired by a report [Craig *et al.*]¹³ that a post hoc analysis of data from the Berinert (plasma-derived C1INH) licensure study showed a greater difference in time-to-initial-relief-of-symptoms, compared to the placebo response, for baseline severe HAE attacks than baseline moderate attacks. For this analysis, the applicant defined 'severe HAE attacks' as those for which the patient-reported VAS score was above the midpoint in the eligibility range, i.e. the VAS score was marked as greater than or equal to 75 millimeters on a 100 millimeter scale.

The following two graphs show the time-to-initial-relief plotted against the baseline VAS for each subject in the U.S. and non-U.S.(ROW) groups:

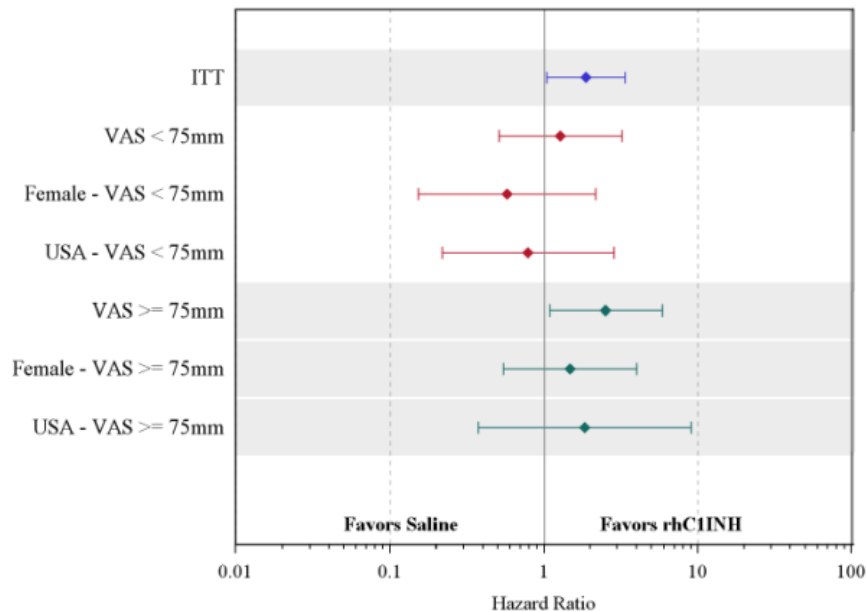


13 *J Allergy Clin Immunol* 124(4):801-808 (2009)

From the distribution of the outcome data (time-to-initial-relief-of-symptoms) it can be seen that the 75 millimeter demarcation is arbitrary, in that it does not demarcate two different outcome distributions.

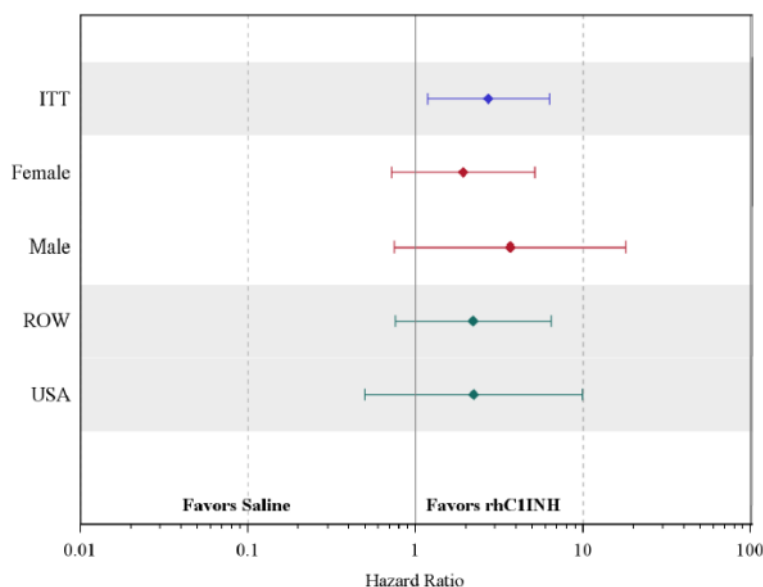
The following charts show the data used for this attack severity analysis and the hazard ratios for the U.S. component of study 1310 and for a comparison of the gender and geographic subgroups for the entire study 1310:

Hazard Ratio for Time to Beginning of Relief of Symptoms with Persistence at the Primary Attack Location (Based on TEQ) by Attack Severity (Based on Baseline VAS) - 1310 RCT ITT Analysis Set (N=75)



Source: Figure 5 through Figure 7, Table 4, Table 6, and Appendix 3, Table 26, Table 27, Figure 12, Figure 14, and Figure 17, 1.11.3 Efficacy Information Amendment, Sequence 0016).

Hazard Ratio for Time to Beginning of Relief of Symptoms with Persistence at the Primary Attack Location (Based on TEQ) Measured from Symptom Onset for Patients with Severe Attacks (Baseline VAS \geq 75 mm) - 1310 RCT ITT Analysis Set (N=43)



Source: Table 7, Appendix 3, Table 30, 1.11.3 Efficacy Information Amendment, Sequence 0016).

It can be seen that limiting the sensitivity analysis to the baseline severe HAE attack subgroup shifts the hazard ratios for the gender and geographic region subgroups to the side favorable for Ruconest. It should be noted that, unlike the Berinert results in Craig *et al.*, the baseline moderate HAE attack outcomes remain unfavorable. This is shown in the following table from the statistical reviewer's memo:

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 \geq 75mm	45 (32, 90) [n=9]	- (35, -) [n=8]
VAS < 75mm	240 (45, -) [n=13]	60 (45, 110) [n=8]

Source: STN125495 statistical review memo of Y. Abigail Luo, Ph.D.

This baseline severity analysis could be the basis for a clinical trial to test a null hypothesis, but it is questionable for decision-making, because it is a post hoc analysis.

III. Applicant Response: Analysis of Use of Rescue Medication

The study 1310 protocol permitted open-label use of rhC1INH at 4 hours after initial treatment for subjects with significant pain, discomfort, or disability from HAE symptoms, and for any subject at any time who had the onset of potentially life-threatening symptoms.

The applicant analyzed rescue medication use by gender and geographic region, and performed a sensitivity analysis in which the time-to-initial-relief was set to 24 hours for rescued subjects. The following shows a table of rescued subjects, a table of the subgroup analysis, and a Kaplan-Meier plot adjusted for the reassigned outcomes of 24 hours for rescued subjects:

Study 1310: Subjects who received open-label rhC1INH as rescue medication

Region	Arm	Subject	Dose Time	Rescue Time	Hours after Dose
non-US	rhC1INH	(b)(6)	9:00	13:50	4:50
US	rhC1INH		18:39	22:27	3:48
US	rhC1INH		12:44	16:50	4:06
US	rhC1INH		21:50	2:04	4:14
US	rhC1INH		8:07	12:45	4:38
non-US	Saline		13:35	14:46	1:11
non-US	Saline		10:15	14:15	4:00
non-US	Saline		13:00	17:30	4:30
non-US	Saline		11:32	16:10	4:38
non-US	Saline		19:12	23:55	4:43
non-US	Saline		9:45	14:45	5:00
non-US	Saline		21:40	3:20	5:40
US	Saline		11:20	12:35	1:15
US	Saline		17:45	19:55	2:10
US	Saline		12:21	16:30	4:09
US	Saline		17:35	21:48	4:13
US	Saline		15:43	20:11	4:28
US	Saline		12:09	16:48	4:39

Source: from databases submitted in STN125495/0

Proportion of Patients Who Received rhC1INH as Rescue Medication Overall and by Gender and Geographical Location - 1310 RCT ITT Analysis Set (N=75)

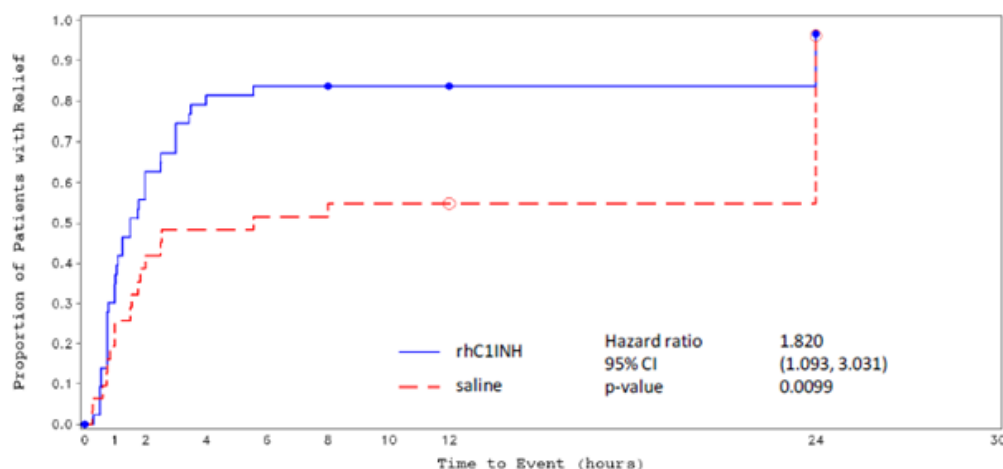
	Saline (N=31) n/N (%)	rhC1INH (N=44) n/N (%)
Patients Who Received Rescue Medication	13/31 (41.9)	5/44 (11.4)
Gender		
Female	6/19 (31.6)	2/28 (7.1)
Male	7/12 (58.3)	3/16 (18.8)
Geographical Location		
ROW	7/15 (46.7)	1/22 (4.5)
US	6/16 (37.5)	4/22 (18.2)

ITT, intent-to-treat; RCT, randomized controlled trial; N, total number of patients; n, number of patients who received rescue medication; ROW, Rest of the World; US, United States.

Source: Table 14.2.12RCT, Listing 16.2.4.1RCT, and Listing 16.2.5RCT, Study 1310 CSR (Sequence 0000).

Analysis of the use of a rescue medication has been considered in the interpretation of the results of other clinical studies of drugs to treat HAE attacks (see Kalbitor[®] Full Prescribing Information); however, the use of this endpoint has the potential to introduce uninterpretable sources of bias (e.g., investigator choice), as can be seen in the differences between the geographic regions (U.S. and ROW), especially in the Ruconest cohort.

Kaplan-Meier Plot of Time to Beginning of Relief of Symptoms at the Primary Attack Location (Based on Questions 1 and 2 of the TEQ with Persistence) Setting Patients who Received Rescue Medication or Disallowed Concomitant Medication to 24 hours - 1310 RCT ITT Analysis Set (N=75)



Source: Table 14.2.1.4RCT, Study 1310 CSR (Sequence 0000).

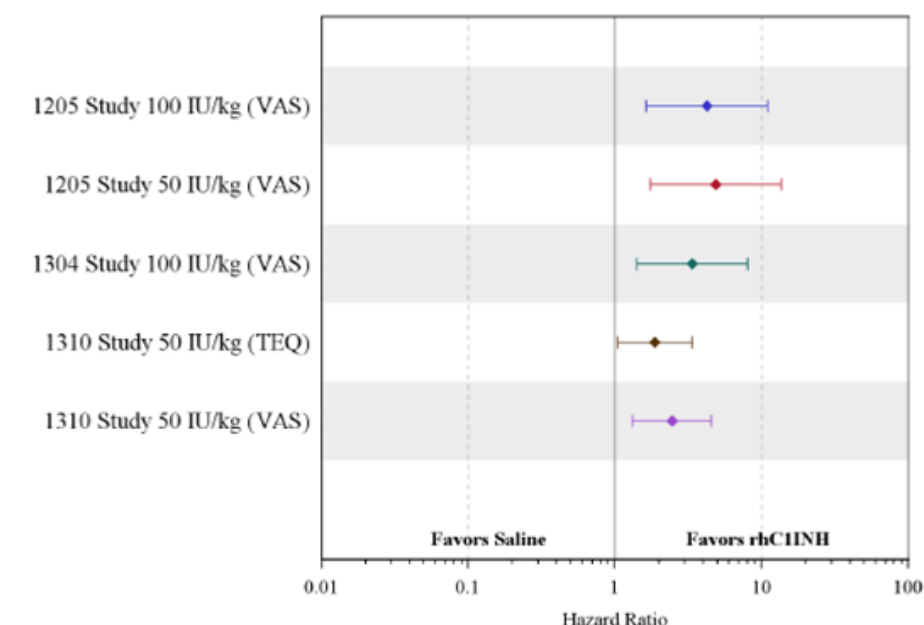
Although the applicant introduces the use of assignment of the response time to 24 hours for subjects who used rescue medication or disallowed medications (which are a pre-specified group of medications that could affect the subjective primary endpoint time-to-initial-relief-of-

symptoms) based on its use in the analysis of clinical trials of Berinert[®], this is a post hoc analysis that is interesting, but also can be subject to introduced bias.

IV. Applicant Response: Hazard Ratios for Studies 1304, 1205, and 1310, and for gender subgroups pooled across studies

The applicant presented data for all efficacy studies and for pooled gender subgroups across all studies as hazard ratios, as shown in the following charts:

Hazard Ratio for rhC1INH Compared with Saline Across Three Randomized, Placebo-Controlled Trials

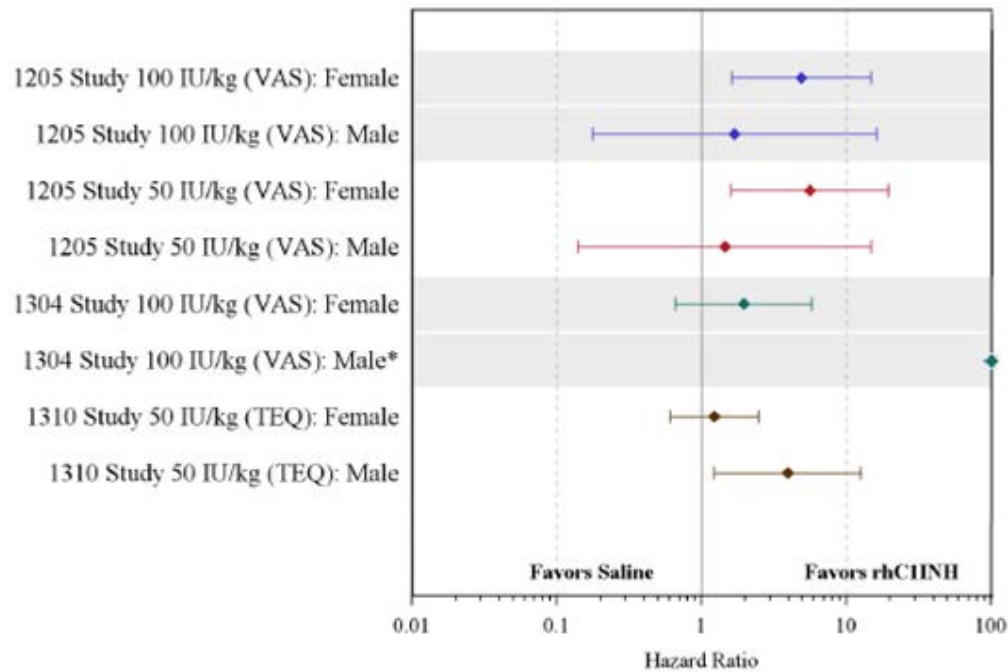


TEQ, Treatment Effects, Questionnaire; VAS, visual analog scale.

Source: Table 14.2.1.1RCT, Table 14.2.1.13RCT and Table 14.2.3.2RCT, Study 1310 CSR; Table 14.2.1.1, Table 14.2.1.15 and Table 14.2.1.16, Study 1205RCT CSR; Table 14.2.1.1, Table 14.2.1.17 and Table 14.2.1.18, Study 1304RCT CSR (Sequence 0000).

This hazard ratio analysis by study does not present any new information beyond the previously discussed overall results for these studies.

Hazard Ratio for rhC1INH Efficacy Across Three Randomized, Placebo-Controlled Trials by Gender



* Hazard Ratio > 100.

TEQ, Treatment Effects, Questionnaire; VAS, visual analog scale.

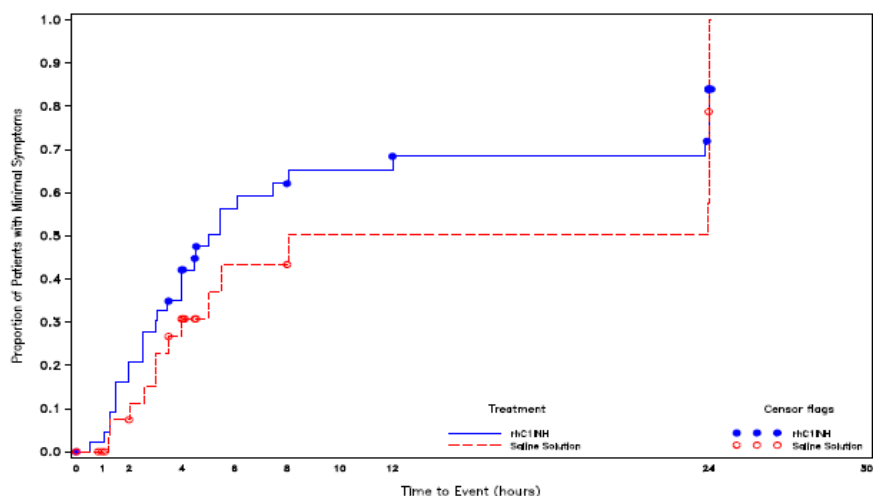
Source: [Table 14.2.1.16RCT](#) and [Table 14.2.3.5RCT](#), Study 1310 CSR; [Table 14.2.1.4](#), Study 1205RCT CSR; [Table 14.2.1.5](#), Study 1304RCT CSR; (Sequence 0000).

This hazard ratio analysis by gender is not informative for resolution of the gender and geographic region anomalous results of study 1310. The applicant directs attention to the fact that the hazard ratio for each group is greater than 1.0 (i.e. the Ruconest response curve preceded the placebo response curve by any amount of time); however, the criticisms of lack of statistical and clinical significance for some of these subgroups remain.

6.3.11.2 Analyses of Secondary Endpoints

The study 1310 RCT results for the secondary endpoint time-to-minimal-symptoms (defined as the VAS less than 20mm) are shown in the following Kaplan Meir Plot:

Figure 3 Kaplan-Meier Plot of Time to Minimal Symptoms (Based on Question 3 of the TEQ) in the RCT Phase: RCT ITT Analysis Set



Source: Figure 14.2.2 IRCT.

TEQ = Treatment Effect Questionnaire; RCT = randomized controlled trial; ITT = intent-to-treat.

Source: STN125495 Study 1310 Clinical Report

Time to Minimal Symptoms (Based on Question 3 of the TEQ) in the RCT Phase: RCT ITT Analysis Set

Time to Minimal Symptoms, minutes	rhC1INH (N=44)	Saline (N=31)
Median (95% CI)	303.0 (240.0, 720.0)	483.0 (300.0, 1440.0)
Log-rank test p-value	0.078	

Source: STN125495 Study 1310 Clinical Report p.95 of 2609

TEQ = Treatment Effect Questionnaire; RCT = randomized controlled trial; ITT = intent-to-treat;

CI = confidence interval.

Note: p-value calculated from a log-rank test stratified by primary attack location.

6.3.11.3 Subpopulation Analyses

In the following table, the applicant presents results for other pre-specified secondary endpoints for study 1310:

Table 15 Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence), Subgroup Analyses: RCT ITT Analysis Set		
	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]

Table 15 Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence), Subgroup Analyses: RCT ITT Analysis Set		
	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=44)	Saline (N=31)
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]
Urogenital	45.0 (22.0, 63.0) [n=3]	60.0 (- , -) [n=1]
Source: STN125495 Study 1310 Clinical Report Table 14.2.1.15RCT to Table 14.2.1.21RCT. TEQ = Treatment Effect Questionnaire; CI = confidence interval; RCT = randomized controlled trial; ITT = intent-to-treat; OFPL = oro-facial-pharyngeal-laryngeal; OPL = oropharyngeal-laryngeal. Notes: In the saline treatment group 11 (35%) patients received rescue medication or disallowed concomitant medication prior to beginning of relief of symptoms, and were therefore censored, resulting in inestimable medians for		

Table 15 Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ, with Persistence), Subgroup Analyses: RCT ITT Analysis Set		
	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=44)	Saline (N=31)
some of the subgroups; values that are not estimable are displayed as '-'.		

The yellow highlighting in the above table is intended to direct attention to the primary endpoint outcomes for the gender and geographic region subgroups, which gave rise to the concern about potential lack of therapeutic effect under some conditions.

The following table shows the results for the secondary endpoint time-to-complete-resolution-of-symptoms by various subgroups:

Time to Complete Resolution, Subgroup Analyses: RCT ITT Analysis Set		
	Median (95% CI) [n]	
Subgroup Category	rhC1INH (N=40)^a	Saline (N=30)^a
Primary Attack Location:		
Abdominal/Urogenital	894.0 (329.0, 1053.0) [n=15]	1920.0 (1420.0, 2234.0) [n=12]
Peripheral	1648.0 (150.0, 2648.0) [n=18]	1930.0 (600.0, 3720.0) [n=13]
Facial	4390.0 (2523.0, 5360.0) [n=5]	- (- , -) [n=2]
Cutaneous (Facial or Peripheral)	2523.0 (1185.0, 2810.0) [n=23]	1930.0 (600.0, 3720.0) [n=15]
OFPL (Facial or OPL)	2523.0 (456.0, 5360.0) [n=7]	1190.0 (180.0, 1190.0) [n=5]
Oropharyngeal-Laryngeal	1128.0 (456.0, 1800.0) [n=2]	1190.0 (180.0, 1190.0) [n=3]
Gender:		
Male	1597.0 (478.0, 2648.0) [n=15]	1430.0 (780.0, 3720.0) [n=11]
Female	1053.0 (329.0, 1765.0) [n=25]	2056.0 (1135.0, 3087.0)[n=19]
Race:		
Caucasian	1053.0 (600.0, 1765.0) [n=38]	1784.0 (1135.0, 2420.0)[n=29]
Asian	[n=0]	- (- , -) [n=1]
Black/African American	4875.0 (4390.0, 5360.0) [n=2]	[n=0]
Age at Screening:		
<18 Years Old	- (- , -) [n=1]	[n=0]
18-65 Years Old	1185.0 (680.0, 1765.0) [n=38]	1784.0 (1135.0, 2420.0)[n=29]

Subgroup Category	Median (95% CI) [n]	
	rhC1INH (N=40) ^a	Saline (N=30) ^a
≥65 Years Old	329.0 (- , -) [n=1]	- (- , -) [n=1]
Geographical Location:		
USA	1597.0 (894.0, 4390.0) [n=18]	2234.0 (1135.0, 3087.0)[n=15]
Rest of World	600 (240.0, 1765.0) [n=22]	1430.0 (780.0, 3138.0) [n=15]
Previous Treatment with rhC1INH:		
Naive	894.0 (456.0, 1800.0) [n=29]	2056.0 (1135.0, 3087.0)[n=21]
Non-naïve	1706.5 (1053.0, 2810.0)[n=11]	1305.0 (600.0, 3138.0) [n=9]

TEQ = treatment effect questionnaire; CI = confidence intervals; RCT = randomized controlled trial;

ITT = intent-to-treat; OFPL = oro-facial-pharyngeal-laryngeal; OPL = oropharyngeal-laryngeal

Note: Values that are not estimable are displayed as ‘-’.

a Five patients treated in the study prior to Protocol Amendment 3 do not have complete resolution data.

Source: STN125495 Integrated Summary of Efficacy p. 73 of 179

Reviewer’s Comment: The yellow highlighting in the above table is intended to direct attention to the outcomes for subjects with oropharyngeal-laryngeal symptoms, and to outcomes for non-naïve subjects (i.e. subjects previously exposed to Ruconest in earlier clinical trials). It can be seen that Ruconest was not significantly different from saline in treating oropharyngeal-laryngeal symptoms, although the number of subjects in this group was very small. It can be seen that Ruconest-treated non-naïve subjects did not experience relief of symptoms earlier than did saline-treated non-naïve subjects, which raises a question about a possible connection between previous treatment and lack of therapeutic effect, although this was not further explored by the sponsor or this reviewer.

6.3.11.4 Dropouts and/or Discontinuations

As pointed out in section [6.3.10](#), of the 75 enrolled subjects, there were 74 subjects who received treatment (and were included in the safety analysis group). There were 4 subjects (2 Ruconest, 2 saline) who were excluded from the per protocol analysis group for the following reasons:

- Subject --(b)(6)-- (Ruconest group) had an abdominal attack but no stool or urine samples were collected.
- Subject -(b)(6)- (Ruconest group) had blood in her urine (attributed to menstruation).
- Subject -(b)(6)- (saline group) had an abdominal attack but no stool or urine samples were collected.
- Subject --(b)(6)-- (saline group) had an ineligible primary attack location (patient’s pre-dose VAS was <50 mm [49 mm]).

Reviewer’s Comment: These dropouts/discontinuations do not appear to affect overall conclusions.

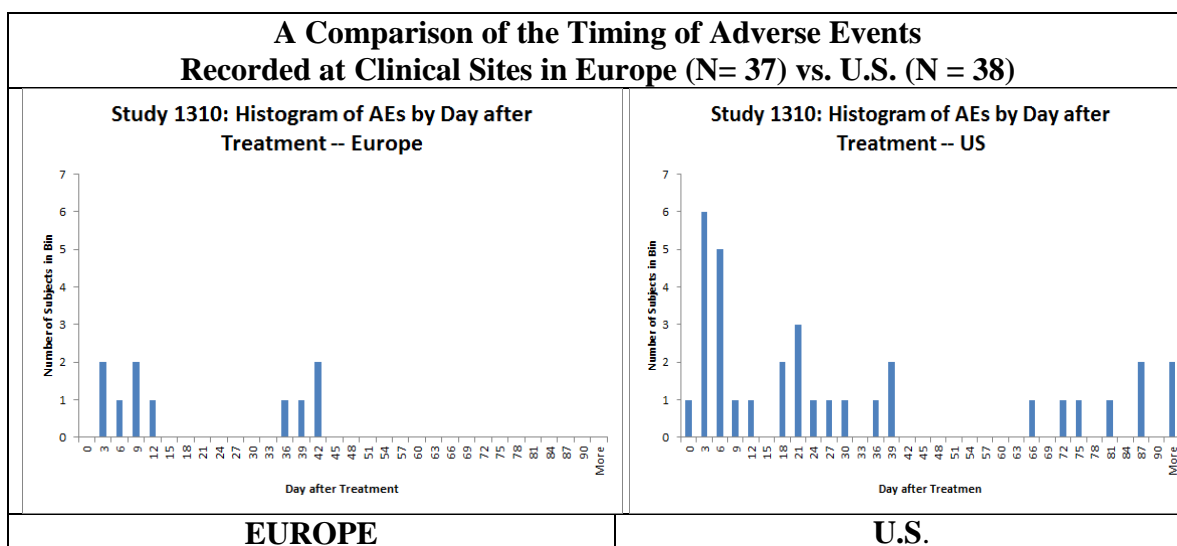
6.3.11.5 Exploratory and Post Hoc Analyses

The following are this clinical reviewer's own analyses of data from Study 1310 to address additional concerns:

There is evidence that monitoring for Study 1310-RCT differed between European and U.S. clinical sites.

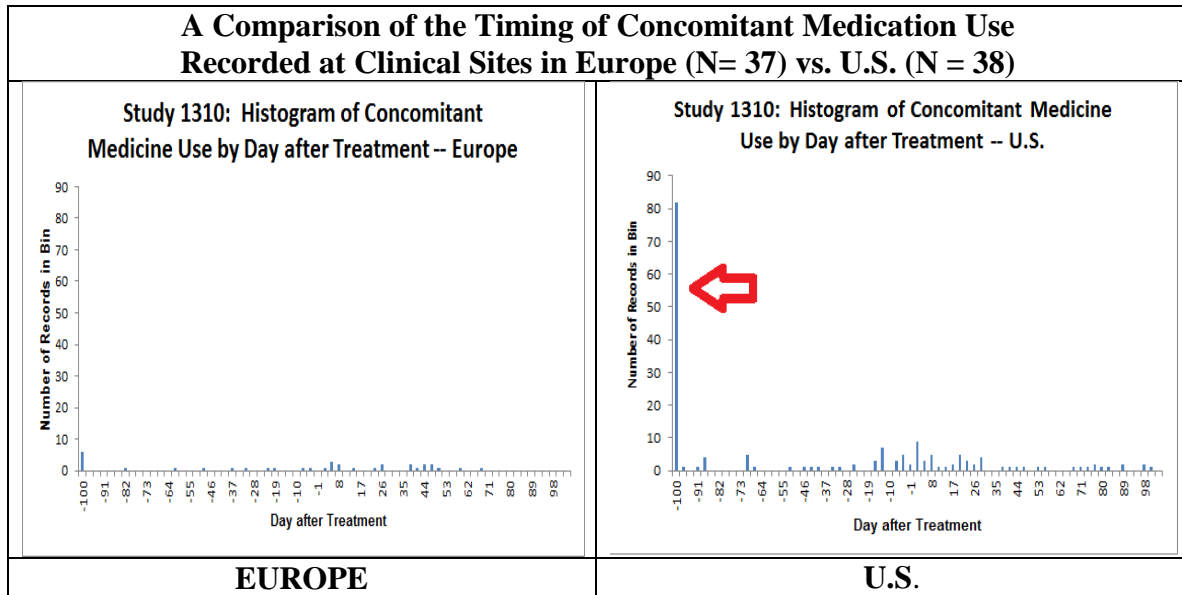
In an effort to understand the strong discrepancies between the outcomes in the geographic subgroups "U.S." and "Europe", the database structure of data from these geographic subgroups was investigated.

The following compares frequency histograms of the timing of adverse events by day after treatment:



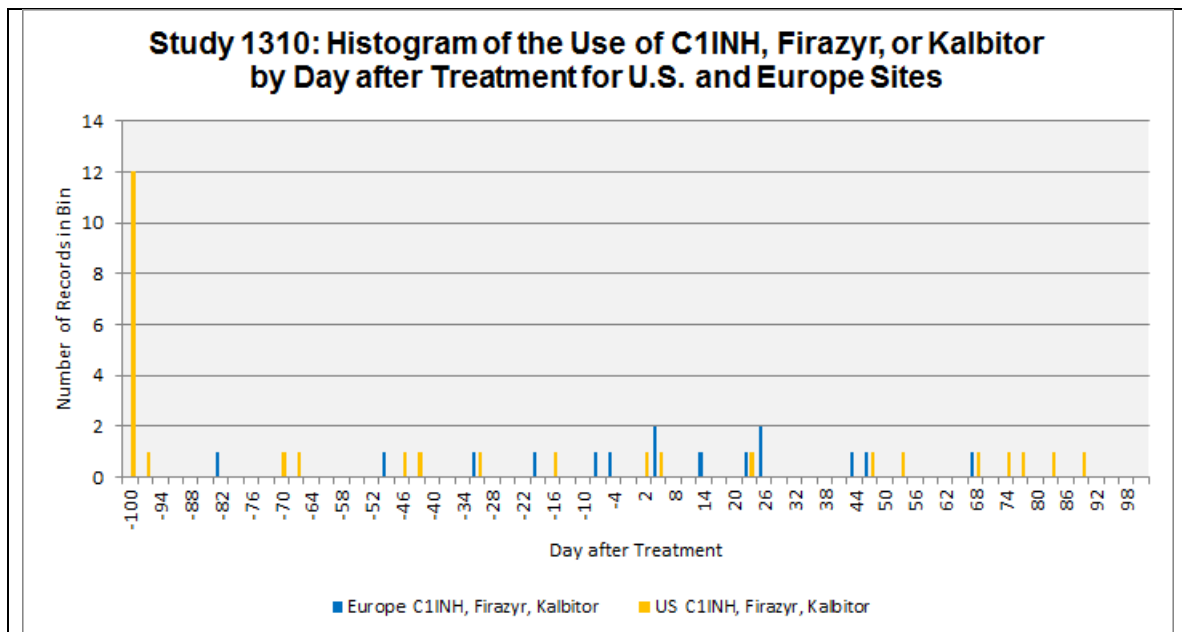
Despite having approximately equal enrollment at Europe and U.S sites, there was greater recording of adverse events at U.S. sites, and the time period over which adverse events were recorded at U.S. sites was almost twice as long as the recording period for Europe sites.

The following compares frequency histogram of the timing of concomitant medication use by day after treatment:



It can be seen that there were more concomitant medications recorded at U.S. sites, and that long-term ongoing medications (represented by the spike at the left side of the histogram – see red arrow) were much more prevalent among U.S. subjects than among Europe subjects.

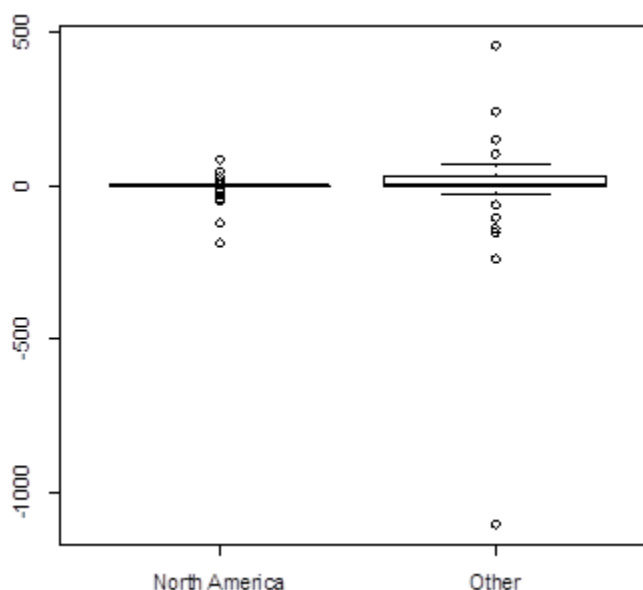
Among the concomitant medications are drugs used to treat HAE. The following frequency histogram compares the use of the HAE drugs C1INH (i.e. any plasma-derived C1INH product, including FFP), Firazyr, or Kalbitor at U.S. and Europe sites:



It can be seen that only the U.S. database recorded long-term ongoing or sporadic use of these anti-HAE agents at times long before the trial began. This may reflect differences in the medical care these patients received, or it may reflect differences in how these databases were recorded/managed.

The difference between the conduct of the U.S. arm of study 1310 and the European arm can also be seen in an analysis of the primary endpoint, as measured by the two measurement instruments, the Treatment Effect Questionnaire (TEQ) and the Visual Analog Scale (VAS). The following graph comparing the difference in the times-to-beginning-of-relief for the TEQ and VAS for the two geographic regions [U.S. and Rest-of World (ROW)] was supplied by the statistical reviewer, Abigail (Yuqun) Luo, Ph.D.:

Difference between times to beginning of relief based on TEQ versus based on decrease of VAS > 20, by region.



It appears that the two instruments yield similar results in the US, compared to the wider difference in ROW.

In response to the observed differences in the conduct of study 1310 between the U.S. and ROW sites, FDA asked the applicant (September 25, 2013) to identify the clinical site monitoring contract research organization (CRO) for all study sites. The applicant responded (October 25, 2013) with the information presented in the following table:

Study 1310: Identification of CRO for Clinical Monitoring

Investigator	No. Subjects	Site Monitor	
		(b)(4)	(b)(4)
Bulgaria - Shirov	1	x	
Hungary - Farkas	3	x	
Israel - Reshef	3		x

Investigator	No. Subjects	Site Monitor	
		(b)(4)	(b)(4)
Italy - Cicardi	3		x
Macedonia - Grivcheva-Panovska	7	x	
Poland - Obtulowicz	7	x	
Romania - Moldovan	9	x	
Serbia - Andrejevic	4	x	
US - Baker	9		x
US - Bernstein	2		x
US - Craig	1		x
US - Davis	2		x
US - Gower	1		x
US - Levy	9		x
US - Li	3		x
US - Lockey	2		x
US - Lumry	2		x
US - McNeil	5		x
US - Wedner	2		x
Grand Total	75		

It can be seen that the European sites (with the exception of the Italy and Israel sites) were monitored by CRO (b)(4), and the U.S. (with the Italy and Israel sites) were monitored by the CRO (b)(4). This supports a conclusion that the clinical studies at U.S. and ROW geographic subgroups were conducted as if they were two separate clinical studies.

Reviewer's Comment: The differences between the geographic region - U.S. and geographic region – ROW in study 1310 presented above support the conclusion that the U.S. and non-U.S. portions of study 1310 were conducted as if they were two separate clinical trials. Therefore, in retrospect, it is questionable whether it is appropriate combine these study results.

6.3.12 Safety Analyses

6.3.12.2 Overview of Adverse Events

All adverse reactions in Study 1310 (RCT + OLE) were non-serious.

Study 1310 RCT & OLE: Adverse Reactions by Time after Treatment Initiation

			4 Hours	24 Hours	28 Days
--	--	--	------------	-------------	------------

VISIT	Body System	Preferred Term	Adverse Events	Subjects	Adverse Events	Subjects	Adverse Events	Subjects
OLE	Eye disorders	Lacrimation increased	0	0	0	0	2	1
OLE	Gastrointestinal disorders	Diarrhoea	0	0	0	0	3	1
OLE	Gastrointestinal disorders	Flatulence	0	0	0	0	4	1
OLE	General disorders and administration site conditions	Chills	0	0	0	0	1	1
OLE	General disorders and administration site conditions	Fatigue	0	0	0	0	1	1
OLE	Infections and infestations	Nasopharyngitis	0	0	1	1	1	1
OLE	Musculoskeletal and connective tissue disorders	Back pain	0	0	1	1	1	1
OLE	Skin and subcutaneous tissue disorders	Pruritus	0	0	1	1	1	1
OLE	Skin and subcutaneous tissue disorders	Rash	0	0	1	1	1	1
RCT	Injury, poisoning and procedural complications	Procedural headache	1	1	1	1	1	1
RCT	Musculoskeletal and connective tissue disorders	Back pain	1	1	1	1	1	1
RCT	Skin and subcutaneous tissue disorders	Skin burning sensation	1	1	1	1	1	1

Source: analysis of database ADAE in STN125495

Reviewer's Comment: These are typical adverse events seen in studies of intravenous biologic agents to treat HAE attacks.

6.3.12.3 Deaths

There were no deaths in study 1310.

6.3.12.4 Nonfatal Serious Adverse Events

Two subjects in the Ruconest study arm experienced serious adverse events (urinary tract infection, abdominal hernia). These serious adverse events do not appear to be related to treatment.

One subject in the saline study arm experienced the serious adverse event of sinus congestion.

All serious adverse events resolved by the end of study 1310.

6.3.12.5 Adverse Events of Special Interest (AESI)

Anti-drug antibody formation is not an adverse event; however, it may cause adverse events. No adverse events are attributable to anti-Ruconest antibody formation. Nevertheless, it is useful to acquire information on the Ruconest immunogenicity rate to inform pharmacovigilance.

Subjects were screened at baseline and a various follow-up times for antibodies against Ruconest and against rabbit (host) proteins.

The anti-C1INH measurement process had three steps as follows:

1. Binding antibodies to Ruconest were detected in an (b)(4).
2. Positives from the (b)(4) were checked for specificity to Ruconest in a -----(b)(4)----- (referred to as a “----- (b)(4)----- assay” in the submission).
3. Specific positive samples were checked for neutralizing activity against C1INH using plasma as a source of C1INH; there were no assays to check for the ability of these samples to neutralize Ruconest.

FDA requested a re-analysis of all anti-rhC1INH positive samples to determine if these antibodies neutralized rhC1INH in an in vitro C1 esterase inhibition assay using rhC1INH in the place of plasma-derived C1INH. The applicant devised an assay using

----- (b)(4) -----
----- to test for Ruconest neutralization activity. All samples lacked Ruconest neutralization activity.

Reviewer’s Comment: The long-term immunogenicity of Ruconest, and the potential clinical effects of anti-Ruconest antibodies, has not been sufficiently elucidated by the submitted study results. Pharmacovigilance may provide more information. From the submitted study results, it appears that at least 10% of subjects will form anti-Ruconest antibodies after treatment for 5 HAE attacks, and approximately 50% of subjects will form anti-rabbit (host) protein antibodies after treatment for 5 HAE attacks, as shown in the following table:

Study 1310 RCT and OLE: Treatment Emergent Antibody Response by HAE Attack Number (rhC1INH exposure)

HAE Attack Number	Blood Sampling Phase during Attack	Number of Subjects Sampled during Attack	Number of Positive Subjects for the Attack with Percent (estimate)		
			Anti-Host Rabbit Protein	Anti-C1INH IgG	Anti-C1INH IgM
1	Screening	43	7 23%	1 3%	0 0%
	At Presentation	43			
	Day 28	31			

HAE Attack Number	Blood Sampling Phase during Attack	Number of Subjects Sampled during Attack	Number of Positive Subjects for the Attack with Percent (estimate)		
			Anti-Host Rabbit Protein	Anti-C1INH IgG	Anti-C1INH IgM
	Day 90	22			
2	At Presentation	40	10 27%	2 5%	1 3%
	Day 28	38			
	Day 90	37			
3	At Presentation	32	11 34%	2 6%	1 3%
	Retest	32			
	Day 28	32			
	Day 90	32			
4	At Presentation	25	11 44%	3 12%	3 12%
	Day 28	25			
	Day 90	25			
5	At Presentation	20	8 40%	3 15%	1 5%
	Day 28	20			
	Day 90	20			
	Early Termination	14			
6	At Presentation	13	6 46%	1 8%	0 0%
	Day 28	13			
	Day 90	13			
7	At Presentation	11	7 64%	1 9%	0 0%
	Day 28	11			
	Day 90	11			
8	At Presentation	10	7 70%	1 10%	0 0%
	Day 28	10			
	Day 90	10			
9	At Presentation	8	6 75%	1 13%	0 0%
	Day 28	8			
	Day 90	8			
10	At Presentation	7	6 86%	1 14%	0 0%
	Day 28	7			
11	At Presentation	7	6 86%	1 14%	0 0%
	Day 28	7			
	Day 90	7			
12	At Presentation	6	5 83%	1 17%	0 0%
	Day 28	6			

HAE Attack Number	Blood Sampling Phase during Attack	Number of Subjects Sampled during Attack	Number of Positive Subjects for the Attack with Percent (estimate)		
			Anti-Host Rabbit Protein	Anti-C1INH IgG	Anti-C1INH IgM
	Day 90	6			
13	At Presentation	5	4	3	1
	Day 28	5	80%	60%	20%
14	At Presentation	5	4 80%	2 40%	1 20%
15	At Presentation	5	4	2	0
	Day 90	5	80%	40%	0%
16	At Presentation	4	4	1	1
	Day 28	4	100%	25%	25%
17	At Presentation	4	4 100%	1 25%	0 0%
	Day 28	4			
	Day 90	4			
18	At Presentation	2	2 100%	0 0%	0 0%
19	At Presentation	2	2 100%	0 0%	0 0%
20	At Presentation	2	2 100%	0 0%	0 0%
21	At Presentation	2	2 100%	0 0%	0 0%
	Day 28	2			
	Day 90	2			
22	At Presentation	1	1 100%	0 0%	0 0%
23	At Presentation	1	1 100%	0 0%	0 0%
	Day 28	1			
	Day 90	1			

Source: Data are from database ---(b)(4)--- for study 1310 in STN125495/0.12

The accuracy of the percentage of responders estimate is limited by the small sample size within an HAE attack cohort, and by the differing numbers of subjects who were monitored at each time point during a given HAE attack.

Anaphylactic Reaction

From the Immunosafety Report:

One anaphylactic reaction occurred in an adult female healthy volunteer subject participating in Study 1106 on first exposure to rhC1INH 100 U/kg. This subject had a clinical history of rabbit allergy that had not been disclosed during the pre-consent screening procedure. No other anaphylactic reactions have been reported in the rhC1INH clinical development program to date (March 13, 2013).

6.3.12.6 Clinical Test Results

Two subjects (1 Ruconest, 1 saline) experienced the treatment emergent adverse event (TEAE) of fibrin D-dime increased, without associated coagulopathic adverse events.

One Ruconest subject had elevated liver function tests, compared to screening values, at presentation and on day 28. The following table show liver function test results for this subject at different times during the study:

Test (normal range)	Screening	Presentation	Day 7	Day 28
Alkaline Phosphatase (30-104 U/L)	80	136	134	122
ALT/SGPT (0-31 U/L)	18	299	260	261
AST/SGOT (0-32 U/L)	15	126	98	122
Bilirubin (Total) (1-17 µmol/L)	7.4	13.4	7.3	11.2
Gamma-GT (9-40 U/L)	47	379	349	409

Reviewer's Comment: It is apparent that the liver function test abnormalities were present at presentation for treatment of the HAE attack, and were not related to treatment.

6.3.12.7 Dropouts and/or Discontinuations

The dropouts/discontinuations discussed in section [6.3.11.4](#) do not appear to affect the overall safety profile.

8. Integrated Overview of Safety

In all clinical studies, there were 205 unique symptomatic HAE subjects exposed to 650 administrations of Ruconest. The doses studied ranged up to 100 U/kg. There were an additional 31 healthy volunteers or asymptomatic HAE subjects exposed in phase 1 studies.

The most frequent adverse events in the efficacy studies 1304, 1205, and 1310 were

recurrent HAE symptoms, headache, nasopharyngitis, urinary tract infection, abdominal pain, diarrhea, and back pain.

Immunogenicity.

Most studies used single-dose administration of Ruconest, with some subjects receiving additional doses for subsequent HAE attacks that were treated in open-label extension studies. Therefore, the safety database is not designed to provide detailed information on Ruconest immunogenicity over long-term use.

The open-label extension (OLE) of the pivotal study 1310 provides the best estimate for Ruconest immunogenicity. In study 1310 OLE, 2 of 32 (5%) of subjects formed IgG anti-Ruconest antibodies after treatment for 3 HAE attacks; 3 of 25 (12%) of subjects formed these antibodies after treatment for 4 HAE attacks; and 3 of 20 (15%) of subjects formed these antibodies after treatment for 5 HAE attacks. These antibodies did not neutralize Ruconest activity in an in vitro C1 esterase inhibition assay. There were no adverse events that could be attributed to anti-Ruconest antibody formation. There were no studies to evaluate whether these antibodies cause more rapid clearance of Ruconest beyond the already rapid clearance of Ruconest compared to plasma-derived C1INH products. The open-label study design of study 1310 OLE is not suitable for deciding whether these antibodies affect Ruconest efficacy.

Study 1310 OLE also shows that approximately 50% of subjects formed antibodies against rabbit host cell proteins after five treated HAE attacks. There were no adverse events attributable to post-exposure antibody formation; however, one normal volunteer in study 1106 who had an undisclosed pre-existing rabbit allergy developed anaphylaxis during Ruconest administration, with complete recovery. The Ruconest label includes a warning about the possibility for a hypersensitivity reaction after treatment and a contraindication in patients with a history of allergy to rabbits or rabbit derived products.

Thrombogenicity.

There were no cases of thromboembolic adverse events in the clinical studies.

Laryngeal HAE Attacks.

There were too few subjects with laryngeal HAE attacks to evaluate efficacy for this anatomical location. In study 1205OLE, one subject who was treated with 50 Units/kg for a facial attack subsequently developed two reported episodes of laryngeal edema on the same day. In study 1310, one subject developed laryngeal edema symptoms after saline treatment and was rescued with Ruconest, but did not report initial relief until 4 hours later. These cases are not supportive for a claim of efficacy for the use of Ruconest to treat laryngeal HAE attacks.

There is a safety concern based on the lack of efficacy information on the use of Ruconest to treat laryngeal HAE attacks. Therefore, a Limitation of Use for the

effectiveness in the treatment of patients with laryngeal attacks was included in the labeling.

Table 10 in STN125495/0.24 shows the time-to-relief for placebo subjects rescued with Ruconest. The 3 subjects (------(b)(6)-----) to which the applicant refers had different times from attack onset to enrollment, different times from treatment to rescue, and different times from rescue to relief. These data are not useful for evaluating the efficacy of Ruconest to treat laryngeal attacks. Subject -(b)(6)- had a time of rescue to relief of 240 minutes (4 hours), which is difficult to consider as a successful treatment. For example, the following table for response time for laryngeal edema is from the current Berinert label:

Table 13: Time to Initial Onset of Symptom Relief and Time to Complete Resolution of HAE Symptoms for Laryngeal Attacks

Statistic	Laryngeal (n=48)
Time to initial onset of symptom relief [hours]	
Median (range)	0.25 (0.10 - 1.25)
95% CI for median	[0.23; 0.42]
Time to complete resolution of HAE symptoms [hours]	
Median (range)	8.4 (0.6 - 61.8*)
95% CI for median	[6.2; 21.5]

CI = confidence interval

HAE = hereditary angioedema

N = number of attacks

* The maximum time to complete resolution of 61.8 hours was an imputed value. Subject (b)(6) had 2 laryngeal attacks with missing times to complete resolution of HAE symptoms, which were imputed with the maximum time to complete resolution of HAE symptoms observed for an abdominal attack in this subject.

STN125495 Table 2.7.3.3.16.7.3 lists the following data:

Time to Beginning of Relief of Symptoms for an Attack (VAS Decrease of ≥ 20 mm with Persistence) - Oro-facial-pharyngeal-laryngeal Attacks: FAS (MITT)

	rhC1IN H (100 U/kg single dose) (N=4)	rhC1IN H (50 U/kg, single or add. dose) (N=20)	rhC1IN H (18-40 U/kg, single or add. dose) (N=24)	Saline Solution (N=10)
Total Number of	4	36	50	10

	rhC1INH (100 U/kg single dose) (N=4)	rhC1INH (50 U/kg, single or add. dose) (N=20)	rhC1INH (18-40 U/kg, single or add. dose) (N=24)	Saline Solution (N=10)
Attacks Treated				
Time to beginning of relief of symptoms with persistence (minutes)				
1st Quartile	62.5	41.0	60.0	70.0
Median	70.0	64.5	120.0	306.0
3rd Quartile	97.5	128.0	470.0	495.0

Source data: STN125495 Listing 2.7.3.3.

The median time listed for the proposed dose of 50 U/kg is 64.5 minutes which is longer than the upper 95% CI for Berinert (25 minutes), and is close to the upper end of the range for Berinert (75 minutes).

Reviewer's Comment: Given the weakness of the Ruconest databases to support the proposed dose of 50 U/kg for abdominal or facial HAE attacks, it would not be reasonable to add the laryngeal HAE attack indication based on these data. Additional clinical data are needed.

8.4.1 Deaths

There were no deaths during the clinical trials. However, one Romanian subject died from HAE laryngeal edema 25 days after completing the routine prophylaxis exploratory study 1207.

Reviewer Comment: This death is remarkable in that a patient known to have a diagnosis of hereditary angioedema and who experienced laryngeal edema and was transported to a hospital, did not receive any C1-INH containing product. The applicant responded to a request for additional information on this death in STN125495/014 (October 25, 2013), and the explanation that no C1INH-containing product was available for the patient at the Romanian hospital at the time of this event is credible.

8.5.8 Immunogenicity (Safety)

The immunogenicity rate after long-term use of Ruconest has not been evaluated.

8.6 Safety Conclusions

Ruconest has an acceptable safety profile.

9.1.3 Pediatric Use and PREA Considerations

PREA does not apply because of orphan product designation.

10. Conclusions

Ruconest is safe and effective for treatment of acute attacks of hereditary angioedema in adult and adolescent patients. There should be a Limitation of Use because of the small number of laryngeal attacks studied.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

The risks associated with use of Ruconest to treat HAE attacks and the measures to address these risks are listed below:

- Lack of therapeutic effect if the labeled dose 50 Units/kg is not sufficient to treat all HAE attacks, especially laryngeal HAE attacks
 - This can be addressed by including information about the anomalous gender and geographic region results of study 1310 in the labeling to alert physicians and patient to the possibility that the administered dose may not be effective in all circumstances.
- Medication errors if physicians or patients assume that dosing by Ruconest activity units is interchangeable with dosing by plasma-derived C1INH product activity units
 - Reports of such errors can be tracked by routine pharmacovigilance procedures, and can be addressed through labeling changes if this problem is observed.
- Anti-Ruconest antibody formation that could interfere with Ruconest efficacy
 - Routine pharmacovigilance may be useful in detecting a problem. Additional studies of Ruconest (ongoing) may provide a better estimate of this risk.
- Anti-rabbit protein antibody formation that could lead to adverse events (anaphylaxis)
 - Ruconest labeling warns against use if a patient is allergic to rabbits.

11.2 Risk-Benefit Summary and Assessment

The risk-benefit assessment is positive.

11.4 Recommendations on Regulatory Actions

Ruconest may be licensed with a Limitations of Use for treating laryngeal edema attacks because of lack of sufficient efficacy information.

11.5 Labeling Review and Recommendations

The submitted labeling may be approved.

11.6 Recommendations on Postmarketing Actions

The applicant is conducting a post-marketing registry as required by the European Medicines Agency. This reviewer does not recommend that a post-marketing registry be required because the data obtained from it is not expected to be of high quality based on previous experience with patient registries. Other reviewers support having a post-marketing commitment for a patient registry. Therefore, the approval letter will contain the following post-marketing commitment:

1. Pharming commits to conduct a study consisting of establishment and maintenance of a registry of HAE patients 13 years of age and older who are prescribed RUCONEST without plasma-derived C1 esterase inhibitors to evaluate the incidence of adverse events and time to symptom relief, as well as to characterize hypersensitivity reactions, thrombotic events, and the safety profile in pregnant and nursing women in the treatment of acute attacks of HAE in adult and adolescent patients. The study will continue until either a) three years have elapsed, or b) 100 patients have been enrolled, 35 of whom will be treated with RUCONEST for at least three attacks.

The sponsor has committed to the following timelines:

- a. Final protocol submission: January 16, 2015
- b. Study completion: July 16, 2018
- c. Complete study report submission: January 16, 2019

Appendix 1. Special Protocol Assessment (SPA) comments in June 15, 2011, FDA letter

Based on our review of your submission, we have determined that the design and planned analysis of your study does not sufficiently address the study's objectives to support a biologics license application.

We have the following responses to your question:

Sponsor Question 1:

Pharming believes that they have designed the protocol and statistical analysis plan in accordance with the guidance provided by FDA during the meeting of March 31, 2001. Does the Agency agree?

FDA Response to Question 1:

You have incorporated many of our suggestions; however, some outstanding issues remain. Please see the comments below:

The following comments and recommendations pertain to your responses to numbered items from our March 18, 2011 advice letter regarding protocol C1 1310:

Item 3:

Why would a subject be enrolled if he/she had no eligible attack locations?

Item 5:

Please amend the protocol to include plans to compare the between-treatment-group differences for each efficacy variable between the first (RCT phase) and second (first OLE phase) HAE attacks as additional secondary outcome variables.

We reserve the right to request a Phase 4 commitment study in which subjects are treated in a randomized double-masked fashion for the first two qualifying HAE attacks.

Item 6:

Unless you halt enrollment of subjects with the anatomical attack locations that "fill up" first, it seems unlikely that you will have sufficient subjects with genitourinary attacks, and possibly oro-facial-pharyngeal-laryngeal attacks, to provide robust estimates of the magnitude of the treatment effect for such anatomical locations. This would have implications for product labeling. Hence, please limit enrollment in this study to subjects with the most frequently occurring HAE anatomical attack locations involved.

Given the size of this study, it seems unlikely that you will have sufficient subjects with acute genitourinary HAE attacks to obtain an indication for their treatment based on the study data.

In addition, we recommend facial attacks be considered in a separate category from oro-pharyngeal/laryngeal attacks because many facial HAE attacks may not have any mucosal surface involvement and their symptoms can be disparate from those encountered during oro-pharyngeal/laryngeal attacks.

Item 7:

Please consider revising the protocol to specify the minimum number of subjects to be entered into the trial for each HAE attack location to be studied. During our March 31, 2011 meeting, we stated that, in addition to seeing statistical and clinical significance in the overall clinical populations, we would like to see sufficient data with each anatomic HAE attack location studied, to be able to determine whether there may be heterogeneity in response by attack location. A strong efficacy trend for each anatomical attack location studied would be needed, as well as statistical and clinical significance for the overall study population, to provide substantial evidence of effectiveness for each attack location studied.

Item 12:

Please submit at this time as an IND amendment an appendix to the SAP which lists all of the drugs in each category of “additional therapy.” We recognize this list may require expansion as the trial progresses and as new concomitant therapies may become available.

Item 14:

The category “other locations,” includes oro-pharyngeal/facial/laryngeal and genitourinary attacks, which can have very disparate symptoms. Thus, significant imbalances in anatomical attack locations might occur despite balance in the “other locations” category. We recommend not including subjects with facial or genitourinary attacks in the study as these occur infrequently, making it difficult to obtain robust quantitative estimates of the efficacy of the product for these attack locations.

Based on your response, it appears that you would place subjects presenting with equal VAS scores in both abdominal and peripheral locations in the “other locations” category. Please explain how this will help to achieve balance in the study. We advise such patients be included in the abdominal attack stratum.

Item 16:

You indicated that, during an interview to explore the content validity of the VAS, many patients, when discussing abdominal attacks referred to their unwillingness/inability to eat during an attack for fear of vomiting, but also to their hunger either before or after an attack. You have not provided evidence that hunger is a symptom *during* an acute abdominal HAE attack. Please remove the hunger VAS from the abdominal attack VAS set from the protocol and CRF.

You have not provided independent literature support for the notion that hunger is a symptom of acute genitourinary HAE attacks. Please be advised that any findings in

regard to the symptom of hunger will not be considered by FDA to be in any way supportive of a conclusion of efficacy of the product.

Item 17:

Although you have added assessment times at 75 and 105 minutes as requested, you have eliminated in clinic assessment times at 4.5, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours. Please retain assessment times at 4.5, 5, 5.5, and 6 hours performed at the study site. Subjects should be observed at the study site for a minimum of 6 hours following administration of the product for at least the first 3 HAE attack treatments, if possible. We expect that this will increase the quality of the data pertaining to both the primary and secondary endpoint, as well as improve the accuracy of the assessment of relapses. We anticipate that there may be a difference in data quality between data collected under the observation of a health care professional in the clinic vs. that collected following discharge.

Item 18:

Please list time to complete resolution of all HAE attack symptoms as an exploratory endpoint in the protocol and SAP.

Item 19:

Please ensure that an adequate number of naïve patients are included in the study.

Item 20:

Please ensure that subjects have the results of vital signs testing and the results of stool hemoccult and urine dipstick testing for the presence of blood and pyuria prior to the final decisions to randomize the subject and administer test product. Alternatively, the study may exclude from enrollment subjects with fever equivalent to oral temperature > 38 degrees Celsius and subjects with presence of blood in urine or stool.

Item 24:

Please repeat the C4 level at presentation of HAE attack and at one additional time point 12 hours after administration of the test article during the RCT phase. C4 should be measured in a central laboratory by a validated assay. Please conduct robustness efficacy analyses in which subjects whose C4 values at presentation fall outside the expected range (i.e., are not less than values at screening) are excluded. In addition, please add a provision to the protocol and SAP to analyze the relationship between rises in C4 level and clinical response of HAE symptoms. The data you have presented depicting changes in C4 levels following various doses of your product are associated with wide error bars. It is desirable to collect additional C4 data to more reliably evaluate the pharmacodynamic response in a larger number of subjects.

Item 25:

Please measure plasma D-dimer levels at baseline and at least 2 time points following exposure to the test article during both RCT and OLE phases. The number of subjects for which you have previously collected D-dimer levels before and after administration of the product is considered insufficient. Subjects who demonstrate rises in D-dimer levels

need to be more carefully evaluated for the possible development of thrombotic and thrombo-embolic (TE) events.

Item 27:

Please reword the first sentence in protocol section 9.6.2 to read “Thrombotic and thrombo-embolic events have been observed following administration of Berinert and of Cinryze plasma derived C1 Esterase Inhibitor at the labeled doses.”

Item 32:

Please confirm that all study monitoring activities other than drug accountability will be performed by monitors blinded to randomization group assignment.

Item 34:

The statement that a *NCR* copy of the VAS and the original TEQ will remain at the study center (protocol section 16.4.4) seems to be in conflict with the preceding statement in the same section which reads, “The results of the VAS and TEQ will be recorded directly in the eCRF without other source documents other than the statement that the named forms are completed.” Please comment.

In addition, we have the following comments and recommendations:

1. Regarding your sample size calculations:

The FDA acknowledges your sample size determination of study 1310 RCT based on the non-parametric approach of Noether, assuming that subjects are followed for 24 hours, and that subjects who have not responded by 4 hours and therefore receiving rescue medication are imputed with 24-hour value. You further propose stratified Wilcoxon rank sum test as the primary analysis to compare treatment groups. Since the distribution of subjects who have not responded by 4 hours and who receive rescue medications is not known between two treatment groups, imputing these subjects with 24-hour values might exaggerate the treatment effect and statistical significance. This may be particularly true when the percentage of patients who receive rescue medications is large.

We request you use time-to-event analysis as the primary analysis method for the primary efficacy endpoint, imputing a 24 hour value for subjects who have received rescue medication or potentially confounding medications between time of product infusion and time to beginning of relief of HAE symptoms, providing the proportion of subjects receiving rescue medication prior to 24 hours in either randomization group does not exceed 49%. We request you perform a censored data analysis (Kaplan-Meier analysis with stratified log-rank test for group comparison) as the primary analysis of the primary efficacy endpoint if the proportion of subjects receiving rescue medication prior to 24 hours exceeds 49% in either randomization group. Please perform whichever method (censoring vs. inclusion of imputed data) is not used as the primary analysis as a sensitivity analyses. Please comment.

2. Regarding your sample size re-estimation:

Please consider the use of time-to-event analysis as the primary analysis method for the primary endpoint. Therefore, we request that your sample size re-estimation be carried out based on the total number of events without knowing or/and accessing treatment group code. Please refer to FDA's Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics for your sample size re-adjustment.

3. You state that a sensitivity analysis of the primary efficacy endpoint to missing data would be performed using the last observation carried forward (LOCF) for patients in the rhC1-INH group and NOCB for patients in the saline group (page 39 of SAP). Please clarify the definition and describe in detail the methodology of NOCB. Please justify the proposed sensitivity analysis. We request your sensitivity analyses include several different methods of handling missing data to examine the robustness of study results due to missing data handling. These methods should be pre-specified in the protocol and SAP.
4. Please plan subgroup analyses for the secondary efficacy endpoint, time to minimal symptoms, as well as the exploratory endpoint, time to complete resolution of HAE attack symptoms.
5. For the comparison of efficacy endpoints for the initial (RCT) and second (OLE) HAE attacks, it will be necessary to perform the primary, secondary, and exploratory analyses in an identical manner. Please comment.
6. Please perform analyses of the secondary efficacy endpoint and of time to complete relief of symptoms with and without data imputation for subjects who receive rescue or other potentially confounding medications between start of HAE attack and complete relief of symptoms.
7. Please include proportion of subjects experiencing beginning of relief of HAE symptoms by (a) 1 hour and (b) 4 hours as exploratory endpoints. These should be analyzed by treatment group with and without stratification by primary attack location.
8. Please analyze and report as an exploratory endpoint the number and proportion of subjects in each treatment group (with and without stratification by primary attack location) who experience (a) relapse within 24 hours and (b) occurrence of HAE attack symptoms at a new attack location within 24 hours.
9. On page 61 of the protocol, you state that a detailed SAP would be prepared based on the analysis described in the protocol. This plan will be finalized before database is

locked. Please finalize the protocol and SAP prior to enrolling any further patients in study 1310.

10. Please revise the study entry criteria to exclude subjects younger than age 13 years.
11. Please consider permitting rescue treatment with rhC1-INH only for subjects with abdominal and oro-pharyngeal-laryngeal attacks (who have not reported beginning of symptom relief by 4 hours).
12. We advise, during the OLE phase, permitting a 2nd 50 U/kg dose of study product to be given only after 1 hour unless symptoms are markedly worsening. We advise that specific criteria or guidance for administering a 2nd 50 U/kg dose be included in the protocol.
13. Please analyze and report as an exploratory endpoint the number and proportion of subjects and HAE treatments for which a 2nd 50 U/kg dose is administered. Please analyze the use of a 2nd 50 U/kg dose as a function of initial HAE attack severity.
14. Please revise the definition of additional treatment to make unambiguous that, if taken following the onset of the attack at a dose above the maintenance dose, only androgens or antifibrinolytics fall into this category. All the other classes of medications are included as “additional treatment” regardless of dose.
15. Please revise the definition of Most Clinically Serious Location of Each Attack to break out facial attacks separately from oro-pharyngeal-laryngeal.
16. Please revise the definition of Response to read, “Response of an attack to treatment is defined as time to the beginning of relief of symptoms at the primary attack location...”
17. Please revise the Time to complete resolution of symptoms to account for the possibility this might occur prior to clinic discharge, and thus might be recorded on source documents and the CRF but not in the subject diary.
18. Please retain the definition of Therapeutic failure, updated to reflect the current list of potential confounding concomitant medications. Please provide a separate definition for relapses at new attack locations which occur within (a) 4 hours and (b) 24 hours of time of start of relief of symptoms of the primary attack location. Please include in the protocol and SAP descriptive analyses of therapeutic failures, of relapses, and of relapses at new attack locations as exploratory endpoints.
19. Please describe the validation status of the revised Investigator Score.

20. We advise a 2nd telephone call from the study site to the subject on day 3 or 4 to encourage timely contemporaneous completion of the diary cards for AEs, etc.
21. Please also express the dose of the product in micromoles. The statement of protein equivalency to units is incomplete without an understanding of the purity of the protein content of the product.
22. Please revise the summary of findings of study C12 1205-01 RCT to include the fact that the randomization did not achieve balance in HAE attack locations across treatment groups.

Appendix 2. Items from February 24, 2011, Refuse-to-File letter for STN -(b)(4)-

We are refusing to file your BLA under 21 CFR 601.2(a) for the following reasons:

1. Scientific incompleteness of the application [i.e., omission of critical data, information, or analyses needed to evaluate safety, purity, and potency or provide adequate directions for use (21 CFR 601.2)]. The concept of "potency" of a biological product includes clinical evidence of effectiveness, demonstrated by adequate and well-controlled clinical trial(s) or acceptable alternative scientific methods [21 CFR 600.3(s)]. FDA has considered the following to arrive at the above conclusion:
 - a. **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.
 - b. You **had not *a priori* validated a clinically meaningful difference for the visual analogue scale analysis** of the primary efficacy criterion in the RCT, subject self-reported time to initial relief of HAE attack symptoms.
 - c. 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, fresh frozen plasma, tranexamic acid, epsilon amino caproic acid, analgesics, and/or anti-emetics, **which may potentially confound the efficacy analyses**.
 - d. The protocols contained a number of deficiencies and inconsistencies [e.g., Protocol study C1 1205-01 was **amended 34 months after the study was underway** to add peripheral attacks, which was not in keeping with the original efficacy objective of the study to explore the efficacy of the product in submucosal acute HAE attacks (and also not in keeping with the primary endpoint of the study as stated in the protocol version in effect when the study began)); (letter dated February 11, 2009 and fax dated January 12, 2009)].
2. The studies were deemed inadequate during the Investigational New Drug (IND) review process and **remain uncorrected after the inadequacies were clearly communicated to you** by FDA. Examples of FDA communications include (also see Appendix 1):
 - a. Fax of January 20, 2010:

“As stated in our earlier communications, we request that you 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. We do not believe a retrospective approach to validation of the primary endpoint is completely remedial and, as noted below in our response to your question # 3, the data you have identified to support your proposed starting dose appears to be insufficient.”

b. Meeting minutes of March 13, 2009:

“CBER questioned whether the sponsor had adequate efficacy data from the single controlled trial that included the 50 microgram [unit] dose for the proposed 50 microgram [unit] dose, given the small sample size. CBER stated they do not consider efficacy assessments for uncontrolled open label use of the product to be very helpful, due to potential bias, and noted that all of the early trials of the product were uncontrolled.”

“CBER noted that the efficacy data supporting use of the 50 microgram [unit] dose in the current placebo controlled studies are very limited. Lack of 2nd study validation of dose ranging was a deficiency of the sponsor’s product development program that had been cited by CDER in 2007 as one reason why CDER had recommended the sponsor conduct an additional phase 3 trial. CBER now also recommends the sponsor conduct an additional phase 3 study...”

“Pharming stated that the VAS validation would be provided to the IND. With regard to confounding medications, the SAP will be amended to account for the use of confounding medications in patients. Rescue medications will be considered as treatment failures.

CBER stated the *post hoc* analysis is an issue of concern. This was not [adequately] pre-specified in the protocol. Confounding medications may be handled by many different methods and the choice of method could maximize bias and potentially may interfere with the assessment of efficacy when such medications were given prior to complete relief of symptoms.”

While not a comprehensive list of deficiencies, the following are intended to provide guidance on information which we would encourage you to consider including in any future submission of the BLA.

1. Please submit the results of planned Phase III clinical study C1 1310. Please note that we will be sending you additional comments on the proposed design of this study in a separate communication.

2. Please correct the error in submitted FDA Form 3454 (OMB approved Forms 0910-0396) with Box 1 checked and the attached list of investigators. Box 1 states in part “I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).” The information in submitted Form 3454 does not appear to be compatible with the information on the submitted FDA form 3455 for Investigator D. Moldovan. According to the latter submitted form, Investigator D. Moldovan of pivotal phase III study CI 1304-01 received compensation totaling --- (b)(6) ---, with the box checked stating he “participated in financial arrangements... as follows: any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.” Such compensation qualifies as “significant payments” as defined by 21 CFR 54.2(f).

In addition we note on submitted forms 3455:

Investigator M. Cancian of pivotal phase III study CI 1304-01, received consultancy fees totaling ----- (b)(6) -----, with the box checked stating he participated in financial arrangements... as follows: any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

Investigator M. Cicardi of pivotal phase III study CI 1304-01, who received consultancy fees totaling ----- (b)(6) -----, with the box checked stating he participated in financial arrangements as noted above.

3. Please submit true intent-to-treat analyses of the primary endpoints of all randomized studies, which include appropriate conservative imputation of missing data.
4. Please include and/or reference validation information for the Investigator Symptom Scoring Systems used in all RCTs.
5. Analyses of time to complete resolution of all HAE attack symptoms should be included in the reports for all RCTs.

Appendix 3. June 14, 2013, File-with-Deficiencies Letter Items

While conducting our filing review, we identified the following potential review issues:

1. Our preliminary review of the results of the pivotal study has identified the following deficiencies:
 - As shown in Table 15 (clinical study report, page 91), the pivotal study 1310 did not demonstrate efficacy at sites in the U.S., which accounted for one-half of the total enrollment.
 - As shown in Table 15 (clinical study report, page 91), the pivotal study 1310 did not demonstrate efficacy for female subjects, who accounted for 63% of the enrollment.

Both subgroup analyses were pre-specified in the plan for statistical analysis.

Please note in the November 30, 2012, pre-BLA meeting briefing package intended for the January 8, 2013, pre-BLA meeting (which was not held) you did not inform CBER of the failure to demonstrate efficacy for subjects enrolled at U.S. sites in pivotal study 1310, and you did not inform CBER of the failure to demonstrate efficacy for female subjects in pivotal study 1310. The pre-BLA meeting package only presented outcomes for pivotal study 1310 for secondary endpoints or subgroups that were favorable for licensure.

Please submit additional data from a randomized controlled study that can provide robust evidence for efficacy of the product.

2. Please compare and submit the outcomes for the primary endpoint in study 1310 for the two groups 1) placebo subjects enrolled at U.S. sites, and 2) placebo subjects enrolled at European sites, using the procedures for the primary efficacy analysis described in section 6.11.1 of the statistical analysis plan for study 1310, and submit the results to STN 125495.
3. Some subjects were enrolled in multiple studies. Please submit a unique subject identifier mapping that identifies unique subjects across all studies.

Appendix 4. Applicant's July 26, 2013, Response to File-with-Deficiencies Letter

1 NATURE AND PURPOSE OF THE AMENDMENT

Responses to the potential review issues identified in the Food and Drug Administration (FDA) filing acceptance letter dated 14 June 2013 are provided in the present filing. FDA's comments are provided in bold, followed by Pharming's response.

The FDA letter dated 14 June 2013 indicated that the pre-Biologics License Application (BLA) meeting Briefing Package (submitted 21 November 2012) did not include all subgroup analyses. Pharming would like to note that all available primary and secondary efficacy endpoint data were included in the pre-BLA Briefing Package, including the subgroup analyses by anatomic location of the attack. **Only these topline results were available at the time the Briefing Package was prepared.** Pharming should have noted that only topline results were available for the Briefing Package at the time of submission.

The Study 1310 Clinical Study Report (CSR) subsequently submitted with the BLA (125495, Sequence 0000, dated 16 April 2013) provided the results of all analyses that were prespecified in the Study 1310 Statistical Analysis Plan (SAP), including subgroup analyses by gender and by geographic location. Study 1310 CSR, Section 11.1.1.4 also discussed the findings of female and US patients.

2 RESPONSE TO FDA ISSUE #1

- **As shown in Table 15 (clinical study report, page 91), the pivotal study 1310 did not demonstrate efficacy at sites in the US, which accounted for one-half of the total enrollment.**
- **As shown in Table 15 (clinical study report, page 91), the pivotal study 1310 did not demonstrate efficacy for female subjects, who accounted for 63% of the enrollment.**

Both subgroups were pre-specified in the plan for statistical analysis.

Please submit additional data from a randomized controlled study that can provide robust evidence for efficacy of the product.

The efficacy of recombinant human C1 esterase inhibitor (rhC1INH) for the treatment of acute angioedema attacks in patients with HAE was established in the randomized, controlled trial (RCT) Phase of Study 1310. This pivotal study demonstrated that rhC1INH was

superior to saline in producing a significantly, and clinically meaningfully, shorter time to the beginning of relief of the symptoms of an acute angioedema attack.

As noted by FDA and as stated in Study 1310 CSR, Section 11.1.1.4, numerical superiority for rhC1INH compared to saline was not observed in the RCT Phase of Study 1310 with regard to the time to beginning of relief in the subgroups of female patients and in patients who were enrolled in the US (Table 1).

Table 1. Time to Beginning of Relief of Symptoms (Based on Questions 1 and 2 of the TEQ at the Primary Attack Location), by Gender and by Geographic Location Subgroups: Study 1310 RCT ITT Analysis Set

Subgroup Category	Median (95% Confidence Interval), minutes [n]	
	rhC1INH (N=44)	Saline (N=31)
Gender		
Male	75 (45, 210) [n=16]	480 (150, -) [n=12]
Female	112.5 (63, 151) [n=28]	105 (60, 334) [n=19]
Geographic Location		
US	97.5 (45, 240) [n=22]	90 (50, -) [n=16]
Rest of World	90 (63, 120) [n=22]	334 (150, -) [n=15]

TEQ = Treatment Effect Questionnaire; RCT = randomized, controlled trial; ITT = intent-to-treat; US = United States of America; “-“ = not estimable.

Source: Study 1310 CSR, Table 15.

As seen above, while median times to beginning of relief of symptoms were similar for patients who received rhC1INH in each subgroup (e.g., US [97.5 min] and Rest of World [90 min]), median times were very different for patients who received placebo (e.g., US [90 min] and Rest of World [334 min]), leading to the lack of numerical superiority for rhC1INH in female and US patients. A reason for this large difference in patients who received placebo is provided below.

Subgroup comparisons of other endpoints generally support the efficacy of rhC1INH. Secondary and key exploratory efficacy endpoint analyses are summarized by both gender and geographic location in Table 2.

Table 2. Secondary and Key Exploratory Endpoint Analyses, by Gender and by Geographic Location Subgroups: Study 1310 RCT ITT Analysis Set

Subgroup Category	Median (95% Confidence Interval), minutes [n]	
	rhC1INH	Saline
Time to Minimal Symptoms (Based on Question 3 of the TEQ at All Locations)		
Gender		
Male	720 (270, -) [n=16]	1440 (1439, -) [n=12]

Subgroup Category	Median (95% Confidence Interval), minutes [n]	
	rhC1INH	Saline
Female	240 (152, 449) [n=28]	300 (180, 1440) [n=19]
Geographic Location		
US	720 (270, -) [n=22]	331 (155, 1440) [n=16]
Rest of World	240 (120, 329) [n=22]	1439 (300, 1442) [n=15]
Time to the Beginning of Relief of Symptoms (Based on Investigator Score)		
Gender		
Male	49 (30, 61) [n=16]	360 (90, 360) [n=12]
Female	69 (60, 93) [n=28]	90 (50, -) [n=19]
Geographic Location		
US	60 (45, 121) [n=22]	90 (49, 120) [n=16]
Rest of World	61 (50, 75) [n=22]	360 (90, -) [n=15]
Time to Complete Resolution of Symptoms (Based on Patient Diary)		
Gender		
Male	1597 (478, 2648) [n=15]	1430 (780, 3720) [n=11]
Female	1053 (329, 1765) [n=25]	2056 (1135, 3087) [n=19]
Geographic Location		
US	1597 (894, 4390) [n=18]	2234 (1135, 3087) [n=15]
Rest of World	600 (240, 1765) [n=22]	1430 (780, 3138.0) [n=15]

RCT = randomized, controlled trial; ITT = intent-to-treat; TEQ = Treatment Effect Questionnaire; US = United

States of America; “-“ = not estimable.

Source: Study 1310 CSR, Tables 14.2.2.6RCT, 14.2.2.9RCT, 14.2.4.2RCT, 14.2.4.3RCT, 14.2.7.5RCT, and 14.2.7.8RCT.

As shown in Table 2, rhC1INH was numerically superior to saline in most gender and geographic location subgroups for the secondary and the key exploratory efficacy endpoints. For example, median times to complete resolution of symptoms in female patients and US patients who received rhC1INH were approximately 1000 and 600 min faster, respectively, than those who received saline. These data support the robustness of the efficacy of rhC1INH in both genders and in patients enrolled in either the US or the Rest of World.

In addition to the data from Study 1310 RCT, integrated data from two earlier RCTs also support the efficacy of the product across gender and geographical location subgroups (Table 3). For example, as defined by visual analog scores (VAS), the time to beginning of relief and time to minimal symptoms were shorter for patients who received either dosage strength of rhC1INH when compared to those who received saline, irrespective of gender or geographical location (some apparent differences in median times for the two

rhC1INH groups may be due to infrequent and widely-spaced assessments; for example, VAS scores were collected at 60 min, 120 min, 240 min, and then at 480 min).

Table 3. Time to Beginning of Relief of Symptoms and Time to Minimal Symptoms, by Gender and by Geographic Location Subgroups: Studies 1205 RCT and 1304 RCT FAS (mITT)

Subgroup Category	Median (95% Confidence Interval), minutes [n]		
	rhC1INH 100 U/kg	rhC1INH 50 U/kg	Saline
Time to Beginning of Relief of Symptoms (VAS Decrease ≥ 20 mm)			
Gender			
Male	64 (40, 128) [n=13]	74.5 (46, 250) [n=4]	496 (480, 720) [n=8]
Female	67 (62, 123) [n=16]	125.5 (72, 148) [n=8]	320 (125, 718) [n=21]
Geographic Location			
US	66 (61, 122) [n=11]	125.5 (72, 243) [n=8]	320 (243, 495) [n=11]
ROW	67.5 (45, 128) [n=18]	62.5 (29, 148) [n=4]	496 (125, 720) [n=18]
Time to Minimal Symptoms (Based on VAS Score < 20 mm at All Attack Locations)			
Gender			
Male	266 (125, 728) [n=13]	492.5 (243, 970)[n=4]	1650 (988, 2880) [n=8]
Female	262.5 (242, 720)[n=16]	246.5 (237, 484)[n=8]	1098 (800, 1494)[n=21]
Geographic Location			
US	242 (124, 266) [n=11]	246.5 (243, 484)[n=8]	1210 (970, 1650)[n=11]
ROW	490 (255, 728) [n=18]	371.5 (71, 740) [n=4]	1098 (720, 2880)[n=18]

RCT = randomized, controlled trial; FAS = full analysis set; mITT = modified intent-to-treat; IU = international units; US = United States of America; VAS = visual analog scale; ROW = Rest of World.
Source: Table 1ISE, Table 2ISE, Table 3ISE, Table 4ISE.

In summary, the lack of numerical superiority observed for rhC1INH in female and US patients for the time to beginning of relief in Study 1310 was not observed consistently across other efficacy endpoints in that study. Additionally, in the integrated analysis of the two supportive RCT studies, numerical superiority was always observed for rhC1INH in these subgroups for the primary and other efficacy endpoints. Taken together, the available data suggest that the observed absence of numerical superiority of rhC1INH when compared with saline for the primary efficacy endpoint in female and US patients in Study 1310 should not be interpreted as a lack of efficacy of rhC1INH in these two subgroups of patients.

We believe that the absence of numerical superiority for rhC1INH compared to saline in the RCT Phase of Study 1310 for the primary efficacy endpoint in female patients and in patients enrolled in the US may be explained by differences in the time from attack onset until evaluation at the study center between US and Rest of World patients.

Table 4 presents the time from attack onset until evaluation at the study center by gender and geography for Study 1310 RCT.

Table 4. Time between Attack Onset and Evaluation, by Gender and by Geographic Location Subgroups: Study 1310 RCT ITT Analysis Set

	Time between Attack Onset and Evaluation, minutes (mean [SD])		
Subgroup Category	rhC1INH (N=44)	Saline (N=31)	Total (N=75)
Gender			
Male	186 (94.5) [n=16]	186 (40.7) [n=12]	186 (75.1) [n=28]
Female	190 (185.5) [n=28]	268 (242.0) [n=19]	222 (211.2) [n=47]
Geographic Location			
US	220 (210.9) [n=22]	289 (259.3) [n=16]	249 (231.7) [n=38]
Rest of World	157 (64.0) [n=22]	180 (38.7) [n=15]	166 (55.7) [n=37]

RCT = randomized, controlled trial; ITT = intent-to-treat; US = United States of America.

Source: Study 1310 CSR, Table 14.1.8.2RCT and Table 14.1.8.3RCT.

On average, female patients and patients enrolled in the US tended to have longer times between attack onset and presentation for evaluation than male patients and patients enrolled in the Rest of World. For example, the average time for female patients was 19% longer than for male patients, while the average time was 50% longer for US patients than for Rest of World patients. These differences were especially pronounced for patients who received saline. For example, female patients who received saline presented for evaluation an average of 82 min (or 44%) longer than male patients who received saline. Similarly, US patients who received saline presented an average of 109 min (or 61%) longer than Rest of World patients who received saline.

In particular, the average time between attack onset and presentation for evaluation for female patients who received placebo was 41% longer than female patients who received rhC1INH, and the average time for US patients who received placebo was 31% longer than US patients who received rhC1INH. We believe it is these differences in the time between attack onset and presentation for evaluation between placebo rhC1INH patients that has led to a lack of numerical superiority for rhC1INH for female and US patients.

To evaluate whether such differences in time to evaluation could impact the onset of relief and explain the lack of numerical superiority for female and US patients, a sensitivity analysis was performed using the Cox proportional hazards model. In the Cox model, the time between attack onset and evaluation for presentation was found to have a statistically significant impact on the time to the beginning of relief of symptoms as measured relative to the time of dosing ($p = 0.031$; see Study 1310 CSR Table 14.2.1.14RCT).

Additionally, since randomization was central and stratified by gender and anatomical location of the attack, by chance a very high proportion (14/16; 88%) of the patients in the US who were randomized to the saline treatment group were female. Thus, the absence of numerical superiority for rhC1INH compared to saline in the female and in US patients could both be due to a single explanation, namely the delayed presentation in these patients.

In most cases untreated HAE attacks eventually are self-limiting. Thus it is not surprising that in patients who did not receive active treatment (i.e., in patients who received saline), the longer the time between attack onset and presentation for evaluation, the shorter the time interval until his/her symptoms abated. Therefore, it is not surprising that the subgroup of the patients in the saline group who were enrolled in the US and who tended to have longer time intervals between attack onset and who were enrolled in the US and who tended to have longer time intervals between attack onset and evaluation, also tended to have shorter time intervals between dosing and the beginning of relief of symptoms compared to the subgroup of the patients in the saline group who were enrolled in the Rest of World. In contrast, the time to the beginning of relief of symptoms was independent of the time between attack onset and evaluation for patients who received rhC1INH. This is further supported by the complete resolution endpoint where significant benefit was observed for female and US patients.

It also should be noted that the study was powered for the primary efficacy analysis, as agreed upon by FDA through a Special Protocol Assessment, but it was not powered for any of the subgroup comparisons that were delineated in the SAP.

The combined data presented support the robustness of the efficacy of rhC1INH for the treatment of acute angioedema attacks in patients with HAE. The available data establish that rhC1INH is superior to saline by producing a significantly, and clinically meaningfully, shorter time to the beginning of relief of the symptoms of an acute angioedema attack. Furthermore, the consistency of the findings across the various efficacy endpoints, demographic subgroups, and studies in the rhC1INH clinical development program, demonstrates that rhC1INH is efficacious overall and in the key patient subgroups of interest, including both gender subgroups and geographic location subgroups.

3 RESPONSE TO FDA ISSUE #2

Please compare and submit outcomes for the primary endpoint in study 1310 for the two groups 1) placebo subjects enrolled at US sites, and 2) placebo subjects enrolled at European sites, using the procedures for the primary efficacy analysis described in section 6.11.1 of the statistical analysis plan for study 1310, and submit the results to STN 125495.

The requested analyses are provided in Table 1.1RCT through Table 1.12RCT, Table 3.1RCT through Table 3.5RCT, Tables 1.1OLE, and Table 1.2OLE. These data confirm

the observed differences in the subgroups were more pronounced for patients who received saline, as discussed above.

4 RESPONSE TO FDA ISSUE #3

Please see listing Listing 1 and the Integrated Summary of Safety, Listing 2.7.4.1.2.