STATISTICAL ANALYSIS PLAN

PROTOCOL: 0624-209

A PHASE 3, OPEN-LABEL, SINGLE-PERIOD STUDY TO EVALUATE THE SAFETY AND TREATMENT EFFECT OF INTRAVENOUS ADMINISTRATION OF CINRYZE® (C1 INHIBITOR [HUMAN]) FOR THE PREVENTION OF ANGIOEDEMA ATTACKS AND TREATMENT OF BREAKTHROUGH ATTACKS IN JAPANESE SUBJECTS WITH HEREDITARY ANGIOEDEMA (HAE)

AUTHOR: PPD

VERSION NUMBER AND DATE: V1.0, 21JUL2017

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Author:	PPD	Version Number:	1.0
		Version Date:	21Jul2017

Template No: CS_TP_BS016 Revision 4
Effective Date: 01Apr2016

Reference: CS_WI_BS005

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 21Jul2017) for Protocol 0624-209.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Document:	C:\Users\yotang\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.Outlook\OA8QTNP9\Shire_0624_209_SAP_v1 0.docx		
Author:	PPD	Version Number:	1.0
		Version Date:	21Jul2017

Template No: CS_TP_BS016 Revision 4   Reference: CS_WI_BS005
Effective Date: 01Apr2016

STATISTICAL ANALYSIS PLAN

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VERSION NUMBER AND DATE: V1.0, 21JUL2017

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Statistical Analysis Plan V1.0 (Dated 21Jul2017) for Protocol 0624-209.

	Name	Signature	Date
Author:	PPD	PPD	PPD
Position:	PPD		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	21JUL2017	PPD	Not Applicable – First Version

Document: \\SW20RND01\VistaTempDir\Temp28232\Shire_0624_209_SAP_v1 0.docx
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AE-QoL	Angioedema Quality of Life
ATC	Anatomical Therapeutic Classification
ECG	electrocardiogram
C1-INH	C1 esterase inhibitor or C1 inhibitor
CI	confidence interval
eCRF	electronic case report form
HAE	hereditary angioedema
HR	heart rate
ITT-S	intent-to-treat safety
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NNA	normalized number of angioedema attacks
PCI	potentially clinically important
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
SAP	Statistical Analysis Plan
SOC	system organ class
VAS	visual analogue scale

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and angioedema quality of life (AE-QoL) parameters as described in the final study protocol Amendment 5 dated 30 August 2016. Specifications for tables, figures, and listings are also contained in this document.

1.1. BACKGROUND

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by an inherited or spontaneous gene mutation on chromosome 11 that results in a quantitative or functional deficiency of C1 inhibitor (C1-INH) protein (Bernstein 2011). Patients with HAE are susceptible to recurrent episodes of debilitating swelling throughout the body. Replacement of C1-INH through intravenous (IV) administration of CINRYZE® (C1 inhibitor [human]) increases serum concentrations of C1-INH antigen (protein volume) and functional C1-INH activity (potency), temporarily restoring the natural regulation of the complement, contact (bradykinin-forming), and fibrinolytic systems. C1 inhibitor replacement therapy can prevent the occurrence of angioedema attacks associated with HAE or stop and control the mechanism that causes swelling if an attack does occur.

CINRYZE® is a highly purified, viral-inactivated, nanofiltered concentrate of C1-INH produced from human plasma.

1.2. STUDY RATIONALE

Currently, there is no product approved in Japan for both prevention of angioedema attacks and treatment of angioedema attacks associated with HAE. In clinical trials conducted outside of Japan, CINRYZE® was proven to be safe, well tolerated, and effective for the prevention and treatment of angioedema attacks in a broad age range of patients with HAE (pediatrics through patients ≥65 years old). Overseas studies have shown that self-administration allows patients to manage their disease symptoms with minimal disruption to their daily activities resulting in reduced absences from work or school and overall improvement in quality of life (Cicardi et al. 2013; Caballero et al. 2013). It is expected that CINRYZE® will fulfill an unmet medical need for Japanese patients with HAE, and the present study is being performed to confirm its safety and efficacy in this patient population.

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2. STUDY OBJECTIVES

The objectives of the study are to assess:

- The safety and tolerability of CINRYZE® administered by IV infusion in Japanese subjects with HAE;

- The pharmacokinetics (PK) and pharmacodynamics (PD) of CINRYZE® administered by IV infusion in this subject population; and

- The treatment effect of CINRYZE® administered by IV infusion for the prevention of angioedema attacks and treatment of breakthrough attacks in this subject population.

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3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This single-period, open-label study will be conducted at multiple investigational sites in Japan. This is an outpatient study; however, subjects may require an overnight stay at the site for those days on which serial PK/PD blood samples are collected. Subjects would be discharged the following day after collection of the 24-hour PK/PD blood sample.

Subjects will be administered CINRYZE® by IV infusion twice weekly (every 3 or 4 days) for 12 weeks. Study drug will be administered to all subjects at the investigational site for Dosing Visits 1 through 8, 16, and 24; during these visits, subjects may also have physical examinations and other procedures performed (see Schedule 1 of the protocol). Other doses of study drug may be administered at the investigational site or at the subject's home.

3.2. DETERMINATION OF SAMPLE SIZE

A sufficient number of subjects will be enrolled to ensure that a minimum of 6 subjects complete the study. When 6 subjects have completed the 12-week treatment period, no further subjects will be enrolled; however, all subjects already enrolled in the study will be followed to study completion.

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4. EFFICACY AND SAFETY VARIABLES

4.1. SCHEDULE OF EVALUATIONS

Schedule of evaluations can be found in Schedule 1 of the protocol.

4.2. EFFICACY VARIABLES

4.2.1. PREVENTION OF ANGIOEDEMA ATTACKS

The following efficacy endpoints for prevention of angioedema attacks will be assessed:

- The normalized number of angioedema attacks (NNA) recorded during the treatment period, normalized for the number of days the subject participated in the period; and the NNA for historical data normalized for 3 months prior to study drug administration.

- Summary of all attacks during the treatment period and historical 3 month data, including:

  o Anatomic location.
  o Severity (intensity).
  o Average duration of attacks.
  o Number of angioedema attacks treated with CINRYZE®, non- CINRYZE® C1-INH or not treated with C1-INH (including attacks treated with any medications other than C1-INH or untreated attacks).

- Effects of therapy on quality of life (results of AE-QoL questionnaire).

4.2.2. TREATMENT OF BREAKTHROUGH ANGIOEDEMA ATTACKS

The following efficacy endpoints for treatment of breakthrough angioedema attacks will be assessed by; CINRYZE® treated attacks, non-CINRYZE® C1-INH treated attacks and other attacks (including any medications other than C1-INH and untreated attacks):

- The number of subjects with breakthrough angioedema attacks.

- The number of subjects with 1, 2, 3 or more angioedema attacks.

- The number of subjects who achieve initial improvement and Complete Resolution. Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack since onset of attack.

- Time to initial improvement and time to Complete Resolution.

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Additional analysis for breakthrough angioedema attacks treated with CINRYZE® will also be presented for:

- The number of subjects with breakthrough angioedema attacks.

- The number of subjects with 1, 2, 3 or more angioedema attacks.

- Time from onset of attack to time treated by CINRYZE®.

- The number of subjects who achieve initial improvement and Complete Resolution. Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack since onset of attack.

- Time from the start of study drug administration, CINRYZE®, for the particular attack to the time of initial improvement and time to Complete Resolution.

4.3. SAFETY ASSESSMENTS

The following will be assessed:

- Adverse events (including treatment-emergent adverse events).

- Summary statistics and changes from baseline to post-baseline for laboratory testing, vital signs, and, if applicable, any electrocardiogram (ECG) findings will be presented.

- Results of C1-INH antibody testing will be reported for individual subjects and summarized as appropriate.

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5. STATISTICAL ANALYSIS

5.1. GENERAL METHODOLOGY

Experimental results will be summarized using descriptive statistics according to data type (n, mean, standard deviation or standard error, median, and range for continuous endpoints; number and percent of subjects in each category for categorical endpoints).

The estimated median time to event and its 95% confidence interval (CI) will be calculated (if at least 50% of subjects in the Full Analysis Set achieved the event) using the Kaplan-Meier estimator. The Kaplan-Meier estimates will also be displayed graphically.

All analyses will be presented by C1 Inhibitor 1000U only. Study drug administrations were planned according to subjects age; 500U for Subjects 2 to 5 years of age and 1000U for Subjects 6 years of age and older. However, only the higher dose of 1000U were administered.

Unscheduled visits data will not be included in analysis, otherwise specified. Unscheduled visits data will merely be presented in listings.

5.2. ANALYSIS POPULATIONS

Enrolled subjects are all subjects who signed signed informed consent and completed screening.

All treated subjects (ie, Intent-to-Treat Safety [ITT-S] Population: subjects who receive any amount of study drug) will be included in the safety analyses.

Full Analysis Set Population (defined as subjects who have at least one post baseline efficacy assessment) will be included in the efficacy analyses.

All subjects with evaluable PK/PD profiles (ie, PK/PD Population) will be included in PK/PD analyses as appropriate.

5.3. SUBJECT DISPOSITION

A summary table of subject disposition will be provided, to show the number of subjects screened, enrolled, and the number of subjects in the ITT-S population.

The number of subjects completing the study and withdrawing from the study will also be tabulated. Withdrawals will be categorized by primary reason for withdrawal.

5.4. PROTOCOL DEVIATIONS

Number of subjects with protocol deviations will be summarised for the following categories:

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- Procedures/tests

- Disallowed medications

- Inclusion/exclusion criteria

- Investigational product administration/study treatment

- Other

The date protocol deviations were identified together with the protocol deviation description will also be presented in a listing.

5.5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics (age, age group of < 18, between 18 – 64, ≥ 65, sex, ethnicity and race) will be summarized.

In addition, the following baseline characteristics will be also be tabulated:

- Weight (kg) at screening

- Height (cm) at screening

- BMI (kg/m^2) at screening

In a separate table, summary of HAE history will also be tabulated for the following:

- Type of HAE

- Family history of HAE

- Time since last angioedema attack (days)

- Total number of angioedema attacks during 3 consecutive months prior to study drug administration

- Typical VAS score (mm) during 3 consecutive months prior to study drug administration

- Average overall duration (days) of angioedema attacks during 3 consecutive months prior to study drug administration, as collected in the Medical/Angioedema History electronic Case Report Form (eCRF)

- Average overall severity of angioedema attacks during 3 consecutive months prior to study drug administration, as collected in the Medical/Angioedema History eCRF

- Typical location(s) of angioedema attack during the 3 consecutive months prior to study drug administration

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Derivations will be constructed as follow:

Body mass index (kg/m²)

$$\dots = \frac{h\ (\quad)}{h\quad h\ (\quad)\quad\frac{}{100}\quad^2}$$

presented to one decimal place.

Time since last angioedema attack (days)

$$\text{time} = \text{first dose date} - \text{onset date of last angioedema attack prior to first dose}$$

5.6. EXTENT OF EXPOSURE

The average daily dose, total dose and duration of exposure will be summarized for study drug taken as 'Long-term prevention'.

Derivations will be constructed as follow:

Duration of exposure (weeks)

$$\text{duration} = (\text{last dose date} - \text{first dose date} + 1)/7$$

Total dose (U)

The sum of all study drug administered.

Average daily dose (U/day)

$$\text{average} = \frac{(\quad)}{\quad - \quad + 1\ (\quad)}$$

5.7. ANALYSIS OF EFFICACY

5.7.1. PREVENTION OF ANGIOEDEMA ATTACKS

An angioedema attack is defined as any subject-reported (or caregiver-reported) indication of swelling or pain at any location following a report of no swelling or pain on the previous day (ie, there must be a full symptom-free calendar day preceding the onset of symptoms for an attack to be considered a new attack). Therefore,

- Attacks that progress from 1 site to another will be considered a single attack;

- Attacks that begin to regress and then worsen before complete resolution will be considered 1 attack; and

- Attacks that begin, appear to resolve, and then reappear without a symptom-free calendar day reported after the appearance of resolution will be considered 1 attack.

An angioedema attack does NOT include swelling due to trauma or arthritis, or symmetrical non-painful swelling of the lower extremities.

The following efficacy endpoints for prevention of angioedema attacks will be tabulated.

- The NNA during the treatment period, compared to the NNA for historical data for 3 months prior to study drug administration.

- Summary of all attacks during the treatment period, including:

  o Anatomic location.
  o Severity (intensity).
  o Average duration of attacks.
  o Number of angioedema attacks treated with CINRYZE®, non-CINRYZE® C1-INH or not treated with C1-INH (including attacks treated with any medications other than C1-INH or untreated attacks).

- The number of subjects with pre- and post-treatment NNA values will also be presented for the following:

  o Number of subjects achieving >=50% reduction in NNA relative to NNA for Histotical data
  o Number of subjects achieving >=70% reduction in NNA relative to NNA for Histotical data
  o Number of subjects achieving >=90% reduction in NNA relative to NNA for Histotical data

- Effects of therapy on quality of life (results of AE-QoL questionnaire).

Derivations will be constructed as follow:

Number of angioedema attacks (per month)

The NNA during the treatment period is the number of angioedema attacks normalized for the number of days the subject participated in the period and multiplied by 30.4:

$$\frac{}{- + 1} \quad 30.4$$

presented to two decimal place.

The NNA for historical data is the number of angioedema attacks during 3 months prior to study drug administration, divided by 3.

$$\frac{h}{3}$$

Anatomic location

The summary of anatomic location will be counted for each of the following location where there is a presence of pain or swelling of any level of severity; mild, moderate or severe at any day during the attack.

- Abdominal/Gastrointestinal

- Genital/Urinary (includes scrotum or vulva)

- Upper airway (includes laryngeal or pharyngeal)

- Cutaneous – facial

- Cutaneous – extremity or peripheral

The historical data of the typical location of subjects angioedema attacks can be obtained from the Medical/Angioedema History eCRF page.

Severity (intensity)

The severity of an attack will be the highest value assigned by the subject to any location at any day during the attack. In order to calculate the average severity of attacks, each mild, moderate, and severe attack will be assigned a score of 1, 2, or 3, respectively. The total severity score will be calculated for multiplying the total number of mild attacks by 1, total number of moderate attacks by 2, and the total number of severe attacks by 3, then adding the results of these three calculations.

The average severity of attack will be summarized. The average severity is derived by dividing the cumulative severity score by the total number of attacks.

For historical data, the average overall severity of subjects angioedema attack are collected in the Medical/Angioedema History eCRF page. The similar scoring system as indicated above will be applied to the average severity level.

Average duration of attacks (days)

The duration of an attack will be measured from the onset of attacks until complete resolution.

The average duration of attacks is calculated by dividing the cumulative duration of attacks by the total number of attacks during the treatment period.

For the historical data, the average duration of attacks recorded on the Medical/Angioedema History eCRF page will be used.

Number of angioedema attacks treated with rescue medication (per month)

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The NNA treated with rescue medication will be summarized for CINRYZE®, non-CINRYZE® C1-INH or not treated with C1-INH (including attacks treated with any medications other than C1-INH or untreated attacks), and is defined as below.

$$\frac{}{\underline{} + 1} \, 30.4$$

For on treatment attacks, only medication taken after study drug administration and had an indication of 'HAE Management – Acute Treatment' selected on the Prior and Concomitant Medications and Therapy eCRF page will be considered as rescue medications. CINRYZE® will only be considered as a rescue medication when treated for 'Breakthrough Attack Treatment'.

For historical data, only medication prior to the start of study drug administration and had an indication of 'HAE Management – Acute Treatment' selected on the Prior and Concomitant Medications and Therapy eCRF page will be considered as rescue medications.

5.7.2. TREATMENT OF BREAKTHROUGH ANGIOEDEMA ATTACKS

A breakthrough attack is defined as an angioedema attack that occurs during long-term prevention therapy with CINRYZE® (i.e, between first study drug and last study drug dose).

The following efficacy endpoints for treatment of breakthrough angioedema attacks will be assessed by CINRYZE® treated attacks, non-CINRYZE® C1-INH treated attacks and all other attacks (including any medications other than C1-INH and untreated attacks):

- The number of subjects with breakthrough angioedema attacks.

- The number of subjects with 1, 2, 3 or more angioedema attacks.

- The number of subjects who achieve initial improvement and Complete Resolution.

- Time to initial improvement and time to Complete Resolution.

Additional analysis for breakthrough angioedema attacks treated with CINRYZE® will also be presented for:

- The number of subjects with breakthrough angioedema attacks.

- The number of subjects with 1, 2, 3 or more angioedema attacks.

- Time from onset of attack to time treated by CINRYZE®.

- The number of subjects who achieve initial improvement and Complete Resolution. Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack since onset of attack.

- Time from the start of study drug administration, CINRYZE®, for the particular attack to the time of initial improvement and time to Complete Resolution.

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Derivations will be constructed as follow:

Complete Resolution

Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack since onset of attack.

Time to Complete Resolution

Time to complete resolution is defined as the time from the onset of attack to complete resolution of symptoms.

The analysis of the time to event endpoint includes only the first attack from each subject meeting the treatment criterion since attacks experienced by the same subject are dependent. Median time to complete resolution and the corresponding 95% CI estimated using the Kaplan-Meier method will be summarized.

Kaplan Meier plots for time from CINRYZE® to initial improvement and to complete resolution will also be presented.

5.7.3. ANGIOEDEMA QUALITY OF LIFE (AE-QoL) QUESTIONNAIRE

The Angioedema Quality of Life (AE-QoL) is a questionnaire on the quality of life of patients suffering from recurrent angioedema. It consists of 17 specific questions that are associated with work, physical activity, free time, social relations, and diet. Each question is then answered with Never, Rarely, Occasionally, Often and Very Often, which will be scored as 1, 2, 3, 4 and 5 respectively. The 17 questions will be grouped into four categories as follow, and a total score will also be calculated:

- Functioning

    o 1. Impairment of work
    o 2. Impairment of physical activity
    o 3. Impairment of spare time activities
    o 4. Impairment of social relations

- Fatigue/Mood

    o 6. Difficulties of falling asleep
    o 7. Waking up during the night
    o 8. Feeling tired during the day
    o 9. Difficulties in concentrating
    o 10. Feeling downhearted

- Fears/Shame

    o 12. Feeling burden at having swellings
    o 13. Fear of new suddenly appearing swellings
    o 14. Fear of increased frequency of swellings
    o 15. Ashamed to visit public places

- o   16. Embarrassed by the appearance of swellings
- o   17. Fear of long-term negative drug effects

- **Nutrition**

  - o   5. General limitations in foods and eating
  - o   11. Limitations in the selection of food or beverages?

- **Total Score**

  - o   Question 1 to Question 17

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Summary and change from baseline for the total score will be presented for all visits.

5.7.4. SENSITIVITY ANALYSIS

The following sensitivity analyses will be performed for efficacy analysis on NNA described in Section 5.7.1.

The first sensitivity analysis includes only subjects with treatment compliance. The definition of treatment compliance will be given in Section 5.8.8. That is, only subjects who have no dose interruption and receive 24 complete infusions are included in the analysis.

In the second sensitivity anlaysis, all FAS subjects will be included in this sensitivity analysis, however data will only include up to the point when non-treatment compliance occurred.

5.8. ANALYSIS OF SAFETY

5.8.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 19.0. Events will be classified by system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events (TEAEs) will be summarized.

Treatment-emergent events include all AEs that start during the treatment period and were not seen at baseline, or were seen at baseline but worsened in frequency and/or severity during the treatment period.

The incidence of injection site reaction AEs will also be summarized at PT and SOC level. Injection site reaction AEs are any PT that include the term 'injection site reaction'.

The incidence of TEAEs will be summarized by intensity ('Mild', 'Moderate' or 'Severe') at PT and SOC level. For each subject and PT, only the most severe AE will be counted.

The incidence of AEs related to study drug will be summarized at PT and SOC level. Events with a relationship to study drug classified as 'Possibly Related', 'Probably Related', and 'Definitely Related' will be categorized as 'Related'. If a subject experiences the same event (at PT level) on more than one occasion, then only one event will be counted, and this event will be categorized as 'Related' if any of the events under that PTs are categorized as 'Related'.

The incidence of AE by PT, the incidence of serious AE by PT and SOC, and the incidence of serious AE by PT will also be presented.

Adverse events will be sorted by SOC in alphabetical order, then within SOC, sort PT in descending frequency.

All AEs for each subject, including the same event on several occasions will be listed, giving both preferred term and the original term used by the investigator. Serious AEs will be presented separately on an additional listing.

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5.8.2. CLINICAL LABORATORY EVALUATION

Laboratory values will be obtained for hematology, clinical chemistry, coagulation, virology and urinalysis at the time points specified in Schedule 1 and Schedule 3 of the protocol. The laboratory tests will be performed by a central laboratory.

Descriptive statistics will be provided hematology, clinical chemistry and coagulation data at time points specified in Schedule 1 and Schedule 3 of the protocol. Descriptive statistics for change from baseline to post-baseline, and shifts with respect to normal ranges for the same period will also be presented. Data listings will be provided for all subjects. Laboratory values outside the normal range will be flagged.

Baseline is denoted as Visit 1.

Number of subjects with potentially clinically important (PCI) lab values will also be presented. Potentially clinically important lab values are defined as per Table 1 below.

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Table 1: Potentially important lab values

Test Item	Unit	Reference range	Criterion *1
WBC (blood)	/micro L	3300 - 9000	> 15000
			< 2000
Eosinophils (rel)	%	0.0 - 8.0	> 10.0
Neutrophils (abs)	/micro L	(N/A)	> 11000
			< 1000
Lymphocytes (abs)	/micro L	(N/A)	> 20000
			< 500
hemoglobin (blood)	g/dL	M: 13.5 - 17.5 F: 11.5 - 15.0	> (BL) + 4.0
			< (BL) − 3.0
platelet count	x10^4 /micro L	14.0 - 34.0	> 60.0
			< 10.0
aPTT-second	sec	25.0 - 36.0	> 90.0
PT-INR	(N/A)	0.85 - 1.15	> 2.875
BUN	mg/dL	8 – 23	> (BL) x 2.0
creatinine	mg/dL	M: 0.61 - 1.04 F: 0.47 - 0.79	> (BL) x 2.0
glucose (serum)	mg/dL	70 - 109	> 250
			< 40
sodium	mEq/L	137 - 147	> 155
			< 130
potassium	mEq/L	3.5 - 5.0	> 6.0
			< 3.0
AST	U/L	10 – 40	> 200
ALT	U/L	5 – 45	> 225
ALP	U/L	100 - 325	> 1625
CPK	U/L	M: 60 - 270 F: 40 - 150	M: > 1350 F: > 750
total bilirubin	mg/dL	0.2 - 1.2	> 3.6
calcium	mg/dL	8.4 - 10.4	> 12.5
			< 7.0
phosphorus	mg/dL	2.5 - 4.5	< 2.0

*1   BL (Baseline) is Visit 1. When the sample is not collected at Visit 1, the alarm for variation (ratio/difference) is not performed.

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5.8.3. ECG EVALUATIONS

12-lead ECG assessments will be recorded only at screening. However, if clinically applicable, additional ECG findings will be collected during treatment period. When applicable, descriptive statistics for change from baseline to post-baseline for the following ECG data will be presented: heart rate (HR), PR interval, QRS duration, QT interval, and QTc interval.

The interpretation of ECG results will also be presented, where 'NA' (not applicable) will be counted as no record of abnormalities, i.e., normal.

For this study, no summary statistics for ECG data will be presented. ECG data will only be presented in listing.

5.8.4. VITAL SIGNS PARAMETERS

Vital sign will be measured at the time points specified in Schedule 1 and Schedule 3 of the protocol. Additional vital signs measurements may be performed during the study if clinically indicated. On dosing days, vital signs should be obtained ≤30 minutes before the start of the infusion, ≤15 minutes after completion of the infusion, and between 30 minutes and 1 hour after completion of the infusion.

Summary statistics for vital signs measured at each treatment visit, and the change from post-infusion to pre-infusion at each visit, will also be presented.

Number of subjects with PCI vital signs data will also be presented. Potentially clinically important vital signs values are defined as follow:

Variable	Potentially Clinically Important Criteria
Systolic Blood Pressure	< 90 mmHg; ≥ 140 mmHg.
Diastolic Blood Pressure	< 60 mmHg ; ≥ 90 mmHg.
Pulse	≤ 50 bpm; ≥ 100 bpm.

Height and weight, obtained at the screening visit, will be summarized within the demographics table.

5.8.5. PHYSICAL EXAMINATION

No summary statistics will be presented for physical examination.

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As per guidance in Completion Guidelines, any baseline abnormal physical examinations will be recorded in the Medical History Form. Any post Dosing Visit 1 clinically significant physical examination findings or worsening of previous conditions will be recorded in the Adverse Event form."

5.8.6. MEDICAL HISTORY

Medical history will be coded according to MedDRA version 19.0 central coding dictionary. Medical history will be presented by SOC and PT, and will be sorted by SOC in alphabetical order, then within SOC, PT will be sorted in descending frequency.

5.8.7. PRIOR AND CONCOMITANT MEDICATION

Prior medications are any medications received for the management of HAE within 12 months before Day 1 and all other medications taken within 1 week before Dosing Visit 1.

Concomitant medications are any medications taken from the start of Dosing Visit 1 through the 1-Month Post-treatment Follow-up Visit.

Prior and concomitant medications will be coded according to World Health Organization (WHO) drug dictionary version 01JUN2016. Summary of medications will be divided into medications given for HAE long-term prevention, HAE short-term prevention, HAE acute treatment which included either C1 Inhibitor or Tranexamic Acid, HAE symptom management which indication included acute treatment and medication is not C1 Inhibitor or Tranexamic Acid, and all other medications used. This will be presented by ATC Level 1 and PT. Preferred Term is defined as basename from WHO drug dictionary. Table will be sorted by indications and ATC Level 1 in alphabetical order, then within ATC Level 1, PT will be sorted in descending frequency. Details of prior and concomitant medications used will be provided in one listing.

5.8.8. TREATMENT COMPLIANCE

Treatment compliance is defined by 24 complete infusions, and no dose interruption. Dose interruption means that the gap between any two consecutive doses is at least 6 days.

The compliance for subjects who have no dose interruption or subjects whose treatment duration is less than 12 weeks (84 days) is calculated as:

$$(\%) = \frac{(\qquad)}{24} \times 100$$

The compliance for subjects who have dose interruption and the treatment duration is greater than 12 weeks (84 days) is calculated as:

$$(\%) = \frac{(\quad actual \quad)}{(\quad - \quad + 1)/3.5} \times 100$$

where 3.5 is the average number of days between 2 infusions in one week.

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5.9. IMMUNOGENICITY (C1-INH ANTIBODY) AND PHARMACOKINETIC CONCENTRATIONS AND PHARMACODYNAMICS LEVELS

The concentrations of C1-INH antigen (protein volume), functional C1-INH activity (potency), and complement C4 and C1q for individual subjects will be determined using fully validated bioanalytical methods, and will be listed and summarized using descriptive statistics at each time point. C1q concentrations will be assessed at baseline only (ie, pre-infusion, Dosing Visit 1).

The Antibody results will be listed and summarized using descriptive statistics at each nominal time point.

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6. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

6.1. CHANGES IN THE CONDUCT OF THE STUDY

No changes in the conduct of the study.

6.2. CHANGES FROM THE ANALYSES PLANNED IN THE PROTOCOL

Due to insufficient data collection, the analysis of clinical relief has not been conducted as planned.

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7. STATISTICAL/ANALYTIC ISSUES

7.1. HANDLING OF DROPOUTS OR MISSING DATA

Only the following missing data will be imputed and analyzed in tables summaries. Imputed data will not be presented in listing. All other missing data will not be imputed.

Severity of AE

If severity of AE is missing, 'Severe' AE will be imputed for analysis.

Causality of AE

If the relationship of AE to investigational product is missing, 'Related' will be imputed for analysis.

7.2. INTERIM ANALYSES AND DATA MONITORING

No interim analyses or data monitoring are planned for this study.

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8. REFERENCES

Bernstein JA. Update on angioedema: evaluation, diagnosis, and treatment. *Allergy Asthma Proc.* 2011; 32(6):408-412.

Caballero T, Sala-Cunill A, Cancian M, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. *Int Arch Allergy Immunol.* 2013; 161(Suppl 1):10-16.

Cicardi M, Craig TJ, Martinez-Saguer I, et al. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration. *Int Arch Allergy Immunol.* 2013; 161(Suppl 1):3-9.

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9. APPENDICES

9.1. APPENDIX I – LIST OF STATISTICAL OUTPUTS

9.1.1. LIST OF PLANNED TABLES

Table 14.1.1.1 Subject Disposition (All Screened Subjects)

Table 14.1.2.1 Protocol Deviations (Intent-to-Treat Safety Analysis Set)

Table 14.1.4.1 Demographic and Baseline Characteristics (Intent-to-Treat Safety Analysis Set)

Table 14.1.4.3.1 Summary of HAE History (Intent-to-Treat Safety Analysis Set)

Table 14.1.4.3.2 Summary of Medical History (Intent-to-Treat Safety Analysis Set)

Table 14.1.4.4 Prior Medications and Therapy (Intent-to-Treat Safety Analysis Set)

Table 14.1.4.5 Concomitant Medications and Therapy (Intent-to-Treat Safety Analysis Set)

Table 14.2.1.1 Summary of Angioedema Attacks during Treatment Period (Full Analysis Set)

Table 14.2.1.2.1 Sensitivity Analysis Completed Schedules - Summary of Angioedema Attacks during Treatment Period (Full Analysis Set)

Table 14.2.1.2.2 Sensitivity Analysis Treatment Compliance - Summary of Angioedema Attacks during Treatment Period (Full Analysis Set)

Table 14.2.1.3 Analysis of Clinical Responder Rate – Achieving at least 50%, 70% or 90% Reduction Relative to Historical Data in NNA (Full Analysis Set)

Table 14.2.2.1.1 Summary of Breakthrough Angioedema Attacks Treated By CINRYZE (Full Analysis Set)

Table 14.2.2.1.2 Summary of Breakthrough Angioedema Attacks Treated By Non-CINRYZE C1-INH (Full Analysis Set)

Table 14.2.2.1.3 Summary of Other Breakthrough Angioedema Attacks Not Treated with C1-INH (Full Analysis Set)

Table 14.2.2.1.4 Summary and Change from Baseline on AE-QoL (Full Analysis Set)

Table 14.2.3.1 C1-INH Antigen, Functional C1-INH activity, Complement C4 and C1q (Intent-to-Treat Safety Analysis Set)

Table 14.2.3.2 Antibody Results (Intent-to-Treat Safety Analysis Set)

Table 14.3.1.1 Overall Treatment-emergent Adverse Events (TEAEs) (Intent-to-Treat Safety Analysis Set)

Table 14.3.1.2.1 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Intent-to-Treat Safety Analysis Set)

9.1.2. LIST OF PLANNED FIGURES

9.1.3. LIST OF PLANNED LISTINGS

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9.2. APPENDIX II - PROGRAMMING CONVENTIONS

DATES & TIMES

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Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings and Graphs
Cinryze 500 U	Cinryze 500 U
Cinryze 1000 U	Cinryze 1000 U

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Dosing Visit 1	V1
Dosing Visit 2	V2
...	...
Dosing Visit 24	V24

LISTINGS

All listings will be ordered by the following: Cinryze 500 U then Cinryze 1000 U.

9.3. APPENDIX III - PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

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ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

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START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

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START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant