Statistical Analysis Plan

Protocol Number: C1 1209

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

Short title: Safety of Ruconest in 2-13 year old HAE patients

Customer: Pharming Technologies B.V., The Netherlands
Compound: Ruconest
Study Phase: Phase II

Version: 3.1.0
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CUSTOMER: PHARMING TECHNOLOGIES B.V., THE NETHERLANDS **1**

VERSION: 3.1.0 ..... **1**

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical, Therapeutic, Chemical
BLQ	Below limit of quantification
C1	Plasma complement component 1
C1INH	C1 inhibitor
C4	Plasma complement component 4
CSR	Clinical Study Report
dL	Decilitre
ELISA	Enzyme-linked immunosorbent assay
fL	Femtolitre
HAE	Hereditary Angioedema
HEENT	Head, Ears, Eyes, Nose and Throat
i.v.	Intravenous
IS	Investigator's score (assessment of the intensity of the symptoms)
ITT	Intent-To-Treat
kg	Kilograms
L	Litre
LOCF	Last Observation Carried Forward
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimoles
NOCB	Next Observation Carried Backward
OPL	Oropharyngeal-Laryngeal
PP	Per Protocol
PT	Preferred Term
rhC1INH	Recombinant human C1 inhibitor
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SI	Système International
SOC	System Organ Class
U	Units
TEAE	Treatment Emergent Adverse Event
TEQ	Treatment Effect Questionnaire
VAS	Visual Analogue Scale
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) is based on protocol C1 1209 dated 10 June 2014. The SAP contains a complete and detailed specification of the statistical analyses.

1.1 Rationale

Clinical trials have evaluated recombinant human C1 inhibitor (rhC1INH) for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE). The clinical and laboratory data demonstrate that rhC1INH represents an effective and well tolerated therapeutic option for the treatment of acute angioedema attacks in this population of HAE patients.

C1INH deficiency is present at birth, and symptoms usually become apparent in the first or second decade of life. Patients typically experience minor swelling in childhood that may go unnoticed, with increased severity of symptoms around the time of puberty.

As a genetic disease, acute attacks of HAE have the same pathophysiology in children and adults. Also as in adults, treatment with plasma-derived C1INH has been the standard of care for acute angioedema attacks in children for several decades. Ruconest was approved in Europe for the treatment of acute angioedema attacks in adults in 2010 and in the US for the treatment of acute angioedema attacks in adults and adolescents in 2014.

In previous studies, adolescents have been exposed to Ruconest without concerns about either efficacy or safety. However, no clinical trial data are available related to Ruconest exposure in patients under the age of 14 years.

2. Summary of the Protocol

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to assess the clinical safety, immunogenicity, and tolerability of Ruconest in the treatment of acute angioedema attacks in 2-13 year old HAE patients.

2.1.2 Secondary Objectives

The secondary objectives of the study are to:

- Assess the pharmacokinetics (PK) and pharmacodynamics (PD) of Ruconest in the treatment of acute angioedema attacks in 2-13 year old HAE patients.
- Assess the efficacy of Ruconest in the treatment of acute angioedema attacks in 2-13 year old HAE patients.

2.2 Study Design

This is an open-label, non-comparative phase II, multinational, multi-center clinical study.

HAE patients from 2 up to and including 13 years of age will be screened for eligibility and enrolled.

Patients up to 84 kilograms (kg) will receive one i.v. injection of Ruconest at a dose of 50 U/kg. The reconstituted solution should be administered as a slow i.v. injection over approximately 5 minutes. Patients of 84 kg body weight or greater will receive one i.v. injection of Ruconest at the dose of 4200 U (2 vials).

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

Table 1 presents the treatment group labels that will be used in all output.

Table 1 Study Treatments

Actual Treatment	Treatment Label
One i.v. injection of Ruconest (weight adjusted dose)	Ruconest

Table 2 presents the visit labels that will be used in all output.

Table 2 Study Visits

	Visit	Visit Label
Pre-attacks	Visit 1 – Screening	Screening
Attack 1, 2...	Visit 2 – Presentation with acute angioedema attack Visit 2 – Day 0, 0 mins Visit 2 – Day 0, 5 mins Visit 2 – Day 0, 30 mins Visit 2 – Day 0, 1 hours Visit 2 – Day 0, 2 hours Visit 2 – Day 0, Between 2 and 4 hours Visit 2 – Day 0, 4 hours Visit 2 – Day 0, Discharge Visit 2 – Day 0, 8 hours	Presentation 0 minutes 5 minutes 30 minutes 1 hour 2 hours 2-4 hours 4 hours Discharge 8 hours
	Visit 3 – Day 1, 24 hours	24 hours
	Visit 4 – Day 28	Day 28
	Visit 5 – Day 90	Day 90
Annual Follow-up	Yearly follow up after screening visit	Yearly Visit 1, Yearly Visit 2…

Treated attack visits will be prefixed by attack number. If a new attack is treated before completing the follow-up visits for the previous attack, the D28 or D90 visit schedule will be reset based on the most recent treated attack. The patient diary will be reviewed at presentation of the new attack and used to partially complete the Day 28 CRF for the previous attack.

2.3 Sample Size Determination

No formal sample size was calculated; it was anticipated that an overall sample of at least 20 completed patients is a sufficient dataset to meet the objectives of the study; this target number of patient is based on feasibility and agreed with the Pediatric Committee of the European Medicines Agency. The enrolment of patients will continue until at least 20 different patients are treated for at least one acute HAE attack, and the Sponsor determines that sufficient data have been collected on repeat treatments.

2.4 Schedule of Events

Table 3 presents the schedule of study events.

Table 3 Schedule of Study Events

Day:	Screen	Occasion									Post			every year after screen
		Day 0									Day 1	Day 28	Day 90	
Type of Visit:	Center Visit	Center Treatment Visit									Phone	Center Visit	Center Visit	Center Visit
Time:		P[2]	0'	5'	30'	1h	2h	4h	at dis-charge[3]	8h[3]	24h	D28	D90	
Study medication infusion[1]			X											
Informed Consent	X													
Demographics	X													
Medical History / HAE-disease history	X													
Evaluation in- and exclusion criteria	X	X												
Physical examination	X	X							X			X	X	
Vital signs (blood pressure, pulse, body T)	X	X			X	X	X	X					X	
ECG		X			----X----									
Pregnancy test[9]		X												
Blood sampling for diagnostic testing[5]	X (4.5 mL)													
IgE testing[6]												X		X
Blood sampling for immunology[7]		X (2.7 mL)										X	X	
Blood sampling for PK/PD[8]				X			----X----							
Blood sampling for hematology / biochemistry		X (10 mL)										X (10 mL)		
Clinical assessment of angioedema signs		X									X[4]			
Investigator's symptom score		X			X	X	X	X						
Patient/Parent's VAS + TEQ		X[2]			X	X	X	X		X	X			
Dispensation of diary									X					
Return and evaluation of diary												X		
Intercurrent HAE episode(s)												X	X	X
Assessment of Adverse events		X	----------X----------								X	X	X	X
Concomitant medication	X	X	----------X----------								X	X	X	X
Total blood volume (mL):	4.5	12.7		1.8			1.8					11.8	1.8	1.8

(1) Catheter system to be used if possible, which can be used for blood sampling and treatment administration (and a second dose if necessary), and can be left for 4 hours. In order to minimize patient distress, local, topical anesthesia may be considered before placing a catheter.

(2) P = at presentation with an acute angioedema attack. Assessments and blood samples should be done as close as possible to the time of treatment administration; the VAS and TEQ should be completed immediately prior to study medication infusion.

(3) The patient may be discharged after 4 hours; in that case the patient questionnaire at T8h will not be completed during hospitalization but at home by the patient/legal guardian; the questionnaire is to be returned at the Day 28 visit.

(4) Telephone interview regarding HAE-symptoms in order to document possible therapeutic failure, or late relapse, registering localization, severity and time course.

(5) C1INH activity, C1q, C4, antibodies against rhC1INH (confirmation + neutralizing antibodies); C4 will be repeated at baseline of each attack.

(6) Anti rabbit epithelium (dander) and anti cow milk IgE testing at screening. Anti rabbit epithelium (dander) IgE only is tested at the Day 28 follow-up visit of each attack and every year after screening.

(7) IgM and IgG antibodies against C1INH (confirmation + neutralizing) and HRI (+confirmation), and C4 (only at screening and baseline of each attack)

(8) C1INH activity (PK) and C4 (PD), only at first attack, at baseline, directly following infusion and one additional sample within the window of 2-4 hours

(9) If relevant, i.e. only for post-menarcheal female patients

3. Patient Analysis Sets

The exclusion of patients from the following protocol defined analysis sets will be decided at a pre-analysis meeting prior to database lock.

It is assumed that these pediatric patients have had informed consent provided as appropriate before or at screening. However, if there are patients who do not meet this criteria, the SAP will be updated prior to database lock to indicate how their data are handled in the analysis.

3.1 Screening Analysis Set

The Screening analysis set is defined as all patients screened for the study, who at screening were eligible for treatment.

The following are reasons for exclusion from the Screening analysis set:

- Failing to meet the inclusion/exclusion criteria.

3.2 Safety Analysis Set

The Safety analysis set is defined as the set of patients who received at least one dose of the study medication.

The following are reasons for exclusion from the Safety analysis set:

- Patient did not receive at least one dose of the study medication.

The Safety analysis set will be used for all safety analyses.

3.3 Intention to Treat Analysis Set (ITT)

The ITT is defined as the set of patients who received at least one dose of the study medication, and for whom any efficacy data is available.

The ITT will be the primary analysis set of interest for all efficacy endpoints.

3.4 Per Protocol (PP) Analysis Set

The PP analysis set is defined as all patients in the ITT analysis set that had at least one attack without any major protocol violations (see Section 4.3.5). Only data from the attacks without major protocol violations will be included for these patients.

The PP analysis set will be used as the analysis set in the confirmatory efficacy analyses.

3.5 Pharmacokinetic (PK)/Pharmacodynamic (PD) Concentration Set

The PK/PD Concentration set is defined as the subset of the Safety analysis set that has at least one PK/PD concentration measured.

3.6 Pharmacokinetic (PK)/Pharmacodynamic (PD) Analysis Set

The PK/PD analysis set is defined as the subset of the Safety analysis set that has sufficient plasma concentration data. A patient will be seen as having sufficient plasma concentration data if at least the peak plasma concentration (C_{max}) can be calculated.

All PK/PD analyses will be performed on the PK/PD analysis set.

4. Study Measures

This section describes the measures that were collected and/or derived during the study at the time points specified in the Schedule of Events (see Section 2.4). This includes efficacy, safety, tolerability and patient characteristics data.

4.1 Efficacy Measures

The efficacy endpoints described in this section will be analyzed according to the analysis methods described in Section 6.7.

Each efficacy measure will be calculated separately for each attack for a patient i.e. if a patient has two attacks then time to beginning of relief of symptoms, time to complete resolution of symptoms etc. will be calculated separately for each attack. Baseline will be calculated separately for each attack too.

4.1.1 Definitions

4.1.1.1 Treatment Effect Questionnaire (TEQ)

TEQ responses are recorded repeatedly throughout the study at the following time-points; Presentation (Pre-dose) and after treatment at 30 minutes, 1, 2, 4, 8 and 24 hours.

The TEQ responses are measured at up to five different locations (Abdominal, Oro-pharyngeal and/or Laryngeal (OPL), Facial, Urogenital or Peripheral), depending on the affected locations.

The TEQ consists of the following questions:

- Question 1
  - Pre-dose – To what extent has the overall severity of your [*abdominal*[1]] HAE attack changed since your arrival at the study center?
  - After treatment – To what extent has the overall severity of your [*abdominal*[1]] HAE attack changed since you received the infusion?
  - Possible responses are 'Much Worse', 'Worse', 'A Little Worse', 'Not Changed', 'A Little Better', 'Better' or 'Much Better'.

- Question 2
  - Pre-dose – Overall, has the intensity of your [*abdominal*[1]] HAE attack symptoms begun to decrease noticeably since your arrival at the study center?
  - After treatment – Overall, has the intensity of your [*abdominal*[1]] HAE attack symptoms begun to decrease noticeably since you received the infusion?
  - Possible responses are 'Yes' or 'No'.
- Question 3

- At this moment, are your [*abdominal*[1]] HAE attack symptoms minimal (barely noticeable)?
- Possible responses are 'Yes' or 'No'.

[1] abdominal is replaced by the relevant attack location.

4.1.1.2 Visual Analogue Scale (VAS)

VAS scores on angioedema signs and symptoms are recorded repeatedly throughout the study at the following time-points; Presentation, 30 minutes, 1, 2, 4, 8 and 24 hours.

The VAS scores are measured at up to five different locations (Abdominal, Urogenital, OPL, Facial, or Peripheral Locations), depending on the affected locations.

A series of location specific VAS assessments are taken with the last VAS question for each location indicating the overall severity of angioedema symptoms as felt by the patient for that location (0 mm corresponding to 'No symptoms' and 100 mm corresponding to 'Extremely disabling'), and is called the Overall VAS score.

Overall VAS: The Overall VAS score is Question 4 for attacks at Facial or Peripheral Locations, Question 5 for attacks at an Abdominal location, Question 6 for attacks at an Urogenital location and Question 7 for attacks at an OPL location.

All VAS tables will be based on the Overall VAS score for a given location, the other VAS scores will be listed only.

The Baseline Overall VAS score for each location is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Time 0 hours for the attack. This would normally be the Presentation Overall VAS assessment.

The change from Baseline Overall VAS score at each post-baseline time-point will be calculated as:

Overall VAS score obtained at the specific post-baseline time-point – Baseline Overall VAS score

4.1.1.3 Investigator Symptom Scores

Investigator Symptom (IS) scores are recorded repeatedly throughout the study at the following time-points:
Presentation, 30 minutes, 1, 2, and 4 hours.

The scores are measured at up to 5 different locations (Abdominal, Urogenital, OPL, Facial, or Peripheral). A 6 point ordinal scale is used to indicate the severity of the symptoms.

Table 4 Investigator Symptom Scoring System

Score	Response
0	No symptoms
1	Almost no symptoms
2	Mild symptoms
3	Moderate symptoms
4	Severe symptoms
5	Life-threatening

The Baseline IS score for each location is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Time 0 hours for the attack. This would normally be the Presentation IS assessment.

The change from Baseline value at each post-baseline time-point will be calculated as:

IS score obtained at the specific post-baseline time-point – Baseline value

4.1.1.4 Eligible Locations

An attack can occur at more than one anatomical location (although usually at only either one or two). Not all locations are eligible for analysis in this study. An eligible location will therefore be defined as a location which fulfills the following criteria:

- Onset of HAE symptoms at the location was less than 5 hours before start time of evaluation;
- IS score at the location was at least 3 at Presentation;

4.1.1.5 Primary Attack Location

For patients who present with multiple eligible attack locations the most severe eligible location will be the eligible location with the highest IS score at Baseline. If the IS score is equal for two locations, the most clinically serious location will be defined as the primary attack location.

The order of clinical seriousness is OPL, followed by Facial, Abdominal, Urogenital and Peripheral. The most severe eligible location will be labeled as “the primary attack location”.

4.1.1.6 Disallowed Concomitant Medication

Patients presenting with attacks who have already received any medication since the onset of the attack likely to interfere with the evaluation of efficacy and safety will **not be eligible** for treatment for this attack. These treatments include:

- Narcotics
- Plasma-derived C1 inhibitor
- Fresh frozen plasma
- Bradykinin receptor antagonist
- Analgesics
- Anti-emetics
- Non Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Paracetamol (within 45 minutes before the administration of Ruconest)

As an exception, for the patient’s comfort, paracetamol may be taken, but not within 45 minutes before the administration of study medication.

Any change in current and optional maintenance therapy (androgens and/or anti-fibrinolytics) from the time of the onset of the current attack is not allowed. The dosage of androgens and anti-fibrinolytics may not be increased earlier than 24 hours after the treatment with study medication.

To minimize impact on the assessment of safety, treatment with other investigational products is not allowed from screening until 30 days after the patient’s last follow-up visit has occurred.

4.1.2 Primary Efficacy Measure

4.1.2.1 Time to beginning of relief based on Overall VAS

The time to beginning of relief will be assessed using the Overall VAS score, where time of beginning of relief will be assessed as the first time point at which the VAS score decreases by at least 20mm at any eligible anatomical location compared to Baseline, with persistence of the decrease at the next time point.

The time of relief will be the first time point at which the Overall VAS score decreases by at least 20mm compared to Baseline. For example, if this was achieved at 2 hours with persistence shown at 4 hours then the time of beginning of relief of symptoms will be 2 hours.

Patients who do not have beginning of relief during the time that they are followed-up will be censored at the last time at which the Overall VAS score is recorded at any eligible anatomical location. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation. Patients who first have a decrease of ≥20mm at the last time Overall VAS score was recorded will not have achieved beginning of relief with persistence. Therefore, they will be censored at the penultimate time that Overall VAS was recorded.

Time to beginning of relief (minutes) will be calculated as:

> Actual date and time of first relief (or date and time of censoring) – Date and time of the Baseline Overall VAS assessment

The actual date and time of beginning of relief will be used in the calculation.

The beginning of relief assessed using Overall VAS will be assessed for the first eligible location at which time to beginning of relief of symptoms by Overall VAS first occurred. Only locations with a populated start date and time and corresponding Overall VAS will be used for the calculation of time to beginning of relief.

For the evaluation of persistence, the decrease of ≥20mm is required at the next assessment time for which the Overall VAS score is not missing. For example, if 2 Overall VAS determinations with ≥20mm decline from Baseline are separated by a missing scheduled assessment then beginning of relief with persistence would have still been achieved.

4.1.3 Secondary Efficacy Measures

4.1.3.1 Time to minimal symptoms based on Overall VAS

The time of minimal symptoms for an attack assessed using the Overall VAS is defined as the time at which the Overall VAS score falls below 20mm for all locations where VAS Scores are recorded.

- Patients who do not have minimal symptoms during the time that they are followed-up will be censored at the last time at which an Overall VAS score is recorded. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.
- A worst-case scenario will be used to impute missing Overall VAS scores for locations. If there are 2 non-missing values either side of missing value(s) then last observation carried forward (LOCF) or next observation carried backward (NOCB) will be used to carry forward or back the largest Overall VAS. If there is only one Overall VAS followed by missing values or after missing values it will be carried forward or back. If the Overall VAS score for a location is blank at Baseline, but then the location is affected by angioedema

post-dosing, a score of 0 will be imputed for all post-baseline time-points up until the first documented Overall VAS score. The worst-case scenario method will then be applied for all subsequent missing Overall VAS scores.

- The time to minimal symptoms for patients who receive disallowed concomitant medication will be censored at the last time at which the patient had an Overall VAS score prior to their receipt of disallowed concomitant medication. If this is Presentation and hence prior to study drug administration then the time to minimal symptoms will be censored at time 0 minutes.

Time to minimal symptoms (minutes) will be calculated as:

Actual date and time of minimal symptoms (or date and time of censoring) – date and time of the Overall VAS assessment at Baseline

Time of the actual date and time of minimal symptoms will be used in the calculation.

4.1.4 Exploratory Efficacy Measures

4.1.4.1 Time to beginning of relief based on IS score

The time to beginning of relief will be assessed using the IS scores, where time of beginning of relief will be assessed as the first time point at which the investigator assesses the severity of an attack as at least one point less (IS decreased by at least 1 point) compared to Baseline at any eligible location.

Patients who do not have beginning of relief during the time that they are followed-up will be censored at the last time at which the IS score is recorded for any eligible location. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.

Time to beginning of relief (minutes) will be calculated as:

Actual date and time of first relief (or date and time of censoring) – Date and time of the Baseline IS assessment

The actual date and time of beginning of relief will be used in the calculation.

4.1.4.2 Time to minimal symptoms based on IS score

The time of minimal symptoms for an attack using the assessment by the investigator is defined as the time at which the IS at the last location falls to 1 point or below.

The time to minimal symptoms for an attack assessed using the IS scores will be assessed for all locations where IS scores are recorded.

- Patients who do not have minimal symptoms during the time that they are followed-up will be censored at the last time at which the IS score is recorded. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.
- A worst-case scenario will be used to impute missing IS scores for locations. If there are 2 non-missing values either side of missing value(s) then LOCF or NOCB will be used to carry forward or back the largest IS score. If there is only one IS score followed by missing values or after missing values it will be carried forward or back. If the IS score for a location is blank at Baseline, but then the location is affected by angioedema post-dosing, a score of 0 will be imputed for all post-baseline time-points up until the first

documented IS score. The worst-case scenario method will then be applied for all subsequent missing IS scores.

- The time to minimal symptoms for patients who receive disallowed concomitant medication will be censored at the last time at which the patient had an Overall VAS score prior to their receipt of disallowed concomitant medication. If this is Presentation and hence prior to study drug administration then the time to minimal symptoms will be censored at time 0 minutes.

Time to minimal symptoms (minutes) will be calculated as:

> Actual date and time of minimal symptoms (or date and time of censoring) – Date and time of the IS assessment at Baseline

The actual date and time of minimal symptoms will be used in the calculation.

4.1.4.3 Time to beginning of relief based on TEQ

Time to beginning of relief of symptoms (TEQ) is assessed using Questions 1 and 2 of the TEQ at the most severe eligible location. The time of relief will be the first time point at which the response to Question 1 of the TEQ was 'A Little Better', 'Better' or 'Much Better' AND the response to Question 2 of the TEQ was 'Yes' with persistence of the improvement at the next time point AND the response to Question 2 of the TEQ was 'Yes'). Persistence of the improvement at the next time point can be defined to mean that at the next available time point, the response to Question 1 of the TEQ was at least as good as the previous response (e.g. if the previous response was 'Better' then the subsequent response would have to be 'Better' or 'Much Better', 'A Little Better' would not be sufficient)

The time of relief of symptoms will be the first time point at which Question 1 of the TEQ was 'A Little Better', 'Better' or 'Much Better' AND the response to Question 2 of the TEQ was 'Yes'. For example, if this was achieved at 2 hours with persistence shown at 4 hours then the time of beginning of relief of symptoms will be 2 hours.

In addition, any patient who did not have beginning of relief of symptoms during the time that they are followed-up will be censored at the last time at which the TEQ is recorded for the primary attack location. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.

Patients who do not have a response of 'A Little Better', 'Better' or 'Much Better' to Question 1 of the TEQ and a response of 'Yes' to Question 2 of the TEQ until the last time the TEQ was recorded will not have achieved beginning of relief with persistence. Therefore, they will be censored at the penultimate time that the TEQ was recorded.

Time to beginning of relief of symptoms (minutes) will be calculated as:

> Actual date and time of first relief of symptoms (or date and time of censoring) – Date and time of first Study Drug Administration

The actual date and time of beginning of relief of symptoms will be used in the calculation.

To allow for missing data in the calculation of time to beginning of relief of symptoms the following rules will be applied. These will ensure that for each patient a conservative approach to estimating missing data is used:

- If a patient has a response of 'A Little Better', 'Better' or 'Much Better' to Question 1 of the TEQ with a missing response to Question 2 of the TEQ then the response to Question 2 will be imputed as 'Yes' if the previous response to Question 2 of the TEQ was 'Yes' and the next response to Question 2 of the TEQ is 'Yes', or else will be imputed as 'No' if either the previous or subsequent responses are not missing.
- If a patient has a response of 'Yes' to Question 2 of the TEQ with a missing response to Question 1 of the TEQ then the response to Question 1 will be imputed as the worst response of the previous and subsequent responses to Question 1.

4.1.4.4 Time to minimal symptoms based on TEQ

Time to minimal symptoms (based on the TEQ) will be defined as the first time at which the response to Question 3 of the TEQ is 'Yes'.

- Patients who do not have minimal symptoms during the time that they are followed-up will be censored at the last time at which the TEQ is recorded. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.
- The time to minimal symptoms for patients who receive disallowed concomitant medication will be censored at the last time at which the patient had an Overall VAS score prior to their receipt of disallowed concomitant medication. If this is Presentation and hence prior to study drug administration then the time to minimal symptoms will be censored at time 0 minutes.

Time to minimal symptoms (minutes) will be calculated as:

> Actual date and time of minimal symptoms (or date and time of censoring) – Date and time of first Study Drug Admin

The actual date and time of minimal symptoms will be used in the calculation.

4.1.4.5 Time to complete resolution

In a diary, dispensed at discharge from the hospital, the patient will be asked to record the date and time at which all angioedema symptoms at all locations have resolved (complete resolution). If needed, depending on the patient's level of understanding, parents may assist in completion. During the Day 28 follow-up visit, the date and time of complete resolution of symptoms, as reported by the patient in the diary, is then recorded in the Day 28 CRF.

Time to complete resolution of all symptoms at all locations will be assessed using the answer recorded on the CRF.

- Time to complete resolution of symptoms will be defined as 'Time HAE attack resolved' on the CRF.
- Patients who do not have complete resolution of symptoms during the time that they are followed-up will be censored at 72 hours if the patient confirms that they did not have complete resolution of symptoms during the follow-up time, or at the time of discharge if the 'Date HAE attack resolved' and 'Time HAE attack resolved' on the CRF were not completed. 72 hours is chosen as this is the average length of time that swelling would be expected to subside without treatment. Note: If a patient was randomized but did not have any post-baseline efficacy data then they will be censored at Presentation.
- The time to complete resolution of symptoms for patients who receive disallowed concomitant medication will be censored at the last time the patient had an Overall VAS

score prior to their receipt of disallowed concomitant medication. If this is Presentation and hence prior to study drug administration then the time to complete resolution of symptoms will be censored at time 0 minutes.

Time to complete resolution of symptoms (minutes) will be calculated as:

Actual date and time of complete resolution of symptoms (or date and time of censoring) – Date and time of Study Drug Admin

4.1.4.6 Therapeutic failure

A patient will be assessed as having had a therapeutic failure if any of the following occurs:

- Time to the beginning of relief of symptoms for the attack based on the Overall VAS occurs later than 4 hours after Baseline.
- Within 4 hours after beginning of treatment administration and after beginning of relief, the Overall VAS increases again to a value of at least the Baseline score.
- The patient has occurrence of HAE at a new location within 4 hours after achieving beginning of relief of symptoms (Based on an IS score of greater than 0 at a new location that had an IS score of 0 at Baseline). Beginning of relief of symptoms here is based on the Overall VAS as defined in Section 4.1.2.1.
- The patient taking any of the medications that may interfere with the assessment of the impact of Ruconest on efficacy measures, between the onset of the attack and prior to time of initial relief of symptoms including:
    - Narcotics
    - Plasma-derived C1 inhibitor
    - Fresh frozen plasma
    - Bradykinin receptor antagonist
    - Analgesics
    - Anti-emetics
    - Non Steroidal Anti-Inflammatory Drugs (NSAIDs)
    - Paracetamol (within 45 minutes before the administration of Ruconest)

  The medical monitor will perform a manual review of the concomitant medications and identify those which fall into the above categories.

4.1.4.7 Receipt of a second dose

The number of patients who received two doses of rhC1INH as treatment for a single HAE attack will be assessed. For each HAE attack the following will be presented:

- The number of patients who received a second dose;
- The Baseline Overall VAS score at the primary attack location, split by attacks treated with a second dose and those that were treated with a single dose.

4.2 Safety Measures

The primary objective of the study is the assessment of safety and tolerability as evaluated by recording of adverse events (AEs) and immunogenicity parameters (anti-HRI, anti-rhC1, anti rabbit epithelium IgE).

4.2.1 Exposure to Study Medication

Patients up to 84 kg will receive one i.v. injection of Ruconest at a dose of 50 U/kg. Patients of 84 kg body weight or greater will receive one i.v. injection of Ruconest at the dose of 4200 U (2 vials). At the discretion of the investigator and depending upon the patient's clinical response, an additional dose may be given to patients following their initial dose as specified above. No more than two doses should be administered within 24 hours.

The following variables will be calculated for each attack and dose. They will be presented separately for the initial and second dose:

- Total volume of medication administered (mL)
- Total Dose in U/kg (patients who weighed less than 84 kg)
- Total Dose in U/kg (patients who weighed more than or equal to 84 kg)
- Duration of Infusion in minutes (only summarized for Attack 1)

Duration of Infusion will be calculated as:

Stop time of last injection – Start time of first injection (for each attack)

For patients who received a second injection for the same attack, the duration of exposure will be calculated as the sum of the duration of exposure for the first and second doses for the attack.

In addition, the following variables will also be calculated:

- Was the total volume of medication administered ('Yes' or 'No')
- Did the patient received a second dose ('Yes' or 'No')
- Did the patient receive a second dose for any of their attacks? (Yes/No – summarized over all attacks)
- Time interval between initial and repeat dose (minutes)
    - Date and time of start of repeat dose - Date and time of end of initial dose

The following endpoints will also be calculated:

- Total number of HAE attacks treated with rhC1INH during the study (categorical and continuous summaries)
- Total number of rhC1INH doses received during the study (categorical and continuous summaries)
- Total dose of rhC1INH received in U/kg (continuous summary)

4.2.2 Adverse Events

An adverse event (AE) is any undesirable physical, psychological or behavioral effect experienced by a patient during the study, in conjunction with the use of the study medication, whether or not product-related. This includes any untoward signs or symptoms experienced by the patient from the time of signing of the informed consent until completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or medical staff.
- Findings at physical examinations.

- Laboratory abnormalities of clinical significance.

HAE attacks (not treated with study medication) will be reported separately from other AEs.

AE data was collected from the time that informed consent was given, for the duration of the trial.

Missing AE data will be handled according to the rules specified in Section 5.5.2.2.

4.2.2.1 Adverse Event Definitions

A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity within 97 days of a dose of study medication. If there are partial or missing dates for when the AE started then it will be assumed that the AE was treatment emergent unless it can be determined from the partial start date or stop date that the AE definitely started before the first dose of study medication, or more than 97 days after the patient last received study medication. Tables will include only TEAEs, but all AEs will be listed.

Serious adverse events (SAEs) reported from the time of informed consent until the last follow-up visit (Day 90) after the last dose of study medication will be recorded as part of the study. SAEs will be any AE where the question 'Does the adverse event meet the criteria of serious?' has been answered as 'Yes'.

A treatment-emergent serious adverse event (TESAE) is defined in exactly the same manner as a TEAE, with the exception that the AE in question must be classified as an SAE.

Each AE will be assigned to an attack based on the start date. If the AE starts after study medication was received for Attack N but prior to study medication being received for Attack N+1 then the AE will be assigned to Attack N. If it is not possible to ascertain from the partial date during which attack the AE occurred then the AE will be assigned to the last possible attack based on the partial date.

The time from previous administration of study drug to onset of an AE will be calculated for all TEAEs as follows:

> Date/Time of onset of AE – Date/Time of the start of previous administration of study drug.

An AE will be classified as related to study medication if the relationship to study medication was recorded (on the 'Study Adverse Events' CRF page,) as, 'Possible', 'Probable', 'Definite'. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as 'Unrelated'.

An AE leading to study discontinuation will be defined as an AE where 'Action taken discontinued study drug' is selected on the Adverse Events CRF page and/or '(Serious) Adverse Event experience' is selected as reason for end of study on the End of Study CRF page.

An AE leading to death will be any AE where the outcome is marked as "4 (Death)".

Adverse Events of Special Interest (AEOSI) are AEs that do not meet any criteria for an SAE but are nonetheless of particular interest in the context of this study, as listed below:

- Type I hypersensitivity reaction due to pre-existing IgE antibodies against rabbit antigens.

- Type I hypersensitivity reaction due to cross reaction with IgE antibodies against cow milk antigens.
- Type I hypersensitivity reaction due to the formation of IgE antibodies against rabbit antigens.
- Type III hypersensitivity reaction due to the formation of antibodies against Ruconest.
- Induction of acquired angioedema due to the formation of anti-C1 inhibitor antibodies.
- Thromboembolic complications.

4.2.2.2 Coding of Adverse Event Terms

The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version 20.

Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA.

The following coding data will be presented:

- LLT
- PT
- SOC

Coding of AEs will be provided by data management at PSR in a coding spreadsheet alongside the coding of CMs and MH. The AE coding data will be merged onto the raw AE data by Subject ID and AE number. The final version of this spreadsheet will be provided prior to database lock.

In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in all summary tables.

AEs will be reported on a per-patient basis. On a per-patient basis this means that even if a patient reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst severity and the strongest relationship to the study medication. The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

4.2.3 Clinical Laboratory Evaluations

Laboratory evaluations were performed at Presentation of attack and Day 28 in accordance with the Schedule of Study Events (Section 2.4). Blood and urine samples were collected and analyzed by local laboratory.

Table 5 presents the quantitative and qualitative laboratory tests that were performed.

Table 5 Laboratory Tests

Laboratory Test (Unit)
Hematology
Erythrocyte sedimentation rate (ESR) (mm/hr)
Hemoglobin (g/L)
Hematocrit (%)
Red blood cell count (RBC) (10^{12}/L)
Mean corpuscular volume (MCV) (fl)
Mean corpuscular hemoglobin (MCH) (pg)
Mean corpuscular hemoglobin concentration (MCHC) (g/L)
Total white blood cell count (WBC) ($x10^9$/L)
Platelet count ($x10^9$/L)
Differential WBC units
Neutrophils ($x10^9$/L)
Lymphocytes ($x10^9$/L)
Monocytes ($x10^9$/L)
Eosinophils ($x10^9$/L)
Basophils ($x10^9$/L)
Biochemistry
Sodium (mmol/L)
Potassium (mmol/L)
Chloride (mmol/L)
Calcium (mmol/L)
Inorganic phosphate (mmol/L)
Total protein (g/L)
Albumin(mg/L)
Glucose (mmol/L)
Creatinine (µmol/L)
Aspartate aminotransferase (AST) (U/L)
Alanine aminotransferase (ALT) (U/L)
Lactate dehydrogenase (LDH) (µkat/L)
Blood urea nitrogen (mmol/L)
Bilirubin (Total) (µmol/L)
Alkaline phosphatase (U/L)
Gamma-GT (U/L)
Uric acid (mg/dL)
Total cholesterol (mmol/L)
HDL cholesterol (mmol/L)
Triglycerides (mmol/L)
C-Reactive Protein (CRP) (mg/L)

Amylase (U/L)
Urine Pregnancy Test

For the quantitative laboratory parameters, if a re-test was performed at any visit, the result from the re-test for the specific visit will be used in all analyses. For the qualitative laboratory parameters, if a re-test was performed at any visit, the results of the test performed at the re-test will be used.

For each laboratory test (quantitative and qualitative), the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study medication administration at 0 minutes.

For the quantitative laboratory test, the change from Baseline value at Day 28 will be calculated as the difference between the measurements obtained at Day 28 and the Baseline value.

Quantitative test results at each visit will be categorized by the laboratory as 'Normal' (within the reference range) or 'Abnormal' (outside the reference range) according to the patients' individual reference ranges provided by the analyzing laboratory (see Appendix 1). Note that Système International (SI) standardized units will have to be used alongside the individual reference ranges, so the process will be to first convert lab data to SI units and then to compare results to the individual reference ranges (also known as "normal ranges").

Abnormal results will further classified as being 'Low' or 'High' depending on whether the result is below or above the reference range limits. For all abnormal values, clinical significance (as determined by the Investigator) should be indicated.

4.2.4 Electrocardiogram (ECG) Evaluations

Electrocardiogram (ECG) evaluations were performed at Presentation of attack and between 30 minutes and 2 hours post infusion with study medication, in accordance with the Schedule of Study Events (Section 2.4).

Only qualitative ECG parameters were collected.

For the qualitative ECG parameters (morphology), it will be recorded whether the parameter at the specific visit was 'Normal' or 'Abnormal'. For all abnormal values, clinical significance (as determined by the Investigator) and any ECG findings should be indicated.

For each qualitative ECG parameter, the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Presentation.

4.2.5 Vital Signs Evaluations

Vital signs evaluations were performed at Screening, Presentation of attack, 30 mins, 1, 2 and 4 hours post infusion with study medication, and Day 90, in accordance with the Schedule of Study Events (Section 2.4).

The following variables were collected:

- Height (cm) (Height was collected only at Screening).
- Weight (kg) (Weight was collected at Screening and Presentation of attack).
- Supine systolic blood pressure (SBP) (mmHg).
- Supine diastolic blood pressure (DBP) (mmHg).
- Pulse rate (bpm).
- Body temperature (°C).

For each vital signs variable, the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Presentation.

Based on the criteria presented in Appendix 1, clinically significant vital sign measurements will be identified at each visit.

4.2.6 Physical Examination

Routine physical examination was performed at Screening, Presentation of attack, Hospital discharge, Day 28 and Day 90 in accordance with the Schedule of Study Events (Section 2.4).

4.3 Other Measures

4.3.1 Diagnostic Assays and IgE Testing

Blood samples for diagnostic assays will be collected at screening. The samples will be analyzed for the following parameters: C1INH activity, C1q, C4 and C1INH auto antibodies (IgM, and IgG anti-rhC1INH).

Assays for IgE antibodies against rabbit epithelium (anti-rabbit epithelium IgE [dander]) will be performed at screening, at Day 28 after each attack, every year following screening and if AEs indicative of a hypersensitivity reaction are observed. Prior to treatment with Ruconest a negative test for anti-rabbit epithelium (dander) (cut off <0.35 kU/L) should be documented.

Similarly, assays for IgE antibodies against cow milk (anti-cow milk IgE) will be performed once at Screening.

4.3.2 PK/PD Assays

Blood samples for PK/PD assays will be collected prior to administration of the study medication for the first acute HAE attack (named Presentation), one blood sample directly following infusion (at time 5 minutes) and another blood sample between 2-4 hours post-infusion (at time 2-4 hours). The samples will be analyzed for C1INH activity (PK) and C4 (PD). C4 is additionally analyzed at Presentation of each subsequent acute HAE attack.

For the first attack, the following PK parameters will be derived, where appropriate, for C1INH activity in plasma from the concentration-time data using standard noncompartmental procedures; C_{max} and AUC_{0-3}.

4.3.3 Immunogenicity

Immunology tests will be performed at Screening and for each attack at Presentation and follow-up visits Days 28 and 90 in accordance with the schedule of study events.

All patients will be tested using ELISA tests to detect for the presence of antibodies against:

- rhC1INH-specific IgG (IgG) [cut-off: >15%]
- rhC1INH-specific IgM (IgM) [cut-off: >50%]
- HRISPeluate-specific AB (HRI) [cut-off: >100%]

Plasma samples found to be above the respective cut-off level are deemed positive and are further analysed in a confirmatory displacement assay (to confirm the initial result and discriminate between specific and non-specific responses).

Three assays will be performed during the confirmatory displacement assay: displacement rAUCa, displacement rAUCb and displacement, %Difference. The value of "displacement, %Difference" is used to determine if a sample is confirmed positive for antibodies (i.e. specific antibodies are confirmed).

The following cut-off levels are used for the confirmatory displacement assay (results above cut-off are deemed positive):

- rhC1INH-specific IgG, displacement, %Difference [cut-off: ≥45% i.e. sample contains rhC1INH-specific IgG antibodies]
- rhC1INH-specific IgM, displacement, %Difference [cut-off: ≥40% i.e. sample contains rhC1INH-specific IgM antibodies]
- HRISPeluate-specific AB, displacement, %Difference [cut-off: ≥35% i.e. sample contains HRISPeluate-specific antibodies]

If specific antibodies are confirmed, a further test with a neutralizing antibody assay is performed. In other words, only samples which have been confirmed to have specific anti-rhC1INH IgG and IgM antibodies were then analyzed in the neutralizing C1INH antibody assay.

The following Neutralizing AB cut-off levels are used (results below cut-off are deemed positive):

- Neutralizing C1INH-specific AB (%) [cut-off: <64%]
- Neutralizing rhC1INH-specific AB (%) [cut-off: <54%]

Note: the original plasma sample and all corresponding confirmatory displacement and neutralizing AB assays will have the same requisition number in the QPS data file.

The anti-C1INH antibodies labels that will be used in all outputs are presented in Table 6.

Table 6 Antibody Labels

Antibodies	Label
Antibodies against rhC1INH-specific IgG	Anti-rhC1INH (IgG)
Antibodies against rhC1INH-specific IgM	Anti-rhC1INH (IgM)
Antibodies against HRISPeluate-specific AB	Anti-HRI
Neutralizing antibodies against C1INH-specific AB	Anti-C1INH NAb
Neutralizing antibodies against rhC1INH-specific AB	Anti-rhC1INH NAb

The actual values and whether these are above or below cut-off will be presented in the listings. Separate listings will be produced of the results of the screening ELISA and the results from the

displacement and neutralizing assays. The associated attack number and visit will be clearly shown for the results from the displacement and neutralizing assays.

4.3.4 Patient Disposition

The following data will also be presented:

- Date of Screening visit.
- Date of informed consent.
- Date and reason for withdrawal from the study, where applicable.

The analysis sets and subgroups defined in Section 3 will be analyzed and presented as part of the patient disposition data.

4.3.5 Protocol Violations

Protocol violations are defined as violations that might affect the efficacy or treatment of a patient, and lead to the exclusion of patients from the analysis sets defined in Section 3.

Protocol deviations are defined in a separate document produced by Pharming prior to database lock. Protocol deviations are determined programmatically by data management, manually during data review and identified by the monitors during site visits. All deviations identified will be added to an excel spreadsheet which shall be sent to Quanticate. Protocol violations which may lead to exclusion from the defined analysis sets will be indentified at the Data Review Meeting prior to database lock.

4.3.6 Demographics and Baseline Patient Characteristics

Patient demographic data was collected on the 'Demographics' CRF page at Screening visit, which comprised of date of birth, gender, Tanner Stage, height, weight and race.

Age (in years) will be calculated relative to the Screening Visit by means of the following algorithm:

Age (Years) = Visit_Y – Birth_Y – (0 < Visit_M < Birth_M OR (Visit_M = Birth_M AND 0 < Visit_D < Birth_D)), with variables as follows:

- Birth_Y = Year of birth.
- Birth_M = Month of birth.
- Birth_D = Day of birth.
- Visit_Y = Year of Screening visit.
- Visit_M = Month of Screening visit.
- Visit_D = Day of Screening visit.

Missing demography data will be handled according to the rules specified in Section 5.5.2.3.

4.3.7 Medical History

Medical history contains information about conditions that a patient might have suffered from prior to the first administration of study medication at Presentation, or conditions that were on-going at the time of the first administration of study medication.

Medical history, relevant HAE history and relevant HAE attack history were collected at Screening.

Each term recorded on the medical history page will be assessed to determine whether the event was a past or present condition at Screening. This will be taken directly from the tick box on the CRF.

4.3.7.1 Coding of Medical History Terms

The medical history term (Investigator term) is assigned to the LLT, and a PT will be classified by a SOC according to the MedDRA thesaurus, Version 18 or higher, depending on the latest version available during the study.

Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA.

The following coding data will be presented:

- LLT
- PT
- SOC

Coding of MH will be provided by data management at PSR in a coding spreadsheet alongside the coding of AEs and CMs. The MH coding data will be merged onto the raw MH data by Subject ID and MH number. The final version of this spreadsheet will be provided prior to database lock.

Medical history will be reported on a per-patient basis. This means that even if a patient suffered the same clinical event repeatedly (i.e., events mapped to the same PT) the event will be counted only once and the earliest date will be regarded as start date of the event and the latest date will be regarded as stop date of the event.

4.3.8 Concomitant Medications

Concomitant medications include all medications and procedures that a patient used at any stage during the study. Any medication started prior to Presentation with attack and used during the study, or medication started at any time after the first study medication administration, thus after Presentation, will be included.

Concomitant medications data was collected throughout the study on the 'Concomitant Medications' CRF page.

Missing concomitant medications data will be handled according to the rules specified in Section 5.5.2.4.

4.3.8.1 Coding of Concomitant Medication Terms

Concomitant medications are classified according to active drug substance using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Index 2015 or later.

The ATC code has 7 characters. The first character gives the anatomical main group (1st level), the first 3 characters give the therapeutic main group (2nd level), the first 4 characters give the therapeutic subgroup (3rd level), the first 5 characters give a further level therapeutic subgroup (4th level), whereas the 7 characters give the subgroup for the chemical substance. In this study, ATC codes are defined to the 4th level.

Although there can be multiple ATC classes for a drug, each drug will be linked with one ATC class which will be assigned manually during the coding process, based on information about the indication and route in relation to the study therapeutic area. This one ATC class will be indicated as the 'primary' ATC class, and only the primary class will be presented.

Coding of CMs will be provided by data management at PSR in a coding spread sheet alongside the coding of AEs and MH. The CM coding data will be merged onto the raw CM data using the variables "Subject ID" and "CM no.". The final version of this spreadsheet will be provided prior to database lock.

4.3.9 Treatment Compliance

As this study involves i.v. administration of the study medication administered by study personnel, patient compliance measures will not be reported (as detailed in Section 9.7 of the study protocol).

4.3.10 Intercurrent HAE attacks

Occurrence of intercurrent HAE-episodes will be recorded at Days 28 and 90 after the treated attack and at yearly follow up visits from the Screening visit thereafter.

5. Statistical Methodology

5.1 General Statistical Methods

5.1.1 General Information

All analysis data sets and output, with the exception of the PK/PD analyses and output, will be produced by the Biostatistics Department of Quanticate Ltd using the SAS® system Version 9.3 or higher.

5.1.2 Default Descriptive Statistics and Data Rules

Unless otherwise stated, summary statistics including the number of patients, mean, standard deviation (SD), median, minimum and maximum, will be presented for all continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the SD, to two more decimal places than the raw values.

For categorical variables, per category, the absolute counts (n) and percentages (%) of patients with data, and if appropriate, the number of patients with missing data, will be presented. All percentages will be presented to one decimal place.

For AEs reported on a per-patient basis, medical history and concomitant medications, the denominator for the percentage calculation will be the number of patients. A patient will be considered at risk if the patient is in the Safety/FAS analysis set.

5.2 Hypotheses and Decision Rules

No formal hypothesis testing will be conducted for this study.

5.3 Covariates

There will be no covariates included in analyses.

5.4 Multi-Centre Data

No analyses by center will be conducted.

5.5 Handling of Missing Data

5.5.1 Efficacy Endpoints

For the time to event efficacy endpoints, if there is insufficient data to ascertain whether a patient has had an event, it will be assumed that they have not had the event.

5.5.2 Safety Endpoints

5.5.2.1 Exposure

If the start of treatment date is missing, the latest possible time of all the pre-dose assessments, will be imputed as the start of treatment date.

5.5.2.2 Adverse Events

Missing and/or incomplete dates/times for AEs are imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking additionally into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is on-going. This will be done as follows:

For a missing/incomplete start date/time the minimum of the following will be imputed:

- The maximum of the earliest possible start date/time and the date/time of first study medication administration.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the maximum of the following will be imputed:

- The minimum of the latest possible stop date/time and the date/time of last study medication administration.
- The earliest possible stop date/time.
- The earliest possible start date/time.

The earliest (latest) possible date is defined as:

- The date itself if it is complete.
- The date of the first (last) day of the month, if month and year are available but day is missing.
- The date of the first (last) day of the year, if year is available but day and month are missing.
- A very early (late) date, e.g., 01JAN1000 00:00hrs (01JAN3000 23:59hrs), if the date is completely missing.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study medication.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, 'Severe' will be imputed. If causality data is missing, 'Related to study medication' will be imputed.

In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in summary tables.

5.5.2.3 Demographics

For determining age when the date of birth is not known completely, a missing day only will be imputed as the 15th, a missing day and month will be imputed as the 2nd of July which is day 183 in the year.

5.5.2.4 Concomitant Medications

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 5.5.2.2.

5.6 Interim Analyses

No Interim Analyses are planned for this study.

6. Statistical Analyses

6.1 Patient Disposition

Patient Disposition recorded at Screening will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data. This will be presented for the Screening Analysis Set and for the ITT Analysis Set.

6.2 Protocol Violations

Protocol Violations will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

6.3 Demographics and Baseline Patient Characteristics

Demographics include collected and derived, continuous and categorical variables. Continuous variables will be summarized by the number of patients, mean, SD, median, minimum and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data. This will be presented for the Screening Analysis Set, Safety Analysis Set, ITT Analysis Set and PP Analysis Set.

6.4 Medical History

Medical History will be summarized by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients. This will be presented for the Safety Analysis Set

Separate summaries will also be presented for Relevant HAE history and Relevant HAE Attack History.

6.5 Concomitant Medication

Concomitant Medications will be summarized by absolute counts (n) and percentages (%) for each PT within ATC class. Percentages will be calculated based on the number of patients at risk. This will be presented for the Safety Analysis Set

6.6 Treatment Compliance

Not applicable as per Section 4.3.9.

6.7 Efficacy Analyses

The efficacy endpoints will include collected and derived continuous and categorical variables. Continuous variables will be summarized by the number of patients, mean, SD, median, minimum and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

The ITT Analysis Set will be the primary analysis set of interest in all efficacy analyses, and the primary and secondary efficacy analysis will be repeated on the PP Analyses set. Individual patient listings will be presented for all efficacy data. Data will be summarized by attack, e.g. First attack, second attack, etc.

6.7.1 VAS

Descriptive statistics for the Overall VAS score and change from Baseline will be presented for each time point for the primary attack location first, followed by each anatomical location separately.

6.7.2 TEQ

Descriptive statistics for the TEQ responses will be presented for each time point for the primary attack location first, followed by each anatomical location separately.

6.7.3 Investigator Symptom Score

Descriptive statistics for the IS score will be presented for each time point for the primary attack location first, followed by each anatomical location separately.

6.7.4 Time to Event Analysis

Kaplan-Meier (KM) analyses will be performed for each of the time to event endpoints (time to beginning of relief and time to minimal symptoms defined using Overall VAS, IS and TEQ, and time to complete resolution). For patients who have been treated for more than one attack, KM analyses for time to beginning of relief and time to minimal symptoms using the Overall VAS score will be repeated for first and last attacks.

Patients who did not have the event of interest will be censored at their last available assessment of that endpoint. For VAS endpoints, in most cases the last available assessment will be at 24 hours post infusion, for IS endpoints it will be 4 hours post infusion.

Additionally, for each endpoint the number and percentage of patients with the event will be presented, along with estimates of the median and quartile time to events with 95% confidence intervals.

6.7.5 Therapeutic Failure

The number and percentage of patients who experienced therapeutic failure for each attack will be presented alongside a categorical summary of the reasons for failure. A bar chart will also be presented for both first and last attack only.

6.7.6 Receipt of a Second Dose

The number of patients who received a second dose will be summarized using counts and percentages. The Baseline Overall VAS score at the primary attack location, split by attacks treated with a second dose and those that were treated with a single dose, will be summarized using summary statistics.

This will be presented by attack number. In addition, a total column will be presented summarizing all attacks. If a patient has more than one attack they will be included multiple times in this column.

Finally the summary will present the number of patients who had received two doses of rhC1INH for any of their attacks.

6.8 Safety Analyses

Unless otherwise stated, safety data will be presented for the Safety Analysis set. Individual patient listings will be presented for all safety data. Where applicable, data will be summarized by attack, e.g. First attack, second attack, etc.

6.8.1 Exposure to Study Medication

Exposure to Study Medication will include derived continuous and categorical variables. Continuous variables will be summarized by the number of patients, mean, SD, median, minimum and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

Exposure to rhC1INH will be summarized by attack, for both initial and second doses. The following variables will be summarized:

- Total volume of medication administered (mL)
- Total Dose in U/kg (patients who weighed less than 84 kg)
- Total Dose in U/kg (patients who weighed more than or equal to 84 kg)
- Duration of Infusion in minutes (only summarized for Attack 1)

In addition, within the same summary, “Time interval between initial and repeat dose (minutes)” will be summarized under the subtitle “Overall”.
Total exposure will also be summarized across the whole study (i.e. not by attack). In particular the total number of HAE attacks treated with rhC1INH, the total number of rhC1INH doses received and the total dose of rhC1INH will be summarized over all attacks.

The total number HAE attacks treated with rhC1INH and total number of doses of rhC1INH received will be summarized as categorical variables and as continuous variables.

6.8.2 Adverse Events

AEs will be recorded throughout the study. These will be coded using the MedDRA dictionary, version 18.0 or later. Tables will only summarize TEAEs; all AEs will be listed.

TEAEs will be summarized using absolute counts (n) and percentages (%). Summaries will be presented by SOC and PT. Results will be sorted by decreasing frequency of the SOC and PT within the SOC.

AE tables will be presented by attack for the Safety Analysis Set. A separate column will be included summarizing AEs reported regardless of attack number. For the overall column, percentages will be presented out of the total number of patients in the Safety Analysis Set and counting will be by patient, so if a patient has the same AE in more than one attack this will only be counted once in the overall column.

The following tables will be produced:

- Overall summary of Adverse Events
- Incidence of Treatment-Emergent Adverse Events
- Incidence of Related Treatment-Emergent Adverse Events
- Incidence of Treatment-Emergent Adverse Events Commencing Within 24 Hours of the Completion of the Infusion of Study Drug Administration
- Incidence of Treatment-Emergent Adverse Events Commencing Within 28 Days of the Completion of the Infusion of Study Drug Administration
- Incidence of Treatment-Emergent Adverse Events by Strongest Relationship (Investigator's Judgment)
- Incidence of Treatment-Emergent Adverse Events by Maximum Severity (Investigator's Judgment)
- Incidence of Treatment-Emergent Serious Adverse Events
- Incidence of Treatment-Emergent Adverse Events Leading to Study Discontinuation
- Incidence of Treatment-Emergent Adverse Events of Special Interest

The Summary of Adverse Events table will be presented by attack and will show the following:

- Number (%) of Deaths
- Number (%) of Treatment-Emergent Deaths
- Number (%) of Subjects With At Least One SAE
- Number (%) of Subjects With At Least One TESAE
- Number (%) of Subjects Who Prematurely Discontinued the Study Due to a TEAE
- Number (%) of Subjects With At Least One TEAE
- Number (%) of Subjects With At Least One Related TEAE
- Number (%) of Subjects Without Any TEAEs

All AEs will be listed. Listings will include CRF collected data, coded terms (primary SOC and PT) and a flag for treatment emergence. The time from last administration of study drug to onset of an AE (hours) will be listed for TEAEs. Separate listings will be produced for any SAEs and any AEs leading to study discontinuation.

6.8.3 Clinical Laboratory Parameters

Clinical Laboratory Parameters include collected and derived quantitative and qualitative parameters. Parameters will be grouped by category (see Table 5 in Section 4.2.3) Quantitative parameters will be summarized by the number of patients, mean, SD, median, minimum and maximum values. Qualitative parameters will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

For each attack, data will be summarized by study visit, and the change from Baseline to Day 28 (if visit occurred before the next treatment) will be presented. Frequency distributions of the status (below, within and above the normal range will be presented by study visit, for each attack. A shift table of status at Baseline and Day 28 (if visit occurred before the next treatment) will be presented for each attack.

6.8.4 Electrocardiogram (ECG) Parameters

ECG Parameters include collected and derived qualitative parameters. Qualitative parameters will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

6.8.5 Vital Signs

Vital Signs include collected and derived continuous and categorical variables. Continuous variables will be summarized by the number of patients, mean, SD, median, minimum and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of patients with data.

6.8.6 Physical Examination

Routine physical examination results will be listed for individual patients.

6.8.7 HAE attacks

Individual patient listings will be presented for the date and location of HAE attacks.

6.8.8 Immunogenicity

Descriptive statistics will be presented at each assessment time, by attack. In addition, summaries will be presented for anti-rhC1INH IgG, anti-rhC1INH IgM and anti-HRI, by attack, for Presentation, Day 28 and Day 90 for the following categories:

- Initial assay “below cut-off”
- Initial assay “above cut-off” but confirmatory assay missing
- Confirmatory assay did not confirm initial result
- Confirmatory assay confirmed initial result

The total number of patients assessed for each antibody will also be summarized by attack and timepoint. Confirmatory assays here include displacement assays for anti-rhC1INH IgG, anti-rhC1INH IgM and anti-HRI and the neutralizing assays for anti-C1INH and anti-rhC1INH.

Separate listings will be produced for the initial assay results and for the confirmatory assay results. Those patients with a confirmed positive result will be highlighted in two further listings (again one for initial and one for confirmatory).

6.9 Other Analyses

6.9.1 Diagnostic Assays and IgE Testing

Descriptive statistics will be presented for the Safety Analysis Set. In particular, a summary will be presented of C1INH, C1q and C4 at Screening and separately of C4 at Presentation.

A shift table of anti-rabbit epithelium IgE results will be presented to indicate the change from Screening to Day 28 of each attack. A negative test for anti-rabbit epithelium has a cut off of <0.35 kU/L and so the shift table will summarize the categories (“Below or equal to 0.35 kU/L” and “Above 0.35 kU/L”).

All individual patient diagnostic and IgE assay results will also be listed.

All values below the limit of quantification (BLQ) for C1INH, C1q and C4 will be set to half the value of the lower limit of quantification (LLQ) for calculation of summary statistics. Similarly, all IgE results BLQ will be set to half the value of LLQ for categorization used in the shift table.

However, in the listings all BLQ values will be reported as "<LLQ", where LLQ will be replaced with the corresponding value for the LLQ of the parameter.

6.9.2 PK and PD Assays

A series of blood plasma samples will be taken for the analysis of C1INH and C4 activity at the following time points relative to a patient's first attack and dosing: Presentation, 5 minutes and 2-4 hours (post-dose). Additionally, for the first attack, PK parameters will be calculated and presented for C1INH activity.

6.9.2.1 PK and PD Concentrations

To assess the single dose PK and PD profiles, PK and PD concentrations will be listed, summarized and plotted for patients in the PK/PD Concentration Set, where missing and BLQ values will be handled as detailed in Section 6.9.2.1.1.

Functional C1INH (PK) concentrations will be in units of % of Normal (i.e. results are expressed as a percent based on a pool of plasma collected from healthy volunteers, which was original set at 100%) whereas C4 concentrations will be in units of µg/mL.

The Baseline concentration is defined as the concentration taken at Presentation.

Summaries and figures will include:

- Listing of all PK and PD concentrations sorted by, patient ID and nominal time post-dose. The listings of concentrations will include the actual sample collection times, the time of dosing and deviations from the nominal time.
- A summary of concentrations by nominal time post-dose, where the set of statistics will include n, mean, geometric mean, median, SD, coefficient of variation (CV) Geometric CV, minimum, maximum and the number of concentrations above the LLQ.
- Boxplots of concentrations paneled by nominal time, presented separately on linear and logarithmic scales.
- Boxplots of concentrations grouped by weight and paneled by nominal time, presented separately on linear and logarithmic scales.
- The ratio (2-4 hours:Baseline) in C4 versus the ratio (2-4 hours:Baseline) in Functional C1INH.

The subgroups for weight for the boxplots of concentrations will be:

1) Weight ≤ 30kg

2) 30kg > Weight ≥ 60kg

3) 60kg > Weight ≥ 84kg

4) Weight > 84kg

Paneling by weight will only be performed if there are a sufficient number of patients in each subgroup.

The range for the x-axes of these plots will be decided on review of the data, and will depend on how long the concentration is quantifiable in the matrix.

For summary statistics and boxplots by sampling time, the nominal PK/PD sampling time will be used.

6.9.2.1.1 Deviations, missing concentrations and anomalous values

In all PK and PD summary tables and plots, plasma concentrations will set to missing if one of the following cases is true:

1. A concentration has been collected as not done (ND) or no sample (NS);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist. These deviations will be defined at the Data Review Meeting.

Note: summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

All concentrations BLQ will be set to half the value of the LLQ for calculation of concentration summary statistics. However, in the listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the corresponding value for the LLQ.

6.9.2.2 PK Parameters

The following PK parameters will be derived, where appropriate, from the PK and PD Analysis Set of plasma concentration-time C1INH data using non-compartmental procedures.

Table 7 defines the PK parameters which will be calculated in this study.

Table 7 PK Parameter Definitions

Parameter	Definition
C_{max}	Peak concentration of C1INH.
AUC_{0-3}	Area under the plasma concentration-time curve from Presentation to 3 hours post-infusion.

Table 7 refers to the timepoint 3 hours for AUC_{0-3}. This is identical to the timepoint 2-4 hours in Table 2: Study Visits. In all summaries the 2-4 hours label will be used rather than 3 hours.

Actual PK and PD sampling times will be used in the derivation of PK parameters and will be calculated as follows:

All concentrations BLQ will be set to half the value of the LLQ for calculation of PK parameters.

AUC(0-3) will be calculated using the linear-up log-down trapezoidal method.

C_{max} will be calculated by taking the maximum C1INH concentration for a patients first attack. It will only be calculated if there are three measurements for all three time points.

If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (i.e. not calculated). Note: NC values will not be generated beyond the time that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented if more than 50% of the data are NC.

If an individual patient has a known biased estimate of a PK parameter (e.g. due to an unexpected event), this will be footnoted in the summary tables and will not be included in the calculation of summary statistics. Biased estimates will be identified and listed during the Data Review Meeting alongside a review of the protocol deviations prior to database lock.

The summary of PK parameters will include the following statistics: n, mean, geometric mean, median, SD, coefficient of variation (CV) Geometric CV, minimum and maximum.

7. Changes to the Planned Analyses

7.1 Changes to the Analyses Described in the Study Protocol and Protocol Amendments

Due to an inadequate number of sampling time points; the only PK parameters calculated will be AUC_{0-3} and C_{max}. See Section 7.3 for further details.

7.2 Changes from the Statistical Analysis Plan Version 1.0.0

Clarification regarding the review of diary data for completion of the Day 28 CRF was made in Section 2.2. Section 6.8.6 was added to describe collection of routine physical examination data. Re-numbering of outputs in Attachment 1 was performed to bring tables, listings and figures in line with ICH E3 reporting guidelines. No changes were made to planned analyses.

7.3 Changes from the Statistical Analysis Plan Version 2.0.0

- The following updates were made to Version 2.0.0. of the SAP:
- Section 3.7 concerning analysis of subgroups was removed.
- Section 4.1 was updated throughout to give further detail on efficacy measures and ensure there are precise instructions for analysis.
- Section 4.2.1 had further detail added to clarify how certain exposure measures will be calculated.

- Section 4.2.2 was updated to better describe definitions of TEAEs and how AEs will be coded. Clarification was also given for how AEs should be linked to attacks.
- Section 4.2.3 was updated to clarify how lab measurements will be converted to standard units.
- Section 4.3.1 Was updated to include details of IgE testing.
- Section 4.3.2 was updated to highlight that AUC(0-3) and Cmax will be the only PK parameters calculated.
- Section 4.3.3 was updated with a more detailed description of the immunogenicity study procedures.
- Section 4.3.5 was updated to better reflect the determination of protocol violations. A list of inclusion and exclusion criteria was removed from this section.
- Section 4.3.7.1 and 4.3.8.1 were updated to reflect how medical history and concomitant medications will be coded.
- Section 4.3.10 was added to give details of intercurrent HAE attacks.
- Section 6.7.1, 6.7.2 and 6.7.3 were updated to indicate that the relevant summaries will be by primary attack first, and then by anatomical location.
- Section 6.7.5 was updated to better reflect the output it describes.
- Section 6.7.6 was added to give details of a summary of those patients who receive a second dose of study medication.
- Section 6.8.1 was updated to better reflect the output it originally described and to include description of an additional output "Total Exposure to rhC1INH".
- Section 6.8.2 was updated to describe in more detail the AE related summaries including the addition of three new tables.
- Section 6.8.8 was updated to better describe immunogenicity related outputs.
- Section 6.9.1 was updated to include description of a new shift table of IgE.
- Section 6.9.2 was updated with more detail and to reflect the change in the output summaries to be produced.
- The following tables were removed from the list of tables, listings and figures:
    - Summary of PK/PD Concentrations
    - Summary of PK/PD Parameters
- The following tables were added to the list of tables, listings and figures:
    - Receipt of a Second Dose of rhC1INH
    - Functional C1INH (% of Normal) Over Time
    - Functional C1INH (% of Normal) Cmax and AUC(0-3) Parameters
    - C4 Concentrations Over Time
    - Incidence of Related Treatment-Emergent Adverse Events
    - Incidence of Treatment-Emergent Adverse Events Commencing Within 24 Hours of the Completion of the Infusion of Study Drug Administration
    - Incidence of Treatment-Emergent Adverse Events Commencing Within 28 Days of the Completion of the Infusion of Study Drug Administration
    - Change in Status of Hematology Laboratory Parameters Based on Laboratory Reference Ranges from Presentation of Attack to Day 28
    - Change in Status of Biochemistry Laboratory Parameters Based on Laboratory Reference Ranges from Presentation of Attack to Day 28
    - Total exposure to rhC1INH
    - Shift Table of IGE
- The following listings were removed from the list of tables, listings, and figures:
    - Listing of Immunogenicity Data
- The following listings were added to the list of tables, listings and figures:
    - Initial ELISA Immunology Results
    - Neutralizing and Displacement Assay Immunology Results
    - Initial ELISA Immunology Results – Patients with a Confirmed Positive Result

    - Neutralizing and Displacement Assay Immunology Results – Patients with a Confirmed Positive Result
- The following figures were removed from the list of tables, listings and figures:
    - Bar Chart of IS Score by Time, Attack Number and Attack Location
    - Median PK/PD Concentrations (Linear Scale)
    - Median PK/PD Concentrations (Logarithmic Scale)
    - PK/PD Concentrations by Patient (Linear Scale)
    - PK/PD Concentrations by Patient (Logarithmic Scale)
- The following figures were added to the list of tables, listings and figures:
    - Boxplot of Functional C1INH (% of Normal) paneled by Time (Linear Scale)
    - Boxplot of Functional C1INH (% of Normal) paneled by Time (Logarithmic Scale)
    - Boxplot of Functional C1INH (% of Normal) grouped by Weight and paneled by Time (Linear Scale)
    - Boxplot of Functional C1INH (% of Normal) grouped by Weight and paneled by Time (Logarithmic Scale)
    - Boxplot of C4 Concentrations paneled by Time (Linear Scale)
    - Boxplot of C4 Concentrations paneled by Time (Logarithmic Scale)
    - Boxplot of C4 Concentrations grouped by Weight and paneled by Time (Linear Scale)
    - Boxplot of C4 Concentrations grouped by Weight and paneled by Time (Logarithmic Scale)
    - Ratio with respect to Baseline in C4 versus Ratio with respect to Baseline in Functional C1INH

7.4 Changes from the Statistical Analysis Plan Version 3.0.0

- The definition of eligible location was updated to be based on the IS score as per protocol rather than Overall VAS score.
- The definition of Therapeutic Failure was updated to be consistent with that of Disallowed Medication in Section 4.1.1.6.
- The definition of how to deal with values below the lower limit of quantification for diagnostic parameters, IM, PK and PD concentrations was updated.
- It was clarified that time to event results censored before exposure to treatment due to Disallowed Medication would be censored at 0 minutes.

7.5 Changes from the Statistical Analysis Plan Version 4.0.0

No changes will be made to Version 4.0.0 of the SAP after database lock. Any changes to the planned analyses occurring after database lock will be described and justified in the Clinical Study Report (CSR).

7.6 Attachments and Appendices

Appendix 1 Clinical Laboratory Evaluations

Laboratory Unit Conversion

All laboratory results will be standardized to Système International (S.I) units at the time of analysis. Laboratory unit conversion factors will be provided by data management at the time of data transfer as a separate spreadsheet that will be formatted and imported into SAS. A final spreadsheet will be provided prior to database lock.

Laboratory reference ranges

Abnormal laboratory results will be classified at the time of analysis as being 'Low' or 'High' depending on whether the result is below or above the reference range limits. Individual reference ranges are assigned based on the center, age and gender of the patient and will be provided by the analyzing laboratory. The individual reference ranges will be provided by data management at the time of data transfer as a separate spreadsheet that will be formatted and imported into SAS. A final spreadsheet will be provided prior to database lock.

Database Specifications

A spreadsheet containing definitions and specification of all collected study parameters has also been provided by data management.

Attachment 1 List of Tables, Listings and Figures

Table Number	Title	Analysis Set	Repeat
Table 14.1.1.1	Summary of Patient Disposition	Screening	Unique
Table 14.1.1.2	Summary of Patient Disposition	ITT	Repeat of 14.1.1.1
Table 14.1.2	Summary of Analysis Sets	All patients	Unique
Table 14.1.3	Summary of Protocol Violations	Safety	Unique
Table 14.1.4.1	Summary of Demographics and Baseline Patient Characteristics	Screening	Unique
Table 14.1.4.2	Summary of Demographics and Baseline Patient Characteristics	Safety	Repeat of 14.1.4.1
Table 14.1.4.3	Summary of Demographics and Baseline Patient Characteristics	ITT	Repeat of 14.1.4.1
Table 14.1.4.4	Summary of Demographics and Baseline Patient Characteristics	PP	Repeat of 14.1.4.1
Table 14.1.5	Summary of Medical History	Safety	Unique
Table 14.1.6	Summary of Relevant HAE History	Safety	Unique
Table 14.1.7	Summary of Relevant HAE Attack History	Safety	Unique
Table 14.1.8	Summary of Concomitant Medication	Safety	Unique
Table 14.2.1.1.1	Summary of Overall VAS Score by Time and Attack	ITT	Unique
Table 14.2.1.1.2	Summary of Overall VAS Score by Time and Attack	PP	Repeat of 14.2.1.1.1
Table 14.2.1.2.1	Summary of Change in Overall VAS Score from Baseline by Time and Attack	ITT	Repeat of 14.2.1.1.1
Table 14.2.1.2.2	Summary of Change in Overall VAS Score from Baseline in VAS by Time and Attack	PP	Repeat of 14.2.1.1.1
Table 14.2.1.3.1	Summary of TEQ by Time and Attack	ITT	Unique
Table 14.2.1.3.2	Summary of TEQ by Time and Attack	PP	Repeat of 14.2.1.3.1
Table 14.2.1.4.1	Summary of Investigator Symptom Score by Time and Attack	ITT	Unique
Table 14.2.1.4.2	Summary of Investigator Symptom Score by Time and Attack	PP	Repeat of 14.2.1.4.1
Table 14.2.1.5.1	Time to Beginning of Relief (VAS, IS and TEQ)	ITT	Unique
Table 14.2.1.5.2	Time to Beginning of Relief (VAS, IS and TEQ)	PP	Repeat of 14.2.1.5.1
Table 14.2.1.6.1	Time to Minimal Symptoms (VAS, IS and TEQ)	ITT	Repeat of 14.2.1.5.1
Table 14.2.1.6.2	Time to Minimal Symptoms (VAS, IS and TEQ)	PP	Repeat of 14.2.1.5.1
Table 14.2.1.7.1	Time to Complete Resolution (Diary)	ITT	Repeat of 14.2.1.5.1
Table 14.2.1.7.2	Time to Complete Resolution (Diary)	PP	Repeat of 14.2.1.5.1
Table 14.2.1.8.1	Summary of Therapeutic Failure	ITT	Unique
Table 14.2.1.8.2	Summary of Therapeutic Failure	PP	Repeat of 14.2.1.8.1
Table 14.2.1.9	Receipt of a Second Dose of rhC1INH	ITT	Unique
Table 14.2.2.1.1	Functional C1INH (% of Normal) Over Time	PK/PD Concentration Set	Unique
Table 14.2.2.1.2	Functional C1INH (% of Normal) Cmax and AUC(0-3) Parameters	PK/PD Analysis Set	Unique
Table 14.2.2.2	C4 Concentrations Over Time	PK/PD	Unique

Table Number	Title	Analysis Set	Repeat
		Concentration Set	
Table 14.3.1.1	Summary of Adverse Events	Safety	Unique
Table 14.3.1.2.1	Incidence of Treatment-Emergent Adverse Events	Safety	Unique
Table 14.3.1.2.2	Incidence of Related Treatment-Emergent Adverse Events	Safety	Repeat of 14.3.1.2.1
Table 14.3.1.2.3	Incidence of Treatment-Emergent Adverse Events Commencing Within 24 Hours of the Completion of the Infusion of Study Drug Administration	Safety	Repeat of 14.3.1.2.1
Table 14.3.1.2.4	Incidence of Treatment-Emergent Adverse Events Commencing Within 28 Days of the Completion of the Infusion of Study Drug Administration	Safety	Repeat of 14.3.1.2.1
Table 14.3.1.2.5	Incidence of Treatment-Emergent Adverse Events by Strongest Relationship (Investigator's Judgment)	Safety	Unique
Table 14.3.1.2.6	Incidence of Treatment-Emergent Adverse Events by Maximum Severity (Investigator's Judgment)	Safety	Unique
Table 14.3.2.1	Incidence of Treatment-Emergent Serious Adverse Events	Safety	Unique
Table 14.3.2.2	Incidence of Treatment-Emergent Adverse Events Leading to Study Discontinuation	Safety	Repeat of 14.3.2.1
Table 14.3.2.3	Incidence of Treatment-Emergent Adverse Events of Special Interest	Safety	Repeat of 14.3.2.1
Table 14.3.4.1.1	Summary of Quantitative Laboratory Parameters	Safety	Unique
Table 14.3.4.1.2	Summary of Change in Quantitative Laboratory Parameters from Presentation of Attack to Day 28	Safety	Repeat of 14.3.4.1.1
Table 14.3.4.1.3	Summary of Quantitative Laboratory Parameter Classifications Based on Laboratory Reference Ranges	Safety	Unique
Table 14.3.4.1.4	Change in Status of Hematology Laboratory Parameters Based on Laboratory Reference Ranges from Presentation of Attack to Day 28	Safety	Unique
Table 14.3.4.1.5	Change in Status of Biochemistry Laboratory Parameters Based on Laboratory Reference Ranges from Presentation of Attack to Day 28	Safety	Unique
Table 14.3.4.1.6	Incidence of Clinically Significant Quantitative Laboratory Parameters	Safety	Unique
Table 14.3.4.1.7	Change in Status of Quantitative Laboratory Parameters According to Clinical Significance from Presentation of Attack to Day 28	Safety	Unique
Table 14.3.4.2.1	Summary of Exposure to Study Medication	Safety	Unique
Table 14.3.4.2.2	Total exposure to rhC1INH	Safety	Unique
Table 14.3.4.3.1	Incidence of Clinically Significant ECG Parameters	Safety	Unique
Table 14.3.4.3.2	Change in Status of ECG Parameters from Presentation of Attack to Post-infusion	Safety	Unique
Table 14.3.4.4	Summary of Vital Signs	Safety	Unique
Table 14.3.4.5.1	Summary of Anti-C1INH and Anti-HRI Immunology Parameters Over Time	Safety	Unique
Table 14.3.4.5.2	Summary of Anti-C1INH and Anti-HRI Immunology Displacement and Neutralizing Antibody Assay Results Over Time	Safety	Unique
Table 14.3.4.6.1	Summary of Diagnostic Parameters at Screening	Safety	Unique
Table 14.3.4.6.2	Summary of Diagnostic Parameters at Presentation of Attack	Safety	Unique
Table 14.3.4.7	Shift Table of IGE	Safety	Unique

Table Number	Title	Analysis Set	Repeat
Listing 16.2.1	Listing of Patient Disposition	All Patients	Unique
Listing 16.2.2	Listing of Protocol Violations	All Patients	Unique
Listing 16.2.3	Patients Excluded from the Efficacy Analysis	All Patients	Unique
Listing 16.2.4.1	Listing of Demographics and Baseline Patient Characteristics	All Patients	Unique
Listing 16.2.4.2	Listing of Medical History	All Patients	Unique
Listing 16.2.4.3	Listing of Relevant HAE history	All Patients	Unique
Listing 16.2.4.4	Listing of Relevant HAE attack history	All Patients	Unique
Listing 16.2.4.5	Listing of Concomitant Medications	All Patients	Unique
Listing 16.2.5.1	Listing of Study Medication Administration	All Patients	Unique
Listing 16.2.6.1.1	Listing of VAS and change from Baseline in VAS	All Patients	Unique
Listing 16.2.6.1.2	Listing of TEQ	All Patients	Unique
Listing 16.2.6.1.3	Listing of Investigator Symptom Score (IS)	All Patients	Unique
Listing 16.2.6.1.4	Listing of time to event endpoints and therapeutic failure	All Patients	Unique
Listing 16.2.6.2.1	Listing of PK/PD concentrations	All Patients	Unique
Listing 16.2.7.1	Listing of Adverse Events	All Patients	Unique
Listing 16.2.7.2	Listing of Serious Adverse Events	All Patients	Unique
Listing 16.2.7.3	Listing of Adverse Events Leading to Discontinuation from Study	All Patients	Unique
Listing 16.2.8.1	Listing of Clinical Laboratory Parameters	All Patients	Unique
Listing 16.2.8.2	Listing of ECG Parameters	All Patients	Unique
Listing 16.2.8.3	Listing of Vital Signs	All Patients	Unique
Listing 16.2.8.4	Listing of Physical Examination	All Patients	Unique
Listing 16.2.8.5	Listing of HAE Attacks	All Patients	Unique
Listing 16.2.8.6.1	Initial ELISA Immunology Results	All Patients	Unique
Listing 16.2.8.6.2	Neutralizing and Displacement Assay Immunology Results	All Patients	Unique
Listing 16.2.8.6.3	Initial ELISA Immunology Results – Patients with a Confirmed Positive Result	All Patients	Unique
Listing 16.2.8.6.4	Neutralizing and Displacement Assay Immunology Results – Patients with a Confirmed Positive Result	All Patients	Unique
Listing 16.2.8.7	Listing of Diagnostic Parameters	All Patients	Unique
Figure 14.2.1.1.1	Kaplan Meier Plot of Time to Beginning of Relief for First Attack (VAS)	ITT	Unique
Figure 14.2.1.1.2	Kaplan Meier Plot of Time to Beginning of Relief for Last Attack (VAS)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.2.1	Kaplan Meier Plot of Time to Minimal Symptoms for First Attack (VAS)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.2.2	Kaplan Meier Plot of Time to Minimal Symptoms for Last Attack (VAS)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.3	Kaplan Meier Plot of Time to Beginning of Relief (IS)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.4	Kaplan Meier Plot of Time to Minimal Symptoms (IS)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.5	Kaplan Meier Plot of Time to Beginning of Relief (TEQ)	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.6	Kaplan Meier Plot of Time to Minimal Symptoms	ITT	Repeat of

Table Number	Title	Analysis Set	Repeat
	(TEQ)		Figure 14.2.1.1.1
Figure 14.2.1.7	Kaplan Meier Plot of Time to Complete Resolution	ITT	Repeat of Figure 14.2.1.1.1
Figure 14.2.1.8.1	Bar Chart of Therapeutic Failure for First Attack	ITT	Unique
Figure 14.2.1.8.2	Bar Chart of Therapeutic Failure for Last Attack	ITT	Repeat of Figure 14.2.1.9.1
Figure 14.2.2.1.1	Boxplot of Functional C1INH (% of Normal) paneled by Time (Linear Scale)	PK/PD Concentration Set	Unique
Figure 14.2.2.1.2	Boxplot of Functional C1INH (% of Normal) paneled by Time (Logarithmic Scale)	PK/PD Concentration Set	Repeat of Figure 14.2.2.1.1
Figure 14.2.2.1.3	Boxplot of Functional C1INH (% of Normal) grouped by Weight and paneled by Time (Linear Scale)	PK/PD Concentration Set	Unique
Figure 14.2.2.1.4	Boxplot of Functional C1INH (% of Normal) grouped by Weight and paneled by Time (Logarithmic Scale)	PK/PD Concentration Set	Repeat of Figure 14.2.2.1.3
Figure 14.2.2.2.1	Boxplot of C4 Concentrations paneled by Time (Linear Scale)	PK/PD Concentration Set	Unique
Figure 14.2.2.2.2	Boxplot of C4 Concentrations paneled by Time (Logarithmic Scale)	PK/PD Concentration Set	Repeat of Figure 14.2.2.2.1
Figure 14.2.2.2.3	Boxplot of C4 Concentrations grouped by Weight and paneled by Time (Linear Scale)	PK/PD Concentration Set	Unique
Figure 14.2.2.2.4	Boxplot of C4 Concentrations grouped by Weight and paneled by Time (Logarithmic Scale)	PK/PD Concentration Set	Repeat of Figure 14.2.2.2.3
Figure 14.2.3	Ratio with respect to Baseline in C4 versus Ratio with respect to Baseline in Functional C1INH	PK/PD Concentration Set	Unique

SOP Deviation

Quanticate
The Clinical Data Experts

Deviation Information	
Deviation Raised by:	[redacted]
Date:	21DEC2017
Deviation ID:	No. 9

SOP(s) Requiring a Deviation		
SOP Number or Attachment Number:	Version Number:	Title of SOP or Attachment:
BIO-SOP-002	Version 5.0 R2	Statistical Analysis Plans
GEN-SOP-004	Version 5.0 R2	Document Management and Version Control

Project(s) Affected	
Customer Name:	Quanticate Project Number(s):
Pharming Group NV, The Netherlands	Q_003/Q_02119

Reason(s) for Deviation
Reason(s): (including any potential risk or impact)
SAP v3.1.0 was created and sent to Pharming on 17OCT17. The SAP v3.1.0 was considered as final by Pharming however v4.0.0 was never created by Quanticate. Hence no final version of the SAP post v3.1.0 was ever signed off as complete. As the analysis of the study has now been finalised Pharming wish to sign off the SAP v3.1.0 dated 17OCT17 without creating an additional v4.0.0 with new date 20DEC2017. Hence it has been decided to consider SAP v3.1.0 dated 17OCT17 as final for the study; SAP v3.1.0 was created before the study analyses hence no changes to the SAP have been made post-analysis. The final version of the SAP will be saved as a PDF named 'Statistical Analysis Plan V3.1.0 FINAL' and will include a signed copy of this SOP Deviation form attached to it. There are hence no risks to the study associated with this SOP deviation and hence the deviation will not impact anything including the CSR.

Approvals			
Name of Author:	[redacted]		
Position of Author:	Technical Point of Contact (Senior Statistician)		
Signature of Author:	[redacted]	Date:	21/12/2017
Name of QA Approver:	[redacted]		
Position of QA Approver:	Senior Director of Quality Assurance		
Signature of QA Approver:	[redacted]	Date:	21/12/17
Name of Pharming Approver:	[redacted]		
Position of Pharming Approver:	Medical Director		
Signature of Pharming Approver:	[redacted]		