STATISTICAL ANALYSIS PLAN

Protocol No.:	0624-301 (SHP616-301)
Protocol Title:	A phase 3, multicenter, randomized, single-blind, dose-ranging, crossover study to evaluate the safety and efficacy of intravenous administration of CINRYZE® (C1 esterase inhibitor [human]) for the prevention of angioedema attacks in children 6 to 11 years of age with hereditary angioedema
Drug:	Cinryze 0624-301 (SHP616-301)
Sponsor:	Shire Development LLC 725 Chesterbrook Boulevard, Wayne, PA 19087 USA
Version No. and Date:	Version final 1.3, Date 25. May. 2017

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Client:	Shire Development LLC 725 Chesterbrook Boulevard, Wayne, PA 19087 USA
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ABBREVIATIONS

AE	adverse event
BLQ	below the limit of quantification
BMI	body mass index
C1 INH	C1 esterase inhibitor or C1 inhibitor
CI	confidence interval
C_{max}	Masimum concentration
eCRF	electronic case report form
EU	European Union
FAS	Full Analysis Set
HAE	Hereditary angioedema
HIV	human immunodeficiency virus
IV	Intravenous
LAoT	Final on treatment assessment
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
n, N	Sample size
NA	Not applicable
PD	Pharmacodynamics
PCI	potentially clinically important
PIP	Paediatric investigation plan
PK	Pharmacokinetics
QoL	Quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SOC	system organ class
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety and efficacy data as described in the final study protocol Amendment 4 dated 26 January 2015. Specifications for tables, figures, and listings are also contained in this document.

2. STUDY DESIGN

2.1 General Study Design

This is a phase 3, multicenter, randomized, single-blind, dose-ranging, crossover study to evaluate the safety and efficacy of intravenous administration of CINRYZE® (C1 esterase inhibitor [human]) for the prevention of angioedema attacks in children 6 to 11 years of age with hereditary angioedema.

Individual participation from screening through the completion of the 1-month safety follow-up visit will be approximately 10 months (1-day screening visit, 12-week baseline observation period, two 12-week treatment periods [consecutive without any washout between treatment periods], and 1-month post-treatment safety follow-up visit). The study design is shown in Figure 1.

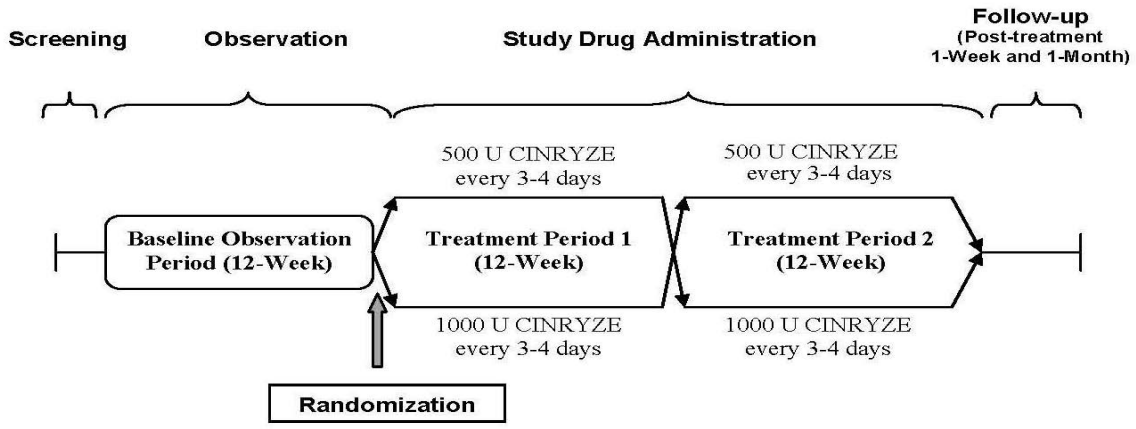
CINRYZE (500 U or 1000 U) will be administered by IV injection twice weekly (every 3 or 4 days) for 12 weeks in two crossover treatment periods.

Participants in this crossover study are expected to receive both treatments (A = 500 U and B = 1000 U), assigned in random order, in sequential treatment periods. Each treatment period will be 12 weeks, without a washout between the two periods. Eligible subjects will be randomized to one of two treatment sequences, A/B or B/A.

- **Treatment sequence A/B**: CINRYZE at a dose of 500 U/1000 U IV twice weekly
- **Treatment sequence B/A**: CINRYZE at a dose of 1000 U/500 U IV twice weekly

This multicenter, randomized, single-blind, dose-ranging, crossover study will be conducted in multiple countries including the United States, Europe and Latin America. Other countries may be added if necessary to complete enrollment.

Figure 1: Study Design Flow Chart



Potential subjects (≥6 to <12 years of age) will have a screening evaluation the day prior to entering the study's baseline observation period. Subjects with qualifying angioedema attack rates, and who meet all other eligibility criteria, will be enrolled and enter the observation period for at least 12 weeks.

2.2 Randomization

Twelve subjects will be randomized to one of two treatment sequences, with each sequence consisting of two 12-week treatment periods. Randomization will occur on Dosing Day 1 (Visit 1a) of Treatment Period 1. Each investigative site will receive a randomization schedule which will be used to assign subjects at that site to one of two sequences (A/B or B/A), with equal probability. Treatment A will be 500 U CINRYZE administered intravenously twice weekly (every 3 or 4 days) for 12 weeks and Treatment B will be 1000 U CINRYZE administered intravenously twice weekly (every 3 or 4 days) for 12 weeks.

2.3 Blinding

This is a single-blind study. Subjects and parents/caregivers will be blinded to the treatment administered. Study site personnel, qualified home healthcare professionals, and the Sponsor will not be blinded to dose and treatment sequence.

To maintain the treatment blind (for subjects and parents/caregivers), each dose of study drug will consist of a single IV injection (total volume of 10 mL).

2.4 Schedule of Assessments

Study assessments are presented in Table 1, Table 2, Table 3, and Table 4; blood collection time points for PK and post-treatment immunogenicity assessments are shown in Table 5.

Table 1 Clinical Study Assessments – Screening and Baseline Observation Period

Procedures	Screening [a]	BASELINE OBSERVATION PERIOD (BY STUDY WEEK) [b]											
		1	2	3	4	5	6	7	8	9	10	11	12
Informed consent (written permission and assent)	X												
Medical/HAE history	X												
Prior/current medications [c]	X	X----------X											
Telephone contact [d]			X		X		X		X		X		X
Daily angioedema attack monitoring/eDiary [e]		X----------X											
EQ-5D-Y/eDiary [f]	X					X				X			

eDiary=electronic study diary; EQ-5D-Y (Youth version of EQ-5D)=health-related quality of life descriptive system for youth

[a] All subjects will have a screening evaluation the day prior to entering Week 1 of the baseline observation period.

[b] Additional weeks of observations will be considered at the discretion of the Investigator and Sponsor to allow a subject to qualify for randomization and entry into the treatment periods of the study. In this case, subjects will maintain the same schedule of assessments by beginning at Week 1 again for the additional weeks of observation (i.e., Week 13 = schedule of assessments for Week 1, Week 14 = schedule of assessments for Week 2, etc).

[c] Parents/caregivers should record in the eDiary any medications taken by the subject for the management of angioedema attacks during the baseline observation period.

[d] Study personnel will contact the parent/caregiver by telephone on Weeks 2, 4, 6, 8, 10, and 12 to discuss study compliance (completion of the eDiary daily) and to evaluate the subject's angioedema attack frequency. Telephone contacts will be documented in the source notes at the clinical site.

[e] During the baseline observation period, parents/caregivers will use an eDiary to record the subject's symptoms or occurrences of angioedema attacks.

[f] In addition, subjects should complete the EQ-5D-Y on each day that they experience signs or symptoms of an angioedema attack.

Table 2 Clinical Study Assessments – Treatment Period 1

Procedures	TREATMENT PERIOD 1 (BY STUDY WEEK) [a]																							
	1		2		3		4		5		6		7		8		9		10		11		12	
	DOSING VISITS (1a to 24a)																							
	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12a	13a	14a	15a	16a	17a	18a	19a	20a	21a	22a	23a	24a
Confirm eligibility	X [b]																							
Randomization	X [c]																							
Medical history update /Physical exam [d]	X [b]											X												X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Body Weight	X [b]																							
Vital signs (BP, HR) [e]	X [f]			X		X		X		X		X		X		X		X		X		X		X
Clinical safety lab testing. (hematology, chemistry, coagulation)	X [b]											X												
Virology screening [g]	X [b]																							
Pregnancy testing [h]	X [b]																							
Study drug administration	X [i]	X	X	X	X	X	X	X	X	X	X	X [i]	X	X	X	X	X	X	X	X	X	X	X	X [i]
Telephone contact [J]						X												X						
EQ-5D-Y/eDiary [k]	X [b]								X								X							
Daily angioedema attack monitoring/eDiary	X---------- X																							
Adverse events	X---------- X																							
PK/PD assessments	Details on timing of blood sample collection for PK/PD assessments is provided in Schedule 5.																							
Immunogenicity testing (C1 INH antibody)	X [b]																							

Table 2 Clinical Study Assessments – Treatment Period 1

Procedures	TREATMENT PERIOD 1 (BY STUDY WEEK) [a]											
	1	2	3	4	5	6	7	8	9	10	11	12
	DOSING VISITS (1a to 24a)											

eDiary=electronic study diary; EQ-5D-Y (Youth version of EQ-5D)=health-related quality of life descriptive system for youth

[a] Study drug administration and scheduled procedures will occur twice weekly (every 3 or 4 days) during the 12-week treatment period (Treatment Period 1, Visits 1a-24a).

[b] Specified study procedures and blood samples should be performed/collected prior to study drug administration, on the same day.

[c] Randomization will occur on Dosing Day 1 (Visit 1a) prior to the first dose of study drug in Treatment Period 1.

[d] Medical history will be updated prior to randomization at Visit 1a. Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.

[e] Vital signs will be measured using standard methods at each study site. On dosing days, vital signs should be obtained prior (within 60 minutes) to the injection of study drug and between 10 to 30 minutes after completion of the injection of study drug. Additional vital signs measurements may be performed if clinically indicated.

[f] Body temperature should be measured prior to randomization at Visit 1a.

[g] HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

[h] Pregnancy testing (urine) will be performed on females who have reached menarche.

[i] Study drug will be administered by qualified personnel to all subjects at the investigational site for Dosing Visits 1a, 12a, and 24a.

[j] For those subjects who are dosed by a qualified home healthcare professional, study personnel will contact the parent/caregiver by telephone on Weeks 3 and 9 (after Dosing Visits 6a and 18a, respectively) to discuss and document study compliance, tolerability of CINRYZE dose, and adverse events. All telephone contacts will be documented in the source notes at the clinical site.

[k] In addition, subjects should complete the EQ-5D-Y on each day that they experience signs or symptoms of an angioedema attack.

See Schedule 4 for details regarding clinical assessments at early discontinuation (if applicable), 1-week post-treatment, and 1-month post-treatment follow-up visits.
In the event a subject prematurely discontinues from treatment and/or the study, Early Discontinuation Visit procedures will be performed as soon as possible.

Note: Investigators will report all SAEs to Shire ViroPharma Drug Safety through 30 days after the last dose of study drug and SAEs considered related to study drug >30 days after the last dose of study drug.

Table 3 Clinical Study Assessments – Treatment Period 2

	TREATMENT PERIOD 2 (BY STUDY WEEK) [a]																							
	1		2		3		4		5		6		7		8		9		10		11		12	
	DOSING VISITS (1b to 24b)																							
Procedures	**1b**	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**	**10b**	**11b**	**12b**	**13b**	**14b**	**15b**	**16b**	**17b**	**18b**	**19b**	**20b**	**21b**	**22b**	**23b**	**24b**
Physical exam [b]	X [d]											X												X
Body Weight	X [d]																							
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR) [c]	X			X		X		X		X		X		X		X		X		X		X		X
Clinical safety lab testing. (hematology, chemistry, coagulation)	X [d]											X												X
Study drug administration	X [e]	X	X	X	X	X	X	X	X	X	X	X [e]	X	X	X	X	X	X	X	X	X	X	X	X [e]
Telephone contact [f]						X												X						
EQ-5D-Y/eDiary [g, h]	X [d]								X								X							
Daily angioedema attack monitoring/eDiary [h]	X----------X																							
Adverse events	X----------X																							
PK/PD assessments	Details on timing of blood sample collection for PK/PD assessments is provided in Schedule 5.																							
Immunogenicity testing (C1 INH antibody)	X [d]																							

eDiary=electronic study diary; EQ-5D-Y (Youth version of EQ-5D)=health-related quality of life descriptive system for youth

[a] Study drug administration and scheduled procedures will occur twice weekly (every 3 or 4 days) during the 12-week treatment period (Treatment Period 2, Visits 1b-24b).

[b] Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.

[c] Vital signs will be measured using standard methods at each study site. On dosing days, vital signs should be obtained prior (within 60 minutes) to the injection of study drug and between 10 to 30 minutes after completion of the injection of study drug. Additional vital signs measurements may be performed if clinically indicated.

[d] Specified study procedures and blood samples should be performed/collected prior to study drug administration, on the same day.

[e] Study drug will be administered by qualified personnel to all subjects at the investigational site for Dosing Visits 1b, 12b, and 24b.

[f] For those subjects who are dosed by a qualified home healthcare professional, study personnel will contact the parent/caregiver by telephone on Weeks 3 and 9 (after Dosing Visits 6b and 18b, respectively) to discuss and document study compliance, tolerability of CINRYZE dose, and adverse events. All telephone contacts will be documented in the source notes at the clinical site.

[g] In addition, subjects should complete the EQ-5D-Y on each day that they experience signs or symptoms of an angioedema attack.

[h] If an angioedema attack is ongoing at Visit 24b, then recording of signs and symptoms and completing the EQ-5D-Y should continue daily until the attack resolves.

See Schedule 4 for details regarding clinical assessments at early discontinuation (if applicable), 1-week post-treatment, and 1-month post-treatment follow-up visits.
In the event a subject prematurely discontinues from treatment and/or the study, Early Discontinuation Visit procedures will be performed as soon as possible.

Note: Investigators will report all SAEs to Shire ViroPharma Drug Safety through 30 days after the last dose of study drug and SAEs considered related to study drug >30 days after the last dose of study drug.

Table 4 Clinical Study Assessments – Early Discontinuation, 1-week Post-treatment, and 1-month Post-treatment Follow-up Visits

Procedures	Early Discontinuation Visit [a]	1-Week Post-treatment Visit [b]	1-Month Post-treatment Follow-up Visit [c]
Concomitant medications	X	X	
Brief physical examination [d]	X	X	
Vital signs (BP, HR) [e]	X	X	
Clinical safety lab testing (hematology, chemistry, coagulation)	X	X	
Pregnancy testing [f]	X	X	
EQ-5D-Y	X	X	
Adverse events	X	X	
Immunogenicity testing (C1 INH antibody)	X	X	X
Virology testing [g]	X	X	

EQ-5D-Y (Youth version of EQ-5D)=health-related quality of life descriptive system for youth

[a] Early discontinuation visit will be performed as soon as possible in the event a subject prematurely discontinues from treatment and/or the study. For those subjects who discontinue prematurely from treatment, every effort should be made to complete protocol evaluations for the 1-month post-treatment follow-up visit.

[b] 1-Week post-treatment visit will be performed at the investigational site 1 week (±2 days) after the last dose of study drug.

[c] 1-Month post-treatment follow-up visit will be performed 30 (±2) days after the last dose of study drug.

[d] Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.

[e] Vital signs will be measured using standard methods at each investigational site.

[f] Pregnancy testing (urine) will be performed on females who have reached menarche.

[g] HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

Note: Investigators will report all SAEs to Shire VIROPHARMA Drug Safety through 30 days after the last dose of study drug and SAEs considered related to study drug >30 days after the last dose of study drug.

Table 5 Blood Sample Collection for PK/PD and Post-treatment Immunogenicity Assessments

TREATMENT PERIOD 1	
Visit / Dose #	**Blood Sampling Time Points** **C1 INH Antigen, C1 INH Function, Complement C4**
1a / Dose 1	Pre Dose 1
	1 h post Dose 1 (± 15 min)
12a / Dose 12	Pre Dose 12
	1 h post Dose 12 (± 15 min)
24a / Dose 24	Pre Dose 24
	1 h post Dose 24 (± 15 min)
	2 h post Dose 24 (± 15 min) – optional sampling time point
	4 h post Dose 24 (± 15 min) – optional sampling time point
	8 h post Dose 24 (± 15 min) – optional sampling time point
TREATMENT PERIOD 2	
Visit / Dose #	**Blood Sampling Time Points** **C1 INH Antigen, C1 INH Function, Complement C4**
1b / Dose 1	Pre Dose 1
	1 h post Dose 1 (± 15 min)
12b/ Dose 12	Pre Dose 12
	1 h post Dose 12 (± 15 min)
24b / Dose 24	Pre Dose 24
	1 h post Dose 24 (± 15 min)
	2 h post Dose 24 (± 15 min) – optional sampling time point
	4 h post Dose 24 (± 15 min) – optional sampling time point
	8 h post Dose 24 (± 15 min) – optional sampling time point

Note: If a subject presents to the investigational site with an angioedema attack, every effort should be made to

Table 5 Blood Sample Collection for PK/PD and Post-treatment Immunogenicity Assessments

obtain a PK blood sample prior to any treatment. In addition, if the subject is treated with commercial C1 INH, every effort should be made to obtain a 1-hour post-treatment sample. These samples will be analyzed for C1 INH antigen and functional C1 INH activity.	
POST-TREATMENT	
Visit	**Blood Sampling Time Points** **Immunogenicity (C1 INH antibody)**
1-week post-treatment	1 week (± 2 days) after the last dose of study drug
1-month post-treatment	30 (± 2) days after the last dose of study drug

2.5 Determination of Sample Size

This study is designed to assess the safety, tolerability, and relative efficacy of two different doses (500 U and 1000 U) of CINRYZE as prevention therapy for angioedema attacks in children 6 to 11 years of age with HAE. Twelve subjects will be randomized in this study. Given the limited number of pediatric subjects with HAE who will fall within this age category and have a history of angioedema attacks appropriate to meet study inclusion criteria (Caballero, 2012), this number is considered a reasonable target with respect to the ability to enroll eligible subjects.

3. OBJECTIVES

3.1 Primary Objective

To assess the relative efficacy of two dose levels of CINRYZE (500 U and 1000 U) administered by intravenous (IV) injection every 3 or 4 days to prevent angioedema attacks in children 6 to 11 years of age.

3.2 Secondary Objective

- To assess the safety and tolerability of two dose levels of CINRYZE administered by IV injection in children 6 to 11 years of age with hereditary angioedema (HAE).
- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of CINRYZE administered by IV injection in children 6 to 11 years of age.
- To assess the immunogenicity of CINRYZE following IV administration.

3.3 Other Objective

To assess the impact of treatment on health status (quality of life) in children 6 to 11 years of age with HAE.

4. SUBJECT POPULATION SETS

For all assessments, the treatment used will be the actual treatment and will be assigned according to the treatment period in which the assessment is performed.

4.1 Enrolled Subjects

Enrolled subjects consists of all subjects who have signed informed consent and some study procedures have begun (e.g., start of eDiary).

4.2 Randomized Set

The Randomized Set will consist of all subjects who have been randomized into a treatment sequence.

4.3 Safety Set

The Safety Set will consist of all subjects who have taken at least 1 dose of investigational product.

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the Safety Set who have at least 1 post-baseline (e.g., randomization) primary efficacy assessment (e.g. a diary entry).

4.5 Pharmacokinetic Set

The Pharmacokinetic Set will consist of all subjects in the Safety Analysis Set with no major deviations related to investigational product intake and evaluable PK profiles. (Note: subjects with missing data in some, but not all the periods, will be included in the analysis set.)

4.6 Pharmacodynamic Set

The Pharmacodynamic Set will consist of all subjects in the Safety Analysis Set for whom the primary pharmacokinetic data is considered sufficient and interpretable.

5. SUBJECT DISPOSITION

The number of subjects who have been enrolled and randomized and included in each subject population set (i.e., Safety, Full Analysis Set, Pharmacokinetic and Pharmacodynamic) will be summarized by treatment sequence, by treatment and overall. The denominator for the percentage calculation will be the number of randomized subjects for the Safety Set, and the number of subjects in the Safety Set for the Full Analysis Set, Pharmacokinetic and Pharmacodynamic Set.

The number and percentage of subjects who completed and prematurely discontinued during the study will be presented for each treatment sequence, treatment at time of discontinuation and overall for the Safety Set. Primary reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment sequence and by most recent treatment received at time of discontinuation for the Safety Set.

Subject disposition, subjects completing and terminating the study, and study analysis sets will be listed by subject for all Enrolled Subjects.

6. PROTOCOL VIOLATIONS AND DEVIATIONS

A summary of the number and percentage of subjects in the Safety Set with protocol violations or deviations will be produced.

For those subjects who enter the observation period but discontinue prior to randomization or who discontinue after randomization but prior to receiving study drug, a listing of those subjects will be provided.

All protocol violation and deviation data will be listed for the Enrolled Subjects with a flag for inclusion in the Safety Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be determined using the screening visit (Day -1) or last observation prior to the dose of investigational product, whichever is later. Descriptive summaries of demographic and baseline characteristics will be presented by treatment sequence for the Safety Set.

Subject demographics including age, sex, race, ethnicity, weight, height, and BMI will be summarized by treatment sequence for the Safety Set. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

Height and weight will be used to calculate BMI using the formula below:

$$\text{BMI} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

A listing will be created to show all the demographics and baseline characteristics for all Enrolled Subjects.

7.1 Medical History

All medical history findings that have been present/active within 1 year prior to enrollment will be recorded in the eCRF regardless of clinical relevance or presence at study start. Medical history will be summarized by treatment sequence for the Safety Set and listed for all subjects in the Enrolled Subjects.

7.2 HAE History

The following information associated with HAE history will be recorded in the eCRF at the screening visit (NOTE: the attack rate may be estimated based on subject or parent/caregiver recall as well as the subject's medical records):

- HAE Type (I or II).
- Any first-degree blood relative (i.e., mother, father, sibling) diagnosed with HAE. (yes/no). If yes, provide the relationship of first-degree blood relative(s).
- Any therapy received during the 9 months prior to screening for management of HAE (yes/no) (see Protocol Section 6.3.1).
- Total number, typical locations, average overall duration (days), and average overall severity of HAE attacks experienced during the 3 months prior to screening (see Protocol Section 6.10.1 for definition of severity).
- Prior HAE On Demand Acute Treatment,Prior HAE Long-Term Prophylaxis, Prior HAE Pre-Procedure/Short-Term Prophylax

HAE history will be summarized by treatment sequence for the Safety Set and listed for all Enrolled Subjects.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational Product

A listing will be created by subject and treatment period and will show the date and time of dose administration for each treatment given for the Safety Set.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance for a specified period is defined as the total number of doses (each dose of study drug will consist of a single IV injection, total volume of 10 mL) actually taken by a subject during that period divided by the number of doses expected to be taken during the same period multiplied by 100. The total number of doses actually taken is calculated by the sum of the number of doses administered on Study Drug Exposure Log. The number of doses expected to be taken for a specified period is calculated as the number of weeks in that period multiplied by the number of doses to be taken per week during that period.

9. PRIOR AND CONCOMITANT MEDICATION

The version dated 01 Mar 2014 of the WHO Drug Dictionary will be used to classify prior and concomitant medications by preferred drug name.

Any therapy received during the 9 months prior to screening for the management of angioedema attacks should be recorded, including overall start and stop dates if known, and the HAE indication (i.e., long-term prevention, acute treatment, short-term prevention). For any medication used in the management of HAE that has a start date prior to Treatment Period 1 and is planned to be continued in the treatment periods of the study, a stop date prior to the first dose of study drug in Treatment Period 1 should be entered into the eCRF. Any subsequent use of this medication should be recorded as a concomitant medication with a new start date.

HAE therapy received 9 months prior to screening will be recorded. Otherwise all medications taken within 1 week prior to Day 1 of Treatment Period 1 will be recorded and entered into the eCRF.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive.

Concomitant medications taken from the start of dosing through 1-week post-treatment will be recorded in the eCRF. For medications associated with management of angioedema attacks, study personnel will record the start/stop dates, dose, unit, frequency, route of administration, and indication (if known) in the subject's eCRF. For medications not associated with the management of HAE, study personnel will record the start/stop dates, route of administration, and indication for which the medication was administered in the subject's eCRF.

Prior medication usage will be summarized by the number and percentage of subjects receiving each medication by treatment sequence within the Safety Set. Concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication by treatment within the Safety Set. Medications can be counted both as prior and as concomitant medication. Multiple medication usage by a subject in the same preferred term category will be counted only once. Concomitant medications will also be summarized by the number and percentage of subjects receiving each medication by treatment within the Safety Set. For this summary, concomitant medications will be assigned to a treatment if they are recorded at least once within the period corresponding to that treatment.

All non-study medications taken during the study will be listed and prior, concomitant (taken from the start of dosing through 1-week post-treatment in the eCRF) and post medications (taken after the 2nd period) will be flagged.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the Full Analysis Set (FAS). The listing of all efficacy variables will be provided for the small sample trial.

10.1 Primary Efficacy Variable(s) and Analysis

The primary efficacy variable is number of angioedema attacks, normalized to a 12-week treatment period.

Analysis of the primary efficacy variable will employ descriptive statistics and will include all subjects randomized and treated with study drug in FAS. Graphic presentation will be provided to view the angioedema attack pattern from the crossover designed study using FAS with both period completers. If warranted by the data, the comparison of CINRYZE doses will employ a paired t-test to perform a two-sided test of superiority (1000 U vs. 500 U) conducted at α=0.1, this comparison will be performed only if the final sample size has 12 or more complete subjects with both period data. The test has low power and so we cannot assert that the lack of significance implies lack of effect.

If the final data 12 or more complete subjects, the between treatment comparison will be performed to test the null hypothesis:

Ho: $\mu_{\Delta(1000-500)} = 0$,

against the alternative hypothesis:

Ha: $\mu_{\Delta(1000-500)} \neq 0$

Where $\mu\Delta$ (1000 – 500) is the population mean of within subject treatment difference for the primary efficacy variable assessed by the point estimate of the sample mean calculated as following:

$$\hat{\mu}_{\Delta(1000-500)} = \bar{x}_{\Delta(1000-500)} = \frac{\sum_{i=1}^{N}(x_{1000_i} - x_{500_i})}{N}$$

,and the corresponding 90% CI will be provided for the point estimate.

Treatment and treatment sequence effects will be tested using mixed effects model at α=0.1, with period, treatment and treatment sequence as fixed effects, and subject nested within sequence as random effect. Adjusted means and 90% CIs will be calculated for both treatments, for both sequences and overall; as well as for the difference between the treatments.

To account for any potential carryover effect, sensitivity analysis using the paired t-test and mixed effect models will be performed by excluding any attacks occurring within the first 2 weeks of Treatment Period 2 for both sequences during which carryover effect is suspected to be maximal.

Furthermore, the sensitivity analysis by will be repeated by excluding first 2 weeks of both treatment periods for both sequences to account for the washout and potential carryover effect.

The following analyses will be performed to explore the potential weight-adjusted dose response relationship in efficacy. The adjusted dose is defined as period specific dose (500 U or 1000 U) divided by the period specific baseline weight (kg). Period specific baseline weight is the weight prior to the first dose in each treatment period. The adjusted dose will be spitted into 4 groups according to 25th, 50th and 75th percentiles of the adjusted dose. Descriptive statistics of the primary efficacy variable will be presented for each of the four dose groups based on the quartiles. The pairwise differences in mean response among the four groups (6 pairs: group 1 versus 2, 1 vs 3, 1 vs 4, 2 vs 3, 2 vs 4, 3 vs 4) will be estimated using the mixed effects model at α=0.1, with period, dose group and treatment sequence as the fixed effects, and subject nested within sequence as random effect. In addition, the weight-adjusted dose response slope for the continuous weight-adjusted dose will be estimated by the mixed effect model at α=0.1, with period, dose and treatment sequence as the fixed effects and subject nested within sequence as random effect.

The scatter plot of normalized number of angioedema attacks versus weight-adjusted dose will be provided.

10.2 Key Secondary Efficacy Variable(s) and Analysis

Not applicable.

10.3 Other Secondary Efficacy Variable(s) and Analysis

All secondary efficacy variables are listed as following:

- Cumulative Attack Severity. This score is the sum of the maximum symptom severity recorded for each angioedema attack in a treatment period.
- Cumulative Daily Severity. This score is the sum of the severity scores recorded for every day of reported symptoms in a treatment period.
- Number of angioedema attacks requiring acute treatment during each treatment period.
- Change from pre- to post-dose in C1 INH functional activity, C1 INH antigen, and C4 levels.

The endpoints based on attack severity are further defined with the following example:

Study Day	Symptoms Present	Maximum[a] Symptom Severity	Symptom Severity Score	Attack Number	Maximum[b] Attack Severity	Daily Severity
1	Yes	Moderate	2	1	-	2
2	Yes	Moderate	2		2	2
3	No					
4	Yes	Mild	1	2	-	1
5	Yes	Severe	3		-	3
6	Yes	Moderate	2		3	2
7	No					
8	Yes	Moderate	2	3	-	2
9	Yes	Severe	3		-	3
10	Yes	Moderate	2		-	2
11	Yes	Moderate	2		3	2

[a] Maximum Severity across all anatomic locations on the corresponding study day.

[b] Maximum Severity across all anatomic locations and days with symptoms for the corresponding attack.

In this hypothetical example, a patient recorded 9 days of symptoms in an 11-day study period. Because individual attacks require at least one symptom-free calendar day between episodes, this diary fragment identifies three angioedema attacks. The maximum severity of each attack is determined on the last day of symptoms and is derived as Mild, Moderate, or Severe. Coding these categories as Mild=1, Moderate=2, and Severe=3 and summing over the three unique attacks, yields a Cumulative Attack Severity of 8. Finally, summing the reported severity scores of each attack multiplied by the duration of each attack a Cumulative Daily Severity of 37. With respect to these defined endpoints, this hypothetical eleven-day symptom diary would be quantitatively described by:

Endpoint	Value
Number of Angioedema Attacks	3
Cumulative Attack Severity	8
Cumulative Daily Severity	37

For the secondary efficacy variables of Cumulative Attack Severity, Cumulative Daily Severity, and number of angioedema attacks requiring acute treatment, the analysis method will be the

same as the primary variable using the normalized numbers (per month) calculated by following steps --

Any subject who completes a randomized treatment period should provide data with which to derive efficacy scores. Thus, for each individual treatment period, let,

X_i = Number of **days** of participation in that treatment period for Subject *i*,

Y_i = **RAW** Efficacy Score expressing the cumulative period score for Subject *i*,

Y^*_i = **NORMALIZED** Efficacy Score for Subject *i*, (expressed as score per **Day**),

$Y^{\dagger}_i$ = **SCALED** Normalized Efficacy Score for Subject *i*, (expressed as score per **Month**),

Then,

$Y^*_i = Y_i \div X_i$ (the normalized score, expressed as the score per D**ay**),

$Y^{\dagger}_i = Y^*_i \times 30.4$ (the scaled normalized score, expressed as the score per **Month**).

In this study, after obtaining the duration of participation (Xi) in each patient-specific treatment period, the following array can be constructed for the following four efficacy endpoints:

Efficacy Variables	**Raw Score**	**Normalized Score**	**Scaled Score**
Number of Angioedema Attack	Y_{1i}	$Y_1{}^*_i$	$Y_1{}^{\dagger}_i$
Cumulative Attack Severity	Y_{2i}	$Y_2{}^*_i$	$Y_2{}^{\dagger}_i$
Cumulative Daily Attack Severity	Y_{3i}	$Y_3{}^*_i$	$Y_3{}^{\dagger}_i$
Number of Angioedema Attacks Requiring Acute Treatment	Y_{4i}	$Y_4{}^*_i$	$Y_4{}^{\dagger}_i$

The Scaled normalized score will be used for all tabulations, summaries, and analyses involving efficacy data.

For available data in observation period, the summary statistics will be provided for efficacy endpoints along with the treatment periods. Change from observation period in normalized number of angioedema attacks during treatment will be summarized as well.

10.4 Exploratory Efficacy Variable(s) and Analyses

Not applicable.

11. SAFETY ANALYSES

The safety analyses will be performed by treatment using the Safety Set. Safety endpoints include AEs, clinical laboratory variables, vital signs, and C1 INH antibody variables. For each safety variable, the last value collected prior to the first dose of the investigational product will be used as baseline for all analyses of that safety variable.

Summary statistics and changes from baseline to post-baseline for laboratory testing and vital signs by dose group will be presented. Adverse events by dose group, by dose group (dose normalized to body weight [U/kg]), and by time of onset (e.g., during administration of study drug or within 24 hours after the end of injection of study drug) will be summarized. Results of C1 INH antibody testing will be reported for individual subjects and summarized as appropriate.

Final on Treatment Assessment (LAoT) will be defined as the last observation recorded within the period in which the treatment is administered.

11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0 adverse events dictionary.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if:

- it has a start date and time on or after the first dose of investigational product and up to 7 days after the last dose of study drug, or
- it has a start date and time before the date and time of the dose of investigational product (i.e. it is part of the patient's medical history), but increases in severity on or after the date and time of the dose of investigational product.

Adverse events will be collected from the start of first dose until 1 week post-treatment visit, which is at 7±2 days after receiving the last dose of investigational product. All SAEs with an onset within 30 days after the last dose of investigational product will be collected. In addition, any related SAEs with an onset >30 days after last dose of investigational product will also be collected.

Any pre-treatment adverse event starting between the first date of the observation period to the administration of investigational product in Period 1 will be considered as medical history. Any AE starting after first dose of investigational product will be captured for this study.

An overall summary of TEAEs will be provided by treatment, by exposure, by time of onset, including the number and percentage of subjects who experience, and absolute count of events by treatment for:

- Any TEAE
- Any serious TEAE
- Any TEAE related to investigational product in the opinion of the investigator

- Any TEAE leading to dose discontinuation from the study
- Any severe TEAE.
- Any TEAEs leading to Death
- The number and percentage of subjects reporting TEAEs will be tabulated in the following ways:
- By SOC, preferred term and treatment (including absolute count of events)
- By SOC, preferred term, and maximum severity
- By SOC, preferred term, and serious TEAE
- By SOC and preferred term for TEAEs related to investigational product in the opinion of the investigator

For Serious AEs and AEs related to the investigational product if there are greater than 5 events, these will be tabulated by SOC and preferred term. For Serious AEs and AEs related to the investigational product, if there are less than or equal to 5 events, a listing will be provided. All information about AEs collected on the eCRF will be listed alongside the treatment, preferred term, and SOC.

To examine if the overall AE incidence varies as the weight adjusted dose increases, the overall summary of TEAE will be presented by weight-adjusted dose group (dose normalized to body weight [U/kg]). The adjusted dose is defined as period specific dose (500 U or 1000 U) divided by the period specific baseline weight (kg). Period specific baseline weight is the weight prior to the first dose in each treatment period. The adjusted dose will be spitted into 4 groups according to 25th, 50th and 75th percentiles of the adjusted dose.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point will be presented by treatment for the following clinical laboratory variables.

Hematology:

Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued): CBC consisting of WBC and differential counts and percentages, RBC count, hemoglobin, hematocrit, and platelet count.

Clinical Chemistry:

Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued): Blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, carbon dioxide (CO2), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK), total bilirubin, calcium, phosphorus, total protein, and albumin.

Coagulation:

Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued): Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Virology:

Dosing Visit 1a (pre-dose) and 1-week post-treatment (or if prematurely discontinued): Human immunodeficiency virus (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

For all females who have reached menarche, urine pregnancy testing will be performed at the site at the time points specified in Schedules 2 and 4.

Clinical laboratory test values are potentially clinical important (PCI) if they meet either the low or high PCI criteria listed in Table 6 and fall outside the laboratory's normal range in the same direction (high or low) as their PCI criteria. Subjects with post-dose PCI values will be listed. A table will be provided for the shift from baseline to LAoT in clinical laboratory results for biochemistry, hematology, and Coagulation.

Table 6 Criteria for Potentially Clinically Important Laboratory Tests

			Criteria for Clinically Significant Laboratory Abnormalities[a]	
Parameter	**Age Range**	**Gender**	**Low**	**High**
Hematology				
Eosinophils (%)	All	Male, Female	NA	>4 x ULN
Hematocrit	All	Male, Female	<0.6 x LLN	>1.3 x ULN
Hemoglobin	All	Male, Female	<0.6 x LLN	>1.3 x ULN
Neutrophils (%)	All	Male, Female	<0.5 x LLN	NA
Platelets	All	Male, Female	<0.4 x LLN	>2 x ULN
Leukocytes (WBC)	All	Male, Female	<0.5 x LLN	>2 x ULN
Coagulation				
Prothrombin Intl. Normalized Ratio (INR)	All	Male, Female	NA	>1.5 x ULN
Activated Partial Thromboplastin Time (aPTT)	All	Male, Female	NA	>2.0 x ULN
Chemistry				
Albumin	All	Male, Female	<0.6 x LLN	NA

Table 6 Criteria for Potentially Clinically Important Laboratory Tests

			Criteria for Clinically Significant Laboratory Abnormalities[a]	
Parameter	**Age Range**	**Gender**	**Low**	**High**
Alkaline Phosphatase	All	Male, Female	NA	>3.0 x ULN
Alanine Aminotransferase (ALT)	All	Male, Female	NA	>3.0 x ULN
Aspartate Aminotransferase (AST)	All	Male, Female	NA	>3.0 x ULN
Bicarbonate	All	Male, Female	<0.5 x LLN	>1.3 x ULN
Total Bilirubin	All	Male, Female	NA	>1.5 x ULN
Blood Urea Nitrogen (BUN)	All	Male, Female	NA	>3.0 x ULN
Calcium	All	Male, Female	<0.7 x LLN	>1.3 x ULN
Chloride	All	Male, Female	<0.8 x LLN	>1.2 x ULN
Creatinine	All	Male, Female	NA	>1.5 x ULN
Potassium	All	Male, Female	<0.85 x LLN	>1.2 x ULN
Glucose	All	Male, Female	<0.6 x LLN	>3.5 x ULN
Sodium	All	Male, Female	<0.9 x LLN	>1.1 x ULN

NA=Not Applicable; LLN=Lower Limit of Normal; ULN=Upper Limit of Normal; Intl.=International.

[a] If criteria in both directions are shown for a single parameter, then abnormalities in each direction are summarized separately.

11.3 Vital Signs

Descriptive statistics for vital signs (e.g. systolic and diastolic blood pressure and pulse) and their changes from baseline at each post-dose visit and final visit will be presented by treatment.

Vital sign values will be considered PCI if they meet the observed value criteria or the change from baseline criteria listed in Table 7. A supportive listing of subjects with post-baseline PCI values will be provided. All vital signs results will be listed for the Safety Set.

Table 7 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria
		Observed Value
Systolic blood pressure (mmHg)	High	Increase of ≥ 20 from baseline value and ≥ 140
	Low	Decrease of ≥ 20 from baseline value and ≤ 90
Diastolic blood pressure (mmHg)	High	Increase of ≥ 15 from baseline value and ≥ 90
	Low	Decrease of ≥ 15 from baseline value and ≤ 50
Pulse rate (beats per minute)	High	Increase of > 15 from baseline value and ≥ 100
	Low	Decrease of > 15 from baseline value and ≤ 45
Temperature (˚C)	High	> 38.3
	Low	< 35

11.4 Electrocardiogram

Not applicable.

11.5 Other Safety Variables

Not applicable.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population and Pharmacodynamics Population

The Pharmacokinetic Set will consist of all subjects in the Safety Analysis Set with no major deviations related to investigational product intake, for whom the primary pharmacokinetic data are considered sufficient and interpretable, will be included in the Pharmacodynamic Set. Subjects with missing data in some, but not all the periods, will be included in the analysis set.

12.2 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set.

12.2.1 Concentration Data

The concentrations of C1 INH antigen in human plasma samples will be determined using an automated nephelometric assay on the Behring Nephelometer 2. The C1 INH activity in human plasma samples will be determined by a chromogenic assay using a commercially available kit.

12.2.2 Handling BLQ Values

The following procedures will be used for plasma concentrations below the lower limit of quantification (LLOQ) (reported as not quantifiable (NQ)):

Plasma samples that are BLQ are reported as zero on the data listings.

Samples that are BLQ are treated as zero in the calculation of summary statistics for the plasma concentrations at individual time points

Mean concentrations are reported as zero if all values are BLQ, and no descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated.

12.2.3 Pharmacokinetic Parameters

The pharmacokinetic parameters using non-compartmental analysis (NCA) will be estimated for subjects who provided optional PK samples and will be reported separately. Population modeling and simulation will be conducted using sparse PK concentrations from all subjects and will be reported separately.

12.3 Statistical Analysis of Pharmacokinetic Data

Plasma concentrations at each nominal sampling time will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, maximum and minimum).

12.4 Pharmacodynamic Methods

All summaries and analyses of the pharmacodynamic data will be based on the Pharmacodynamic Set.

12.4.1 Concentration data

The concentrations of C4 complement in human plasma samples will be determined using an automated nephelometric assay on the Behring Nephelometer 2.

12.4.2 Pharmacodynamic Parameters

Pharmacodynamic parameters will be determined from the plasma concentration-time data for C4. All calculations will be based on actual sampling times. The analysis will be reported separately.

12.5 Statistical Analysis of Pharmacodynamic Data

Plasma concentrations of C4 at each nominal sampling time will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, maximum, minimum).

12.6 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

12.7 Changes in the Pharmacokinetic, Pharmacodynamic, PK/PD or Statistical Methods from Those stated in the Protocol

There will not be a formal PK/PD analysis as stated in the protocol since this was not listed as part of the objectives in the protocol. This analysis will be done outside of the CSR for this study.

12.8 Pharmacokinetic References

Not applicable.

12.9 Pharmacokinetic and Pharmacodynamic Tables and Listings

Formats and numbering of the tables and listings will be finalized prior to the completion of the Clinical Study Report. No revision to this document is required for changes which do not affect the statistical or pharmacokinetic methods, definitions, or rules defined in this document.

In the event that a limited number of samples yield measurable concentrations, the pharmacokinetic tables and listings will be generated as deemed appropriate. No revision of this document will be required.

Detailed information will be presented in Section 20.

13. OTHER ANALYSES

13.1 Quality of Life Analyses

EQ-5D-Y1 (Youth version of EQ-5D) is a descriptive system of youth health-related quality of life states consisting of five dimensions, each of which can have one of three responses. The responses record the level of severity within a particular EQ-5D dimension. EQ-5D-Y is not intended for use in children 6 years of age (Noyes and Edwards, 2011); however in this study all subjects (6 to 11 years of age and where translated language version is available) will be assessed. The EQ-5D-Y will be completed by the subject at the time points specified in Schedules 1-4, as well as on each day that a subject experiences signs or symptoms of an angioedema attack.

Results of the EQ-5D-Y health status questionnaire will be presented in accordance with the EQ-5D-3L User Guide (version 4.02), and adapted as appropriate for the youth version. EQ-5D-Y will be summarized by the number of subjects and the percentage of subjects in each category at each timepoint. Descriptive statistics for VAS Score and changes from baseline at each post-dose visit and final visit will be presented by treatment. The baseline for VAS Score is defined as the average of all pre-dose visits in Baseline Observation Period.

13.2 Health Economics and Outcomes Research Analyses

Not applicable.

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1 EQ-5D™ is a trade mark of the EuroQol Group.

2. EQ-5D-3L User Guide: Basic information on how to use the EQ-5D-3L questionnaire. Version 4.0, April 2011. Published by the EuroQol Group Executive Office on behalf of the EuroQol Group.

14. INTERIM ANALYSIS

Not applicable, as no interim analysis is planned for this study. However, there will be an administrative look at N = 6 subjects for EU regulatory purposes which is described in the protocol amendment version 4.0 (26. Jan. 2015). Requested TFL will be described in Section 20.

15. DATA MONITORING/REVIEW COMMITTEE

Not applicable, as no data monitoring review is planned for this study.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.1.3 (or newer) of SAS® on a suitably qualified environment.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Analysis populations to analyses specified in the protocol are modified in using Shire standard definition and wording for SAP. Details are presented in Section 4.1, Section 4.2, Section 4.3, Section 4.4, and Section 4.5.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Unless specified otherwise, median, min/max will be presented to the same decimal places as the raw data. Percentage, mean will be presented to 1 more decimal places than the raw data. Standard deviation and standard error will be presented to 2 more decimal places than the raw data.

p-values will generally be presented to 4 decimal places; values less than 0.0001 will be presented as <0.0001.

Treatment Columns Displayed in Summary Tables

The treatment columns displayed will differ between summary tables. Tables that summarize information solely from the pre-therapy or post-therapy periods will generally have the following three treatment columns displayed:

Sequence A/B

Sequence B/A

Total

Tables that summarize efficacy information solely from the on-therapy period will generally have the following six treatment columns displayed:

A/B: Period 1 Cinryze 500 U

A/B: Period 2 Cinryze 1000 U

B/A: Period 1 Cinryze 1000 U

B/A: Period 2 Cinryze 500 U

Treatment A: Cinryze 500 U

Treatment B: Cinryze 1000 U

Tables that summarize information across on-therapy visits will generally have the following 3 treatment columns displayed:

Treatment A: Cinryze 500 U

Treatment B: Cinryze 1000 U

Total (if needed)

Tables that summarize information across visits, including pre-therapy (observation period) and on-therapy visits, will generally have the following 8 treatment columns displayed:

Observation Period (prior to A/B)

A/B: Period 1 Cinryze 500 U

A/B: Period 2 Cinryze 1000 U

Observation Period (prior to B/A)

B/A: Period 1 Cinryze 1000 U

B/A: Period 2 Cinryze 500 U

Treatment A: Cinryze 500 U

Treatment B: Cinryze 1000 U

The "Observation Period (prior to A/B)" and " Observation Period (prior to B/A)" columns will be the only columns populated for the pre-therapy visit (observation period) in such tables.

18.2 Derived Efficacy Variables

Not applicable.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the date and time of dose of investigational product, then the results from the final assessment made prior to the date and time of dose of investigational product will be used as baseline. If clinical discharge assessments are repeated or unscheduled, the latest assessment will be used as the clinical discharge assessment for generating descriptive statistics. However, all post-baseline assessments will be used for post-baseline overall PCI value determination, and all assessments will be presented in the data listings.

In the following sections, where missing times are seen on the database, they are handled using the same underlying assumptions as for missing dates.

18.4 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

18.5 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

MISSING DAY, MONTH AND YEAR

- The entire date is missing, then the first dose date of investigation product will be assigned to the missing fields.

MISSING DAY AND MONTH

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is not the same as the year of the date of the first dose of investigational product, then set day to "01" and month to "01".

MISSING MONTH ONLY

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

MISSING DAY ONLY

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If the month and year of the incomplete start date are not the same as the month and year of the date of the first investigational product, then set day to "01".

18.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

MISSING DAY, MONTH AND YEAR

- If the entire date is missing, then the last dose date of investigation product will be assigned to the missing fields.

MISSING DAY AND MONTH

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational

product will be assigned to the missing fields.

- If the year of the incomplete end date is not the same as the year of the date of the last dose of investigational product, then set day to "31" and month to "12".

MISSING MONTH ONLY

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

MISSING DAY ONLY

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.
- If the month and year of the incomplete end date are not the same as the month and year of the date of the last investigational product, then set day to last day of the month of the incomplete end date.

18.6 Missing Date Information for Adverse Events

18.6.1 Incomplete Start Date

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date

Follow same rules as in Section 18.5.2.

18.7 Missing Severity Assessment for Adverse Events

If the severity is missing for an AE starting on or after the date of the dose of the investigational product, then a severity of "Severe" will be assigned. If the severity is missing for an AE began before the date of the first dose of investigational product, then a severity of "Mild" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the dose of the investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

Not applicable.

19. REFERENCES

Caballero T. Angio-oedema due to hereditary C1 inhibitor deficiency in children. Allergol Immunopathol (Madr). 2012; Mar 12. [Epub ahead of print]

Noyes J, Edwards RT. EQ-5D for the assessment of health-related quality of life and resource allocation in children: a systematic methodological review. Value Health. 2011; 14(8):1117-1129.

20. TABLE OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

20.1 Tables

Table	Title	Shire Std	EU PIP
1.1.1	Disposition by Treatment Sequence (Enrolled Set)	Y	Y
1.1.2	Disposition by Treatment (Safety Set)	Y	Y
1.2	Demographic and Baseline Characteristics by Treatment Sequence (Safety Set)	Y	Y
1.3.1	Prior Medications/Treatments by Treatment Sequence (Safety Set)	Y	Y
1.3.2	Concomitant Medications/Treatments by Treatment (Safety Set)	Y	Y
1.5.1	Protocol Deviations and Violations by Treatment (Safety Set)	Y	Y
1.6.1	Summary of General Medical History (Safety Set)	N	Y
1.6.2	Summary of HAE History (Safety Set)	N	Y
2.1	Summary of C1 INH Antigen Plasma Concentrations by Treatment (Pharmacokinetic Set)	N	Y
2.2	Summary of C1 INH Functional Activity by Treatment (Pharmacokinetic Set)	N	Y
2.3	Summary of C4 Plasma Concentrations by Treatment (Pharmacodynamic Set)	N	Y
2.4	Summary of C1 INH Antigen and Functional Activity Pharmacokinetic Parameters by Treatment (Pharmacokinetic Set)	N	Y
3.1	Analysis of Efficacy Endpoints During Treatment (Scaled Score Normalized per Month) (Full Analysis Set)		
3.1a	Analysis of Efficacy Endpoints During Treatment (Scaled Score Normalized per Month) Excluding First Two Weeks of Period 2 (Full Analysis Set)		
3.1b	Analysis of Efficacy Endpoints During Treatment (Scaled Score Normalized per Month) Excluding First Two Weeks of Both Period (Full Analysis Set)		
3.2	Summary of Efficacy Endpoints (Scaled Score Normalized per Month) (Full Analysis Set)	N	Y
3.3	Analysis of Efficacy Endpoints (Scaled Score Normalized per Month) using Mixed Effect Model (Full Analysis Set)	N	N
3.3a	Analysis of Efficacy Endpoints (Scaled Score Normalized per Month) using Mixed Effect Model Excluding First Two Weeks of Period 2 (Full Analysis Set)	N	N
3.3b	Analysis of Efficacy Endpoints (Scaled Score Normalized per Month) using Mixed Effect Model Excluding First Two Weeks of Both Period (Full Analysis Set)	N	N

3.4	Summary of Change from Observation Period in Normalized Number of Angioedema Attacks during Treatment (Full Analysis Set)	N	Y
3.5	Summary of Efficacy Endpoints (Scaled Score Normalized per Month) by Weight-Adjusted Dose Group (Full Analysis Set)	N	N
3.6.1	EQ-5D-Y by Treatment and Scheduled Visits (Full Analysis Set)	N	N
3.6.2	EQ-5D-Y VAS Scores by Treatment and Scheduled Visit (Full Analysis Set)	N	N
4.1.1	Investigational Product Exposure by Treatment Sequence and Period (Safety Set)	Y	Y
4.1.2	Investigational Product Exposure by Treatment (Safety Set)	Y	Y
4.2.1	Overall Treatment-Emergent Adverse Events by Treatment (Safety Set)	Y	Y
4.2.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment (Safety Set)	Y	Y
4.2.3	Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment (Safety Set)	Y	Y
4.2.4	Treatment-Emergent Adverse Events by Preferred Term, and Treatment (Safety Set)	Y	Y
4.2.5	Overall Treatment-Emergent Adverse Events by Weight-Adjusted Dose Group (Safety Set)	Y	Y
4.3.1.1	Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term, and Treatment (Safety Set)	Y	Y
4.3.1.2	Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term, and Time of Onset (Safety Set)	Y	Y
4.3.2	Treatment-Emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term, and Treatment (Safety Set)	Y	Y
4.6.1	Quantitative Clinical Laboratory Results by Treatment: Biochemistry (Safety Set)	Y	Y
4.6.2	Normal Ranges and PCI Criteria: Biochemistry	Y	Y
4.6.3	Quantitative Clinical Laboratory Results by Treatment: Hematology (Safety Set)	Y	Y
4.6.4	Normal Ranges and PCI Criteria: Hematology	Y	Y
4.6.5	Quantitative Clinical Laboratory Results by Treatment: Coagulation (Safety Set)	Y	Y
4.6.6	Normal Ranges and PCI Criteria: Coagulation	Y	Y
4.6.7	Subjects with Potentially Clinically Important Laboratory Results (Safety Set)	Y	Y

4.6.8	Shift from Baseline to LAoT in Clinical Laboratory Results: Biochemistry (Safety Set)	Y	Y
4.6.9	Shift from Baseline to LAoT in Clinical Laboratory Results: Hematology (Safety Set)	Y	Y
4.6.10	Shift from Baseline to LAoT in Clinical Laboratory Results: Coagulation (Safety Set)	Y	Y
4.7.1	Actual Values and Change from Baseline in Vital Signs by Treatment (Safety Set)	Y	Y
4.7.2	Subjects with Potentially Clinically Important Vital Signs (Safety Set)	Y	Y

20.2 Figures

Figure	Title	Shire Std	EU PIP
3.1	Overview of Number of Angioedema Attacks during Treatment Period in Crossover Design Study Scatter Plots, Subject Profiles by Treatment Sequence, and Mean Number of Angioedema Attacks of each Period by Treatment (Full Analysis Set)	N	Y
3.2	Subject Angioedema Attacks and Severity Profile by Treatment (Full Analysis Set)	N	Y
3.3	Overview of Efficacy Endpoints (Scaled Score Normalized per Month) in Crossover Design Study Spaghetti Plots by Subject Profiles (Full Analysis Set)	N	Y
3.4	Bar Plot of Normalized Number of Angioedema Attacks by Treatment (Full Analysis Set)	N	Y
3.5	Scatter Plot of Normalized Number of Angioedema Attacks versus Weight-Adjusted Dose (Full Analysis Set)	N	Y

20.3 Data Listings

Listing	Title	Shire Std	EU PIP
1.1	Subject Disposition (Enrolled Subjects)	Y	Y
1.2	Subjects Who Terminated from the Study (Enrolled Subjects)	Y	Y
1.3	Study Analysis Set Classification (Enrolled Subjects)	Y	Y
2.1	Deviations from Inclusion/Exclusion Criteria (Enrolled Subjects)	Y	Y
2.2	Protocol Deviations (Enrolled Subjects)	Y	Y
4.1	Subject Demographic and Baseline Characteristics (Enrolled Subjects)	Y	Y
4.2.1	Medical History (Enrolled Subjects)	Y	Y
4.2.2	HAE History (Enrolled Subjects)	N	Y
4.3.1	Prior and Concomitant Medications (Enrolled Subjects)	Y	Y
4.3.2	Prior and Concomitant Treatments (Enrolled Subjects)	Y	Y
5.1	Investigate Product Accountability (Safety Set)	Y	Y
5.2	Pharmacokinetic Plasma Sampling (Safety Set)	Y	Y
5.3	Individual C1 INH Plasma Concentrations and Functional Activity (Pharmacokinetic Set)	N	Y
5.4	Individual C1 INH Antigen and Functional Activity Pharmacokinetic Parameters (Pharmacokinetic Set)	N	Y
5.5	Individual C4 Plasma Concentrations (Pharmacodynamic Set)	N	Y
6.1	Listing of Efficacy Endpoints (Full Analysis Set)	N	Y
6.2	Listing of Subject Data for Each Angioedema Attack (Full Analysis Set)	N	Y
6.5	EQ-5D-Y (Full Analysis Set)	N	N
7.1.1	Adverse Events (Safety Set)	Y	Y
7.1.2	Serious Adverse Events and Adverse Events Leading to Discontinuation (Safety Set)	Y	Y
7.1.3	Treatment-Emergent Adverse Events Considered Related to Investigational Product (Safety Set)	Y	Y
8.1	Clinical Laboratory Test Results: Biochemistry, Hematology, and Coagulation (Safety Set)	Y	Y

Listing	Title	Shire Std	EU PIP
8.1a	Clinical Laboratory Test Result: Antibody Against C1-Inhibitor (Safety Set)	Y	Y
8.2	Vital Signs (Safety Set)	Y	Y