STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP616-300
Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults with Hereditary Angioedema
Drug:	SHP616, C1 esterase inhibitor [human] liquid for injection
Sponsor:	Shire Development LLC and International Affiliates 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date:	Final Version 1.0, Date 17AUG2017

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ABBREVIATIONS

AE	adverse event
AE-QoL	angioedema quality of life (questionnaire)
AAS	Angioedema Activity Score
ATE	arterial thromboembolism
AUC	area under the curve
AUC_{last}	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0-\infty}$	area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
C1 INH	C1 esterase inhibitor or C1 inhibitor
CI	confidence interval
CL	clearance
CL/F	total body clearance for extravascular administration divided by the fraction of dose absorbed
C_{max}	maximum concentration occurring at the time of maximum observed concentration sampled during a dosing interval
C_{min}	minimum concentration occurring at the time of maximum observed concentration sampled during a dosing interval
CRF	case report form
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
EQ-5D-5L	EuroQol 5-dimensional 5-level descriptive system
EU	European Union
FDA	Food and Drug Administration
HAE	hereditary angioedema
HIV	human immunodeficiency virus
HRUA	health resource utilization assessment
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
NNA	normalized number of attacks
PD	pharmacodynamics
PE	pulmonary embolism

PK	pharmacokinetics
PCI	Potentially clinical important
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDS	Sheehan Disability Scale
$t_{1/2}$	terminal half-life
TCSR	time-to-subject-assessed-complete-symptom resolution
TEAE	treatment-emergent adverse event
TISI	time-to-subject-assessed-initial-symptom improvement
t_{max}	time of maximum observed concentration sampled during a dosing interval
US	United States
VAS	Visual Analogue Scale
WPAI-GH	Work Productivity and Activity Impairment-General Health (questionnaire)

1. INTRODUCTION

This is the full analysis Statistical Analysis Plan (SAP) for Study SHP616-300. The SAP provides a technical and detailed elaboration of the statistical analyses of safety and efficacy data as described in the study protocol amendment 4.0 dated 08 February 2017. Specifications for tables, figures, and listings will be provided in a separate document.

2. STUDY DESIGN

2.1 General Study Design

This is a phase 3, randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study to evaluate the efficacy and safety of subcutaneous (SC) administration of 2000 IU of C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks in adolescents and adults with hereditary angioedema (HAE).

Individual participation from the screening visit through the 1-month post-treatment visit will be approximately 9 months (up to 21-day screening period, two 14-week treatment periods [total 28 weeks] with no washout between treatment periods, and 1-week and 1-month post-treatment follow-up visits). A study flow chart is shown below (Figure 1).

Participants are expected to receive blinded investigational product (C1 esterase inhibitor [human] liquid for injection or placebo) twice weekly (every 3 or 4 days) for 14 weeks in each treatment period. Eligible subjects will be randomized to one of the three treatment sequences, A/B, B/A, or A/A (Table 1).

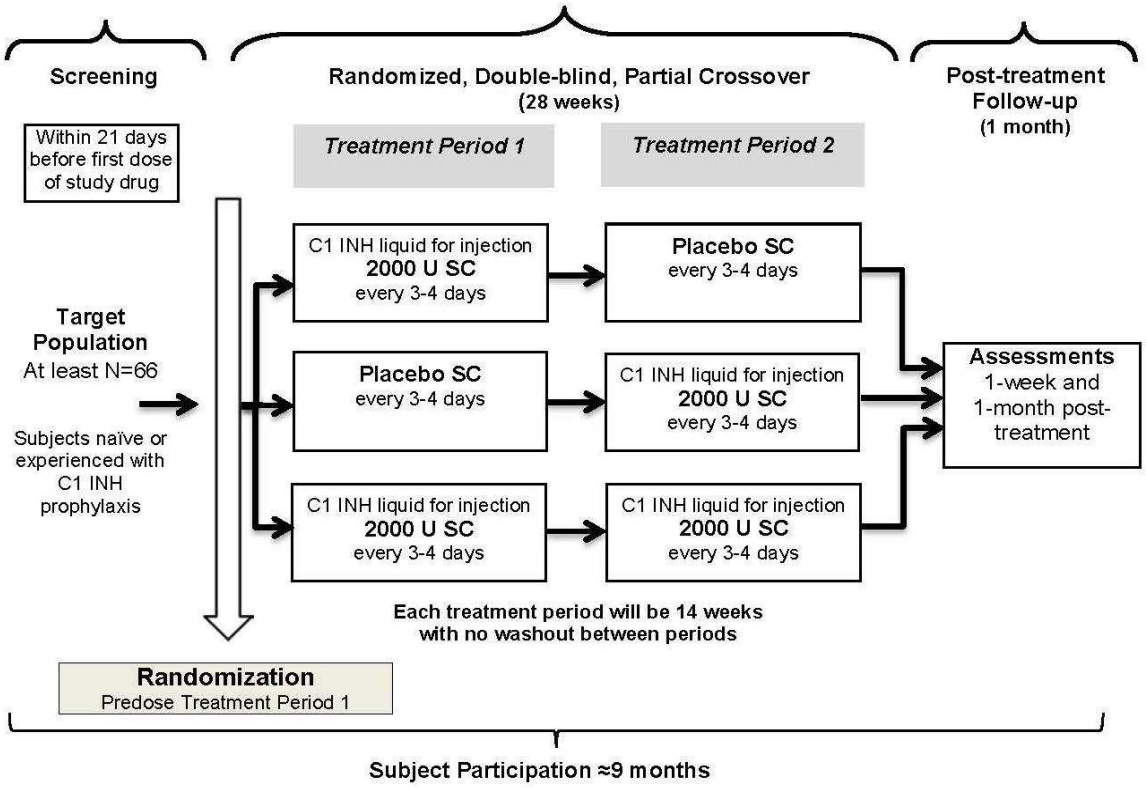
Table 1: Treatment Sequences

Sequence	Treatment: Period 1/Period 2	Approximate Number of Subjects Randomized
1	A/B	26
2	B/A	26
3	A/A	14

Treatment A=2000 IU (4.0 mL) C1 esterase inhibitor [human] liquid for injection administered SC twice weekly (every 3 or 4 days) for 14 weeks.

Treatment B=Placebo (4.0 mL) administered SC twice weekly (every 3 or 4 days) for 14 weeks.

Figure 1: Study Design Flow Chart



2.2 Randomization

The randomization schedule will be stratified for use of prophylactic therapy with C1 INH at the time of enrollment versus no prophylactic therapy with C1 INH at the time of enrollment. At least 66 eligible subjects will be randomized to 1 of 3 treatment sequences prior to the first dose of investigational product in Treatment Period 1. The actual treatment sequence given to individual subjects is determined by a randomization schedule automatically assigned by the IRT.

2.3 Blinding

The study will be double-blinded. All study site personnel, subjects, qualified home health professionals, and the sponsor will be blinded to treatment sequence.

2.4 Schedule of Assessments

Table 2: Schedule of Assessments – Treatment Period 1

		TREATMENT PERIOD 1 (BY STUDY WEEK)																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		DOSING VISITS (1a to 28a)																											
Procedures	**Screen[a]**	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**	**18a**	**19a**	**20a**	**21a**	**22a**	**23a**	**24a**	**25a**	**26a**	**27a**	**28a**
Informed consent	✔																												
Medical history	✔																												
Inclusion/Exclusion criteria	✔	✔[c]																											
Adverse events[b]	✔	✔ ----------																											✔
Randomization (predose)		✔[c]																											
Physical examination	✔	✔[c]							✔								✔								✔				✔
Prior/concomitant meds	✔	✔[c]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Height and body weight	✔																												
Vital signs (BP, pulse)[d, e]	✔	✔	✔	✔	✔				✔								✔								✔				✔
12-lead ECG[d]	✔																												
Safety labs[f]	✔	✔[c]							✔								✔								✔				✔
UA with microscopy		✔[c]																											✔
Virology screening[g]	✔																												
Pregnancy testing[h]	✔	✔[c]																											
IP injection		✔[i]	✔	✔	✔	✔	✔	✔	✔[i]	✔	✔	✔	✔	✔	✔	✔	✔[i]	✔	✔	✔	✔	✔	✔	✔	✔[i]	✔	✔	✔	✔[i]
ISR assessment[j]		✔							✔								✔								✔				✔[j]
Acceptability survey[k]																													✔
Self-administration survey[k]																													✔
Angioedema attack monitoring[k, l]		✔ ----------																											✔
AAS[k]		✔ ----------																											✔
AE-QoL questionnaire[k]		✔[c]								✔								✔								✔			
EQ-5D-5L[k, m,]		✔[c]																							✔				
WPAI-GH and SDS[k]		✔[c]		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔	
HRUA-HAE		✔[c]							✔								✔								✔				
Anti-C1 INH antibodies		✔[c]							✔[c]								✔[c]								✔[c]			✔[c,n]	✔[c,n]
PK/PD sampling	**A detailed blood sample collection schedule for PK/PD assessments is provided in Table 5**																												

Table 2: Schedule of Assessments – Treatment Period 1

		TREATMENT PERIOD 1 (BY STUDY WEEK)																									
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		DOSING VISITS (1a to 28a)																									
Procedures	**Screen[a]**	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**	**18a**	**19a**	**20a**	**21a**	**22a**	**23a**	**24a**	**25a**	**26a**	**27a**	**28a**

AAS=angioedema activity score; AE-QoL=angioedema quality of life; aPTT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 esterase inhibitor; CRF=case report form; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; HAE=hereditary angioedema; HIV=human immunodeficiency virus; HRUA=health resource utilization assessment; INR=international normalized ratio; IP=investigational product; ISR=injection site reaction; PD=pharmacodynamic; PK=pharmacokinetic; PT=prothrombin time; SDS=Sheehan Disability Scale; UA=urinalysis; WPAI-GH=Work Productivity and Activity Impairment General Health Questionnaire

[a] All subjects will have a screening evaluation within 21 days prior to the first dose of investigational product (Visit 1a=Dosing Day 1).

[b] Adverse events will be collected from the time of informed consent through 7 days after the last dose of investigational product.

[c] Specified procedures should be performed prior to investigational product administration.

[d] Vital signs and ECGs will be measured using standard methods at each study site. Additional vital signs measurements and ECGs may be performed during the study if clinically indicated.

[e] On dosing days, vital signs should be measured ≤30 min before the start of the injection, ≤10 min after the end of the injection, and then between 30 min and 1 h after the end of theinjection. Note: Vital sign measurements are not required at Visits 2a, 3a, and 4a for subjects self-administering investigational product without supervision (ie, assessment may not be possible).

[f] Biochemistry, hematology, and coagulation (aPTT, PT, INR, D-dimer). In addition, D-dimer should be evaluated in any subject who presents at a study visit with signs and symptoms consistent with suspected venous thromboembolism.

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

[h] Female subjects of childbearing potential; serum pregnancy test at screening and urine pregnancy test at all other time points.

[i] Investigational product will be administered by qualified personnel at the investigational site at Dosing Visits 1a, 8a, 16a, 24a, and 28a.

[j] Injection site reaction assessments will be performed 15 min, 30 min, and 1 h after the end of the injection. At Visit 28a the overall impact on daily living (yes/no) and the duration of injection site reactions will be assessed for each subject.

[k] In the electronic subject diary.

[l] The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary.

[m] In addition to the scheduled time points, subjects should complete the EQ-5D-5L on each day that they experience signs or symptoms of an angioedema attack.

[n] Collection of blood sample for the immunogenicity assessment should coincide with the subject's PK/PD sampling schedule and will occur at either Visit 27a or Visit 28a (see Table 5).

Table 3: Schedule of Assessments–Treatment Period 2

	TREATMENT PERIOD 2 (BY STUDY WEEK)																									
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	DOSING VISITS (1b to 28b)																									
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**	**25b**	**26b**	**27b**	**28b**
Adverse events[a]	✔ ----------																									✔
Physical examination	✔ [b]							✔								✔								✔				✔
Concomitant medications	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Body weight	✔																											
Vital signs (BP, pulse)[c]	✔	✔	✔	✔				✔								✔								✔				✔
Safety labs[d]	✔ [b]							✔								✔								✔				✔
UA with microscopy	✔ [b]																											✔
Pregnancy testing[e]	✔ [b]																											
IP injection	✔ [f]	✔	✔	✔	✔	✔	✔	✔ [f]	✔	✔	✔	✔	✔	✔	✔	✔ [f]	✔	✔	✔	✔	✔	✔	✔	✔ [f]	✔	✔	✔	✔ [f]
ISR assessment[g]	✔							✔								✔								✔				✔ [g]
Acceptability survey																												✔
Self-administration survey[h]																												✔
Angioedema attack monitoring[h, i]	✔ ----------																											✔
AAS[h]	✔ ----------																											✔
AE-QoL questionnaire[h]	✔ [b]								✔								✔								✔			
EQ-5D-5L[h, j]	✔ [b]																							✔				
WPAI-GH and SDS[h]	✔ [b]		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔	
HRUA-HAE	✔ [b]							✔								✔								✔				
Anti-C1 INH antibodies	✔ [b]							✔ [b]								✔ [b]								✔ [b]				✔ [b]
PK/PD sampling	**A detailed blood sample collection schedule for PK/PD assessments is provided in Table 5**																											

Table 3: Schedule of Assessments–Treatment Period 2

	TREATMENT PERIOD 2 (BY STUDY WEEK)																									
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	DOSING VISITS (1b to 28b)																									
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	25b	26b	27b	28b

AAS=angioedema activity score; AE-QoL=angioedema quality of life; aPTT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 esterase inhibitor; CRF=case report form; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; HAE=hereditary angioedema; HRUA=health resource utilization assessment; INR=international normalized ratio; IP=investigational product; ISR=injection site reaction; PD=pharmacodynamic; PK=pharmacokinetic; PT=prothrombin time; SDS=Sheehan Disability Scale; UA=urinalysis; WPAI-GH=Work Productivity and Activity Impairment-General Health Questionnaire
Note: ECGs may be performed during Treatment Period 2 if clinically indicated, using standard methods at each study site.
[a] Adverse events will be collected from the time of informed consent through 7 days after the last dose of investigational product.
[b] Specified procedures should be performed prior to investigational product administration.
[c] Vital signs will be measured using standard methods at each study site. Additional vital signs measurements may be performed during the study if clinically indicated. On dosing days, vital signs should be measured ≤30 min before the start of the injection, ≤10 min after the end of the injection, and then between 30 min and 1 h after the end of the injection. Note: Vital sign measurements are not required at Visits 2b, 3b, and 4b for subjects self-administering investigational product without supervision (ie, assessment may not be possible).
[d] Biochemistry, hematology, and coagulation (aPTT, PT, INR, D-dimer). In addition, D-dimer should be evaluated in any subject who presents at a study visit with signs and symptoms consistent with suspected venous thromboembolism.
[e] Urine pregnancy test for female subjects of childbearing potential.
[f] Investigational product will be administered by qualified personnel at the investigational site at Dosing Visits 1b, 8b, 16b, 24b, and 28b.
[g] Injection site reaction assessment will be performed 15 min, 30 min, and 1 h after the end of the injection. At Visit 28b, the overall impact on daily living (yes/no) and the duration of injection site reactions will be assessed for each subject.
[h] In the electronic subject diary.
[i] The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary.
[j] In addition to the scheduled time points, subjects should complete the EQ-5D-5L on each day that they experience signs or symptoms of an angioedema attack.

Table 4: Schedule of Assessments–Early Discontinuation, 1-week and 1-month Post-treatment Visits

Procedures	Early Discontinuation Visit[a] [If Applicable]	1-Week (±1 day) Post-treatment Visit [All Subjects]	1-Month (±2 days) Post-treatment Visit [All Subjects]
Concomitant medications	✔	✔	
Physical examination	✔	✔	
Vital signs (BP, pulse)[b]	✔	✔	
Safety labs[c]	✔	✔	
UA with microscopy	✔	✔	
Pregnancy testing[d]	✔	✔	
Adverse events/ SAEs[g]	✔	✔	✔
Angioedema attack monitoring[e, f]	✔	✔	
AAS[e]	✔	✔	
Acceptability survey[e]	✔		
Self-administration survey[e]	✔		
AE-QoL questionnaire[e]	✔	✔	
EQ-5D-5L[e]	✔	✔	
WPAI-GH and SDS[e]	✔	✔	
HRUA-HAE			✔
Immunogenicity (anti-C1 INH antibodies)	✔	✔	✔
PK/PD	✔	✔	✔

AAS=angioedema activity score; AE-QoL=angioedema quality of life; aPTT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 esterase inhibitor; CRF=case report form; EQ-5D-5L=EuroQol 5-dimension 5-level descriptive system; HAE=hereditary angioedema; HRUA=health resource utilization assessment; INR=international normalized ratio; PT=prothrombin time; SAE=serious adverse event; SDS=Sheehan Disability Scale; UA=urinalysis; WPAI-GH=Work Productivity and Activity Impairment-General Health Questionnaire

Note: Investigators will report all SAEs that occur ≤30 days after the last dose of investigational product and related SAEs that occur >30 days after the last dose of investigational product to Shire Pharmacovigilance Department.

[a] If a subject prematurely discontinues investigational product, regardless of the reason, the early discontinuation visit procedures are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-week and 1-month post-treatment follow-up visits.

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

[c] Biochemistry, hematology, and coagulation (aPTT, PT, INR, D-dimer).

[d] A urine pregnancy test will be performed for all female subjects of childbearing potential.

[e] In the electronic subject diary. If possible, subjects should complete the subject diary on the day of discontinuation or at the 1-week post-treatment visit.

[f] The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary.

[g] Serious Adverse Events (SAEs) are to be followed until 1 month post-treatment visit.

Table 5: Blood Sample Collection for PK/PD Analyses

TREATMENT PERIOD 1	
	Blood Sampling Time Points[a]
Visit / Dose #	**C1 INH Antigen, C1 INH Functional, C4**
1a / Dose 1[b]	Predose 1 (within 15 min)
2a / Dose 2[c]	Predose 2 (within 15 min)
8a / Dose 8	Predose 8 (within 15 min)
16a / Dose 16	Predose 16 (within 15 min)
24a / Dose 24	Predose 24 (within 15 min)
Either 27a or 28a / Dose 27 or 28[d]	Predose 27 or 28 (within 15 min)
	48 hours postdose 27 or 28 (±3 hours)
TREATMENT PERIOD 2	
1b / Dose 1	Predose 1 (within 15 min)
2b / Dose 2[c]	Predose 2 (within 15 min)
8b / Dose 8	Predose 8 (within 15 min)
16b / Dose 16	Predose 16 (within 15 min)
24b / Dose 24	Predose 24 (within 15 min)
28b / Dose 28	Predose 28 (within 15 min)
	24 hours postdose 28 (±3 hours) – optional sampling time point
	48 hours postdose 28 (±3 hours)
	72 hours postdose 28 (±6 hours) – optional sampling time point
	96 hours postdose 28 (±6 hours)
EARLY DISCONTINUATION (if applicable) and POST-TREATMENT	
Early discontinuation	
1-week (± 1 day)	
1-month (± 2 days)	

C1 INH=C1 inhibitor; PD=pharmacodynamics; PK=pharmacokinetics
[a] The actual date and time of each sample collection will be recorded, therefore the sampling window is provided for guidance is as an approximate value.
[b] C1q concentration will also be assessed using the baseline sample (predose at Dosing Visit 1a).
[c] Subjects who self-administer investigational product without supervision are not required to have a blood sample collected at Visit 2a or 2b.
[d] To avoid collecting a PK/PD blood sample during the weekend, subjects have the option for a predose and 48 h postdose sample to be collected at either Visit 27a or 28a.

2.5 Determination of Sample Size

The enrollment goal for this study is to randomize at least 66 subjects to ensure 54 subjects complete both treatment periods (44 for the crossover sequences, 10 for the active/active sequence).

For the primary efficacy endpoint, the normalized number of angioedema attacks (NNA), a sample of 44 subjects will provide 90% power at an alpha level of 0.025 (1-sided) to detect a difference of 1.0 attacks per month between active treatment and placebo assuming a standard deviation of the difference of 2.0.

Regarding the analysis of the key secondary endpoint, the proportion meeting criterion P_R relative to placebo, 44 subjects will provide 90% power to test the hypothesis H_0: proportion

≤0.2 against H_1: proportion >0.2, assuming the true proportion is 0.44 by using a 1-group Chi-square test at an alpha level of 0.025 (1-sided).

With respect to safety, a Safety Analysis Set of 60 subjects ensures that if the true population event proportion of any subject with a particular event is at least 5%, then the probability of observing at least 1 such event in the Safety Analysis Set is >95%.

The sample size calculation was conducted using nQuery + nTerim 2.0.

3. OBJECTIVES

3.1 Primary Objective

To demonstrate superior efficacy of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks relative to placebo based on the NNA during a treatment period.

3.2 Secondary Objectives

The key secondary objectives are to demonstrate the superior efficacy of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks relative to placebo as measured by:

1. The proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo perio

2. The NNA during each treatment period excluding the first 2 weeks

3. The proportion of subjects meeting the criterion of at least a 50% reduction in the NNA for the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period excluding the first 2 weeks of each treatment period.

Other secondary objectives are:

- To assess the proportion of responders during treatment with 2000 IU C1 esterase inhibitor [human] liquid for injection relative to treatment with placebo, where the proportion of responders is defined as achieving at least a 50% reduction, and/or achieving reduction to less than 1 NNA during a treatment period relative to the pretreatment assessment (ie, the subject's attack rate without prophylactic treatment)

- To assess the severity of angioedema attacks during treatment with 2000 IU C1 esterase inhibitor [human] liquid for injection relative to treatment with placebo

- To assess the number of attack-free days during treatment with 2000 IU C1 esterase inhibitor [human] liquid for injection relative to treatment with placebo

- To assess the number of angioedema attacks requiring acute treatment during treatment with 2000 IU C1 esterase inhibitor [human] liquid for injection relative to treatment with placebo

- To assess the safety and tolerability of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection

- To assess the immunogenicity of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection

- To characterize the PK and PD of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection
- To assess the clinical response and safety/tolerability of icatibant (Firazyr®) for the treatment of acute angioedema attacks (applicable for subjects ≥18 years of age)
- To assess disease activity as measured by the Angioedema Activity Score (AAS)
- To evaluate subject experience with self-administration of SC 2000 IU C1 esterase inhibitor [human] liquid for injection
- To evaluate the impact of treatment on health status (quality of life) in this patient population

4. SUBJECT POPULATION SETS

4.1 Screened Set

All subjects who have signed an informed consent will be included in the screened set.

4.2 Enrolled Set

All subjects who have signed an informed consent and some study procedures have begun will be included in the enrolled set.

4.3 Randomized Set

All subjects in the Screened Set for whom a randomization number has been assigned will be included in the randomized set.

4.4 Safety Set

All subjects who have taken at least 1 dose of investigational product will be included in the safety set.

4.5 Full Analysis Set

All subjects in the Safety Set who have at least 1 post-baseline (i.e., randomization) primary efficacy assessment will be included in the full analysis set.

4.6 Per-protocol Set

All subjects in the Full Analysis Set who complete scheduled primary assessments for 6 study weeks and who do not have pre-defined protocol deviations that may affect the primary efficacy endpoint will be included in the Per-protocol Set. Refer to Appendix 19.4 for the protocol deviations that exclude subjects from the Per-protocol Set.

4.7 Completer Set

All subjects in the Full Analysis Set who have completed the final scheduled primary assessment for the study will be included in the completer set.

4.8 Pharmacokinetic and Pharmacodynamic Set

All subjects in the Safety Set for whom the primary PK and PD data are considered sufficient and interpretable will be included in the pharmacokinetic and pharmacodynamic set.

5. SUBJECT DISPOSITION

The number and percentage of subjects who have been randomized and included in each subject population set will be presented by treatment sequence and overall. The denominator for the percentage calculation will be the number of randomized subjects.

The number and percentage of subjects who prematurely discontinued during the study will be presented for each treatment sequence, treatment at time of discontinuation and overall for the Safety Set and Full Analysis 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 treatment received at time of discontinuation for the Safety Set and Full Analysis Set.

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

Subjects who are excluded from the Per-protocol Set will be listed for the Full Analysis Set. Deviations from Inclusion/Exclusion criteria will be listed for the Screened Set.

6. PROTOCOL VIOLATIONS AND DEVIATIONS

Protocol deviation is defined as a variation from processes or procedures defined in a protocol. Deviations usually do not preclude the overall evaluability of subject data for either efficacy or safety, and are often acknowledged and accepted in advance by the sponsor.

Major Protocol deviation (violation) is defined as a significant departure from processes or procedures that were required by the protocol. Violations often result in data that are not deemed evaluable for a per-protocol analysis, and may require that the subject(s) who violate the protocol be discontinued from the study.

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

All protocol violation and deviation data will be listed for the subjects in the Safety Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Subject demographics including age, age group (<18 yrs, 18-<=64 yrs, and >=65 yrs), sex, race, ethnicity, weight, height, BMI, and use of prophylactic therapy with C1 INH at randomization use will be summarized by treatment sequence for the Safety Set,Full Analysis Set, and Per-protocol Set. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), 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 subjects in the Enrolled Set.

7.1 Medical History

A medical history will be taken at the screening visit. All medical history findings that have been present/active within the 5 years prior to enrollment or any relevant history beyond 5 years that is considered important by the investigator will be entered into the CRF regardless of clinical relevance or presence at study start. The number and percentage of subjects in each primary system organ class (SOC) and each preferred term (PT) will be summarized by treatment sequence, a total of crossover sequences, and a total of all sequences on Safety set and Full Analysis Set. Medical history findings will also be listed for all subjects in the Enrolled Set.

7.2 HAE History

The following information associated with HAE history will be recorded in the CRF 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)
- Estimated date of last angioedema (swelling) attack prior to the screening visit
- Any therapy received during the last 12 months for management of HAE
- Any use of prophylactic therapy with C1 INH or Androgens prior to screening
- Any long-term prevention at randomization
- Total number, typical locations and average overall duration (days), and average overall severity of angioedema attacks experienced:

during the 3 consecutive months prior to the screening visit (all subjects)

and (if applicable)

during the 3 consecutive months prior to starting prophylactic therapy with C1 INH or androgens.

- Typical Visual Analogue Scale (VAS) score for the subject's angioedema attack pain:

  during the 3 consecutive months prior to the screening visit (all subjects)

  and (if applicable)

  during the 3 consecutive months prior to starting prophylactic therapy with C1 INH or androgens.

HAE history will be summarized by treatment sequence for the Safety Set and Full Analysis Set, and also be listed for all the subjects in the Enrolled Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational Product

For all treated subjects, including the ones who had early termination, treatment exposure is the duration between the first dose date and last dose date in each treatment period. Average daily dose, total dose, total number of doses, total exposure, length of exposure to investigational product (<=1 wk, >1 - <=2 wk, >2 - <=5 wks, >5 - <=10 wks, >10 - <=14 wks, >14 – <=18 wks, >18 - <=24 wks, >24 - <=28 wks, >28 wks), and treatment compliance will be summarized by treatment for the Safety Set and Full Analysis Set.

A listing will be created by subject and treatment 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 volume of investigational product actually taken by a subject during that period divided by the volume of investigational product expected to be taken during the same period, multiplied by 100. Each complete dose of investigational product will consist of a total volume of 4 mL. For doses where the drug administration was not complete, the dose is the total volume administered. The volume expected to be taken for a specified period is calculated as the number of weeks in that period multiplied by 4ml and multiplied by the number of doses to be taken per week (twice weekly) during that period.

Descriptive statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum will be presented for exposure to investigational product and compliance by treatment for the Safety Set and Full Analysis Set. The treatment compliance will be categorized and summarized as follow: < 85, >= 85 - < 100, >= 100 for the Safety Set and Full Analysis Set.

9. PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHODRUG) Version June 2017.

Prior medications are defined as medications with start time prior to the time of investigational product administration.

Concomitant medications are defined as medications with a start times after the time of investigational product administration or medications with a start time prior to investigational product administration but continuing after treatment, and with a start time before the 1-month post-treatment visit, inclusive.

Medical/surgical procedures performed during the treatment (between the dates of the first dose and the 1-month post-treatment visit, inclusive) will be recorded on the CRF, along with the date, time, and reason for the procedure.

Prior medication usage will be summarized using the number and percentage of subjects receiving each medication by treatment sequence, a total of crossover sequences and a total of all sequences, by indications, level 1 of the Anatomic Therapeutic Chemical (ATC) classification system and preferred term (PT) within the Safety Set and Full Analysis Set. Multiple medication usage by a subject in the same preferred term category will be counted only once. Concomitant medications will be summarized by the number and percentage of subjects receiving each medication/procedure by treatment, indications, ATC level 1, and preferred term (PT) within the Safety Set and Full Analysis 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. Medical/surgical procedures will be listed for the Safety Set.

All non-study medications taken during the study will be listed and flagged with prior, concomitant and post treatment (taken after the 1-month post-treatment visit, exclusive) medications for Safety Set. Medical/surgical procedures performed during the treatment (between the dates of the first dose and the 1-month post-treatment visit, inclusive) will also be listed for the Safety Set.

10. EFFICACY ANALYSES

10.1 Primary Efficacy Variable(s) and Analysis

The primary efficacy analysis will be conducted over the subjects in the Full Analysis Set that are randomized to Treatment Sequence 1 (A/B) or 2 (B/A) to evaluate of the efficacy of SC administration of C1 esterase inhibitor [human] liquid for injection compared to placebo.

The primary efficacy endpoint is defined as the normalized number of angioedema attacks during a treatment period. The NNA is expressed as the number of attacks per month (ie, 30.4 days) of exposure:

NNA = 30.4 x (number of attacks during treatment period)/(days of treatment period)

If a subject discontinues during the treatment period, the denominator of the NNA will be the days on treatment for that subject; this is equivalent to the last observation carried forward imputation method to impute the missing information following the subject's discontinuation.

To test the hypothesis that the NNA of C1 esterase inhibitor [human] liquid for injection is greater than or equal to the NNA of placebo, and the alternative hypothesis that the NNA of C1 esterase inhibitor [human] liquid for injection is less than the NNA of placebo as below:

$H_{0:}\ \mu_{C1\ INH} - \mu_{placebo} \geq 0$

vs

$H_{1:}\ \mu_{C1\ INH} - \mu_{placebo} < 0$

A linear mixed effect model will be performed to analyze the primary efficacy endpoint with period, sequence, use of prophylactic therapy with C1 INH, which is derived by long-term prevention with C1 INH at randomization, and treatment as fixed effects, and subject nested within sequence as a random effect. If the variance-covariance matrix of random effects is not positive definite, a mixed effect model with the same fixed effects and subject nested within sequence as repeated measurements will be performed instead; the repeated measurement is equivalent to the random effect in terms of statistical testing and point estimates of coefficients of fixed effects, however, the variance covariance matrix of random effects will not be estimated. The mean treatment difference ($\mu_{C1\ INH} - \mu_{placebo}$) will be estimated with a 95% CI provided. The upper confidence bound of 95% CI must be less than 0 in order for C1 INH to be considered superior to the placebo.

A summary of NNA during each treatment period by treatment sequences will be provided for the Full Analysis Set.

In addition, the NNA will be presented graphically for subjects randomized to the first 2 treatment sequences (A/B or B/A) in the Full Analysis Set, with the observed NNA on the vertical axis and the treatment periods (with assigned treatments) on the horizontal axis.

10.2 Key Secondary Efficacy Variable(s) and Analysis

The key secondary efficacy variables are listed as following:

1. The proportion of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the NNA during the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period.

2. The NNA excluding the first 2 weeks of each treatment period.

3. The proportion of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the NNA for the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period excluding the first 2 weeks of each treatment period.

Key secondary efficacy endpoints 1 and 3 are defined as achieving a ≥50% reduction in the NNA (P_R) during the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period.

The Key secondary endpoints 1 and 3 will be analyzed as the proportion of subjects meeting the above clinical response criterion (P_R). The analysis will be conducted over the Full Analysis Set from the first two treatment sequences. The null hypothesis is that P_R is less than or equal to 0.2, and the alternative hypothesis is that P_R is greater than 0.2 as below:

$$H_0: P_R \leq 0.2$$

vs

$$H_1: P_R > 0.2$$

The proportion P_R will be estimated with an exact 95% CI. The lower limit of the 95% CI for the proportion will be compared with 0.2. This is equivalent to testing the null hypothesis against the alternative hypothesis at a 1-sided alpha level of 0.05 using the binomial distribution.

Analysis of key secondary endpoint 2 will follow the same methods (ie, the linear mixed effect model) used for the primary efficacy endpoint.

The key secondary analyses will be performed using the Full Analysis Set and the Per-protocol Set.

10.3 Adjustments for Multiplicity

To control the overall type 1 error, the primary and key secondary endpoints will be tested at the 0.05 significance level in the pre-specified order of the primary endpoint, key secondary endpoint 1, key secondary endpoint 2, and key secondary endpoint 3. Once one hypothesis test is not significant, the significance of all subsequent tests will not be assessed. The determination of a successful study is based solely on the results of the primary endpoint analysis regardless of the results for the key secondary endpoints.

10.4 Other Secondary Efficacy Variable(s) and Analysis

Data from subjects in the Full Analysis Set that are randomized to Treatment Sequence 1 (A/B) or 2 (B/A) will be used to assess the secondary efficacy endpoints in the evaluation of the efficacy of SC administration of C1 esterase inhibitor [human] liquid for injection compared to placebo. If a subject discontinues during the treatment period, the days of the treatment period will be the days on treatment for that subject; this is equivalent to the last observation carried forward imputation method to impute the missing information following the subject's discontinuation.

Other secondary efficacy variables are listed as following:

- To determine the proportions of subjects with a clinical response to treatment as defined by: Achieving at least a 50%, 70%, 90% and 100% reduction as well as subjects achieving reduction to less than 1 NNA during a treatment period relative to the pretreatment assessment.
- The summary of clinical response to treatment will be repeated using the Per-protocol Set
- Cumulative attack severity: the normalized sum (per month) of the maximum symptom severity recorded for each angioedema attack in a treatment period.
- Cumulative daily severity: the normalized sum (per month) of the severity scores recorded for every day of reported symptoms in a treatment period.
- Number of attack-free days during a treatment period: the normalized number (per month) of attack-free days.
- Number of angioedema attacks requiring acute treatment during a treatment period: the normalized number of angioedema attacks requiring acute treatment.
- Disease activity as measured by the 98-day AAS: the normalized sum of the daily AAS during a treatment period, where the daily AAS is the sum of AAS items per day. Each AAS item is scored between 0 and 3 points, with the minimum and maximum daily AAS ranging between 0 and 15 points.
- Results of the AE-QoL questionnaire: the questionnaire consists of 17 specific questions that are associated with work, physical activity, free time, social relations, and food.
- Number of angioedema attacks requiring icatibant by the number of icatibant injections during the first three attacks of the treatment period.
- Kaplan-Meier estimate of time to initial improvement and time to complete resolution since acute treatment administration by attack order during the treatment period.
- Kaplan-Meier estimate of time to initial improvement and time to complete resolution since onset of attack by attack order during the treatment period.

The treatment differences in clinical responder rates, both of which are defined within treatments, i.e., the difference in the proportions of subjects with a clinical response to C1 INH

or placebo, each of them will be analyzed using McNemar's test for testing equality of proportions of responders within treatments.

Cumulative attack severity, cumulative daily severity, number of attack-free days during a treatment period and the 98-day AAS will be analyzed using a linear mixed effect model with period, sequence, use of prophylactic therapy with C1 INH, which is derived by long-term prevention with C1 INH at randomization, and treatment as fixed effects, and subject nested within sequence as a random effect. If the variance-covariance matrix of random effects is not positive definite, a mixed effect model with the same fixed effects and subject nested within sequence as repeated measurements will be performed instead. The results will be summarized by the point estimate of within-subject treatment differences or response rates and the corresponding 95% CI.

Kaplan-Meier analysis will be performed on all subjects in the Full Analysis Set without censoring. Median, 25%, 75% quartiles and their CI's will be estimated for time to initial improvement / complete resolustion since acute treatment administration / onset of attack.

Summary statistics (n, mean, SD, median, minimum and maximum) will be provided on each dimension and total score of AE-QoL by treatment and visit. A table will be provided summarizing the change from baseline to each visit and the last observation recorded within the treatment period for a subject's response to each dimension and the total score of AE-QoL.

In addition, angioedema attacks will be summarized by the maximum symptom severity of the attack and treatment for all subjects in the Full Analysis Set. Acute angioedema attacks will be summarized by acute therapy, the maximum symptom severity of the attack and treatment for all subjects in the Full Analysis Set.

Cumulative attack severity, cumulative daily severity and number of attack-free days will be plotted by treatment for the subjects who are randomized to the first two treatment sequences (A/B or B/A) in the Full Analysis Set.

Details on derivation of normalized efficacy variables are provided in the Appendix.

10.5 Exploratory Efficacy Variable(s) and Analyses

10.5.1 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary and key secondary efficacy endpoint 1 to evaluate the robustness of the results. Data summaries will parallel those described for the primary analysis of the primary and key secondary efficacy endpoint 1. If not otherwise specified, the sensitivity analyses will be performed in the Full Analysis Set.

- To assess any carryover effect, a sensitivity analysis will be conducted by excluding any angioedema attacks occurring within the first 2 weeks of Treatment Period 2 for sequence A/B, when carryover is suspected to be maximal.
- To assess carryover effect with an assumption that it exists for both A/B and B/A treatment sequences, a sensitivity analysis will be conducted by excluding any

angioedema attacks occurring within the first 2 weeks of Treatment Period 2, when carryover is suspected to be maximal.

- The analyses for the primary and key secondary endpoint 1 will be repeated using Per-protocol Set.

- The analyses for the primary and key secondary endpoint 1 will be repeated using Completer Set.

- One subject (PPD) reported atypical clinical presentation, an extensive number of HAE attacks, and very few symptom-free days between attacks throughout the study duration. During the study the subject underwent abdominal computer tomography imaging to identify potential for alternative diagnosis. Sensitivity analyses are planned prior to study data unblinding in order to assess the robustness of the study results by considering this subject's attacks differerently.

    - Exclude this subject from the full analysis set

- The primary efficacy endpoint will be compared for the active treatment to the placebo treatment using a generalized estimating equation (GEE) for count data assuming a negative binomial distribution with a log-link function. The model will include fixed effects for treatment, sequence, period, and use of prophylactic therapy with C1 INH, which is derived by long-term prevention with C1 INH at randomization, and the logarithm of time in days each subject was observed during a treatment period will be used as an offset variable in the model.

- The primary efficacy endpoint will be compared for the active treatment to the placebo in the Full Analysis Set, including subjects in the A/A treatment sequence. In this analysis, the same method used in the analysis for the primary efficacy endpoint will be applied.

- The primary efficacy analysis will be repeated with exclusion of data after any major protocol deviation.

10.5.2 Multiple Imputation Analysis

Analysis based on imputing missing values by drop out reason (Protocol Section 4.4.1) are added as sensitivity analysis to the primary efficacy analysis. The primary imputation method within the sensitivity analysis will be the multiple imputation method for the Full Analysis Set described below in this section.

A subject is considered to have missing values in case he/she leaves the study prematurely. The fraction of non-missing data (f) and normalized number of HAE attacks ($NNA_{observed}$) will be determined per treatment period and subject as follows:

Category	Level of Participation per Treatment Period	Fraction of non-missing data (f) per Treatment Period	Observed normalized number of HAE attacks ($NNA_{observed}$)
A	Subject is not discontinued from the study	1	As outlined in Section 8.1
B	Subject is discontinued from the study in a treatment period	Days of participation / scheduled length of treatment period (days)	As outlined in Section 8.1
C	Treatment period 2 among subjects who discontinued during treatment period 1	0	

Days of participation will be calculated as defined in Section 8.1 and scheduled length of treatment period is the intended length, i.e., 14 weeks for analysis equals 14×7=98 days.

The missing data will be imputed with NNA according to the sensitivity analysis by drop out reason. The normalized number of HAE attacks to be used for the sensitivity analysis ($NNA_{analyzed}$) will be calculated based on the observed number ($NNA_{observed}$) and the imputed number ($NNA_{imputed}$) taking into account the fraction of non-missing data (f) as:

$$NNA_{analyzed} = f \times NNA_{observed} + (1 - f) \times NNA_{imputed.} \qquad \text{(Equation 10.1)}$$

Values for $NNA_{observed}$ will be determined as outlined in the above table; values for $NNA_{imputed}$ will be determined for each subject and period with missing data depending on the sensitivity analysis as described below.

If a subject discontinues prematurely in treatment period 1, his/her $NNA_{analyzed}$ value during treatment period 2 will be imputed by the median of the non-missing $NNA_{observed}$ from all subjects who have complete data within the same treatment as that the subject is expected to take in treatment period 2.

If a subject discontinues prematurely from a treatment period, the remaining part of this period ($NNA_{imputed}$) will be imputed using the bootstrap method. The same imputation method used for treatment period 1 missing data will be used for treatment period 2 missing data

1. Draw a bootstrap sample with replacement from all Full Analysis Set subjects of the same treatment sequence with no missing values using PROC SURVEYSELECT with a seed of 300.

2. Use the following rules to calculate $NNA_{imputed}$ for the missing data for each bootstrap sample.

a) Missing data are considered as missing at random (MAR) if the dropout reasons are not related to the investigational product and study termination by sponsor (subjectdid not want to be in this study, site was closing, other personal reasons). For subjects with MAR data, the value of $NNA_{imputed}$ will be the median of $NNA_{observed}$ of all subjects who have complete data within the same treatment.

b) Data which are missing due to dropout for the following reasons are considered missing not at random (MNAR): discontinued due to AEs, death or lack of efficacy. For subjects with MNAR data, the median of the worst 25% observed data of the bootstrap sample from subjects who have complete data within the same treatment ($\tilde{x}$) will be determined. The value of $NNA_{imputed}$ equals the maximum $NNA_{observed}$ among all these subjects if $NNA_{observed} > \tilde{x}$, and $\tilde{x}$ otherwise.

c) Data which are missing because of protocol violations, other, withdrawal by subjects, or physician decision will be reviewed, and a decision of classifying them into the categories as described in a) or b) will be made and documented prior to unblinding.

3. After $NNA_{imputed}$ is calculated, use Equation 10.1 to calculate $NNA_{analyzed.}$ The complete bootstrap sample with imputed values ($NNA_{analyzed}$) will be analyzed by fitting the primary analysis model

4. Repeat the above 3 steps for 1000 times.

5. The model adjusted summaries will be combined from the 1000 imputed bootstrap samples using Rubin's formulae from PROC MIANALYZE. These estimates include: the model adjusted NNA, the overall difference of NNA between the study drug and the placebo, and the type III tests p-values of fixed effects.

11. SAFETY ANALYSES

The safety analyses will be performed by treatment using the Safety Set. Safety endpoints include adverse events (AE), clinical laboratory assessments, vital signs, ECG findings, SC injection site reactions, C1 INH antibody status and patient-reported tolerability of icatibant therapy for acute angioedema attacks. The last assessment prior to the first dose of investigational product in treatment period 1 will be used as baseline for all safety analyses.

11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0 adverse events dictionary.

Adverse events will be collected from the time of informed consent through 7 days after the last dose date of investigational product. All serious adverse events (SAE) that occur ≤30 days after the last dose date of investigational product and related SAEs that occur >30 days after the last dose date of investigational product will be collected.

An adverse event that increases in severity will be captured as a new event. An AE that develops into a SAE will be captured as a new event from the date it met the seriousness criteria. Worsening of pre-treatment events, after initiation of investigational product, will be recorded as new AE. An AE (classified by preferred term) that occurs during the study will be considered a treatment emergent adverse event (TEAE) if the start date and time of the AE is on or after the first dose date of investigational product and up to 7 days after the last dose of investigational product, or if the start date of the SAE is on or after the first dose date of investigational product and up to 30 days after the last dose of investigational product, or with an increase in severity on or after the date and time of the first dose.

In addition, angioedema attacks and ISRs will not be considered AEs unless they satisfy serious criteria according to the protocol.

The number and percentage of subjects reporting any TEAEs, SAEs, and TEAEs related to investigational product, TEAEs leading to withdrawal, Severe TEAEs and absolute count of events will be summarized. Angioedema attacks and ISRs will not be considered AEs unless they satisfy serious criteria according to the protocol.

The number and percentage of subjects reporting any TEAEs, and absolute count of events will also be summarized in the following ways:

- By SOC, preferred term and treatment
- By SOC, preferred term, treatment and maximum severity
- By SOC, preferred term, treatment and relationship to investigational product in the opinion of the investigator
- By preferred term

TEAEs leading to withdrawal, SAEs, and deaths will be similarly summarized as TEAEs.

TEAEs related to investigational product, serious TEAEs related to investigational product and TEAEs related to investigational product leading to withdrawal will be similarly summarized as TEAEs. Summaries of TEAE or TEAE related to investigational product within 24 hours after the end of injection of investigational product will be provided by treatment.

A sensitivity analysis will be conducted by attributing TEAEs that occur during the first 2 weeks of Treatment Period 2 to Treatment Period 1 for the A/B (C1 INH to placebo treatment sequence.

To assess carryover effect with an assumption that it exists for both A/B and B/A treatment sequences, a sensitivity analysis will be conducted by excluding any TEAEs occurring within the first 2 weeks of Treatment Period 2, when carryover is suspected to be maximal.

All information about AEs collected on the eCRF will be listed alongside the treatment, preferred term, and SOC. Listings will also be provided on TEAEs related to investigational product, TEAEs leading to withdrawal, SAEs, and deaths.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point (baseline, 8a, 16a, 24a, 28a, 8b, 16b, 24b and 28b) will be presented by treatment for the following clinical laboratory variables:

Hematology: WBC count (total and differential), RBC count, hemoglobin, hematocrit, and platelet count.

Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK), Blood urea nitrogen (BUN), creatinine, carbon dioxide (CO2), albumin, total protein, glucose, potassium, sodium, chloride, and phosphorus

Coagulation: Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) and D-dimer.

Urinalysis with microscopy: pH, Dipstick (protein, glucose, ketones, hemoglobin), Specific gravity, Microscopic evaluation (red blood cells, white blood cells, crystals, casts, bacteria).

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 summarized by treatment and also listed. In addition, The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized by visit and treatment.

Table 6: Criteria for Potentially Clinically Important Laboratory Tests

			Criteria for Clinically Significant Laboratory Abnormalities[1]	
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				
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
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
Blood Urea Nitrogen (BUN)	All	Male, Female	NA	>3.0 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

Table 6: Criteria for Potentially Clinically Important Laboratory Tests

			Criteria for Clinically Significant Laboratory Abnormalities[1]	
Parameter	**Age Range**	**Gender**	**Low**	**High**
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.
[1] 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 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. Subjects with post-baseline PCI values will be summarized by treatment and a supportive listing of subjects with post-baseline PCI values will also 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

Table 7: Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria
		Observed Value
	Low	Decrease of > 15 from baseline value and ≤ 45
Temperature (˚C)	High	> 38.3
	Low	< 35

11.4 Electrocardiogram

All 12-lead ECG collected at the screening visit will be listed for the Safety Set.

11.5 Injection Site Reaction

A summary of SC injection site reactions will be summarized by treatment. The categories in this summary include: any injection site reaction, any severe reaction, any mild reaction, and any moderate reaction. Subjects will be counted in each category only once, the worst reaction among 15 assessments will be counted. The percentage will be calculated from the total number of subjects in each treatment. The incidence of SC injection site reactions will be summarized by treatment, time points post-injection, reaction, and severity (absent, mild, moderate, and severe). Injection site reaction will also be summarized by maximum severity and visit at 15 minutes, 30 minutes and 1 hour post injection. The proportion of the most extreme reactions among injections throughout all 5 visits will be calculated. In addition, the overall impact on daily living (severity and duration) of subject's injection site reactions will also be summarized by treatment. A listing will also be provided.

11.6 Tolerability of Icatibant Therapy

TEAEs considered related to icatibant therapy will be summarized by treatment according to system organ class (SOC) and preferred terms (PT).

12. OTHER ANALYSES

12.1 Pharmacokinetic and Pharmacodynamic analyses

Plasma concentrations will be used to perform non-compartmental analysis (NCA) as appropriate. Further details of the pharmacokinetic modeling and simulation will be documented in a PK population analysis plan (PAP). Statistical Analysis of Pharmacokinetic and Pharmacodynamic Data

All of the PK/PD analyses will be performed using the PK/PD Set.

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all PK/PD parameters derived by NCA, as appropriate.

Plasma concentrations of C1 INH antigen, C1 INH functional activity, C4 and C1 q at each nominal sampling time with and without baseline-adjustment will also be summarized using descriptive statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean).

12.2 C1 INH Antibody

Results of C1 INH antibody testing will be summarized by treatment and visits, and listed by individual subjects for the Safety Set.

12.3 Health-related Quality of Life Analyses

Details of the health-related quality of life analyses will be documented in a quality of life SAP. The health-related quality of life analyses will be summarized using the Full Analysis Set.

The 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 food. Subjects will be asked how often they were restricted by—as well as the difficulties and problems that could be associated with—recurrent swellings (angioedema) during the previous 4 weeks. The result of the AE-QoL questionnaire is specified as a secondary efficacy endpoint (see Section 10.3).

The EuroQol 5-dimensional 5-level descriptive system (EQ-5D-5L) is a descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take 1 of 5 responses. The responses record 5 levels of severity within a particular dimension. Results of the EQ-5D-5L health status instrument will be summarized on each question using descriptive statistics in accordance with the EQ-5D-5L user guide (version 2.0) by treatment and visit.

The Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire includes 6 questions about work and activity impairment due to health problems during the past 7 days. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less work or productivity. Results of the WPAI-GH questionnaire will be summarized on each question using descriptive statistics by treatment and visit.

The Sheehan Disability Scale (SDS) is a 5-item, self-rated questionnaire designed to measure the extent to which a subject's disability due to an illness or health problem interferes with work/school, social life/leisure activities, and family life/home responsibilities. Results of the SDS will be summarized on each question using descriptive statistics by treatment and visit.

Study personnel will ask subjects specific questions regarding their utilization of health care resources for the management of their HAE disease. Assessment (HRUA-HAE) will be completed at the time points specified protocol. Study personnel will enter the survey response into the eCRF. Results of the HRUA-HAE will be summarized on each question using descriptive statistics by treatment and visit.

12.4 Surveys on SC Administration and Self-administration of Investigational Product

Subjects will be asked to rate their overall experience in receiving twice weekly SC injections of investigational product. Subjects who have previously received C1 INH products via IV administration will be asked to indicate the preferred route for medication administration.

Those subjects, who choose to self-administer the investigational product during Treatment Period 1 or 2 under supervision, will be asked specific questions about their experience with self-administration of SC administration of C1 INH.

Results of the surveys for subject acceptability of SC administration and subject experience with self-administration of investigational product will be summarized by treatment and period using the Full Analysis Set.

12.5 Subgroup Analyses

Subgroup analyses are planned for exploratory purposes; p-values will be presented as descriptive statistics. Subgroup analyses will be performed for the primary and key secondary efficacy endpoint 1 using the Full Analysis Set, and for the analysis of safety endpoints (AEs) using the Safety Set. Data will be summarized by treatment within subgroup.

12.5.1 Age Group

A subgroup analysis of age will be conducted using 18 years and 64 years as cut points to examine the treatment effect in adolescent vs. adult subjects.

- <18 years
- 18-64 years
- >= 65 years

12.5.2 Sex

A subgroup analysis will be conducted to examine the treatment effect in male vs. female subjects.

- Male
- Female

12.5.3 Race Group

Subgroup analyses will be conducted by race to examine the treatment effect in White vs. those subjects of other races.

- White
- Other Races

12.5.4 Use of Prophylactic therapy with C1 INH at Randomization

Subgroup analyses will be conducted by prophylactic therapy with C1 INH at randomization (defined as taken within 5 days prior to randomization).

- Use of prophylactic therapy with C1 INH at randomization: Yes
- Use of prophylactic therapy with C1 INH at randomization: No

12.5.5 Use of Prophylactic Therapy with C1 INH or Androgens Prior to Screening

Subgroup analyses will be conducted by prophylactic therapy with C1 INH or androgens prior to screening for the primary endpoint only.

- Use of prophylactic therapy with C1 INH or androgens prior to screening: Yes
- Use of prophylactic therapy with C1 INH or androgens prior to screening: No

12.5.6 Long-Term Prevention at Randomization

Subgroup analyses will be conducted by long-term prevention at randomization.

- Any long-term prevention
- C1 INH prophylaxis
- Oral Androgen
- Oral other
- No long-term prevention

12.5.7 Region

Subgroup analyses will be conducted by region.

- North America
- Europe

12.5.8 Location

Subgroup analyses will be conducted by location.

- Upper airway (includes laryngeal or pharyngeal)
- Gastrointestinal/abdominal (including symptoms of pain, nausea, vomiting, swelling, and/or change in bowel habits)

- Genitourinary (including scrotum or vulva)
- Cutaneous (facial)
- Cutaneous (extremity, peripheral, or torso [eg, buttocks, external head/neck, trunk])
- Non upper airway

12.5.9 Mucosal and Non-Mucosal Location

Subgroup analyses will be conducted by mucosal and non-mucosal location.

- Mucosal
- Non-mucosal
- Both mucosal and non-mucosal

13. INTERIM ANALYSIS

There is no planned interim analysis in this study.

14. DATA MONITORING/REVIEW COMMITTEE

There is no planned data monitoring committee in this study.

15. COMPUTER METHODS

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, PPD, PPD) on a suitably qualified environment.

16. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not applicable.

17. DATA HANDLING CONVENTIONS

17.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, SD, median, 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, min/max will be presented to the same decimal places as the raw data. Percentage, mean and median 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.

In addition, *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 only from the prior treatment or post-treatment periods will generally have the following treatment columns displayed:

Sequence A/B

Sequence B/A

Sequence A/A

Total

Tables that summarize efficacy and safety information only from the treatment period will generally have the following treatment columns displayed:

Treatment A: 2000 IU C1 INH

Treatment B: Placebo

Total (if needed)

Tables that summarize efficacy and safety information from the treatment period and treatment sequence will generally have the following treatment columns displayed:

Sequence A/B: Period 1: 2000 IU C1 INH

Sequence A/B: Period 2: Placebo

Sequence B/A: Period 1: Placebo

Sequence B/A: Period 2: 2000 IU C1 INH

Sequence A/A: Period 1: 2000 IU C1 INH

Sequence A/A: Period 2: 2000 IU C1 INH

Tables that summarize efficacy and safety information from the treatment period with different treatment sequence combinations will generally have the following treatment columns displayed:

Treatment A from Sequence A/B and B/A: 2000 IU C1 INH

Treatment A from Sequence A/A: 2000 IU C1 INH

Treatment A Overall: 2000 IU C1 INH

Treatment B: Placebo

17.2 Derived Efficacy Variables

Details on normalized efficacy variables: cumulative attack severity, cumulative daily severity, number of attack-free days, number of angioedema attacks requiring acute treatment and 98-day AAS are provided in the Appendix.

17.3 Repeated or Unscheduled Assessments of Efficacy and Safety Parameters

If a subject has repeated assessments before the date and time of the first dose of investigational product, then last assessment prior to or on the date and time of the first dose of treatment period 1 will be used as baseline. If clinical discharge assessments are repeated or unscheduled, the last 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.

For repeated and/or unscheduled assessments, the assessment that is following the rules in the next section will be used for efficacy and safety analysis. However, all visit data (including repeated and unscheduled) will be included in subject data listings.

17.4 Termination visits for patients who discontinued investigational product or study early

For assessments collected by visits (laboratory parameters, ECG variables, vital signs parameters, scheduled questionnaire, etc), the nominal visits (CRF visits) will be used in the by-visit summaries. Only laboratory data from available visits for these assessments will be used in the analysis according to the following order:

- First, if the scheduled visit assessments exist, they will be used in the analysis;
- Second, if the scheduled visit assessments do not exist but the remapped visit assessments from TERMINATION visit exist, these assessments will be used in the analysis;
- Third, if both the scheduled visit assessments and the remapped visit assessments from termination visit do not exist but unscheduled visit assessments exist, then these assessments will be used in the analysis.

The termination visits for patients who discontinue the investigational product prematurely, are not time point specific visits. In addition to serve as the last on study assessment, they will also be remapped to nominal visits based on the following rules:

- If these visits fall into a specific visit window and the corresponding scheduled visit is missing, then these visits will be remapped to be that scheduled visit. The visit windows are defined relative to study day (if visit exists) or target day (if visit does not exist) as follows
  - ± 3 days for visits that occur every week
  - ± 7 days for visits that occur every other week
  - ± 14 days for monthly visits
  - ± 45 days for all quarterly visits

17.5 Missing Date of Investigational Product

If 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.

17.6 Missing Date Information for Prior and Concomitant Medications

For prior and 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, the start date will be imputed first.

17.6.1 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 start date will be set to null.
- Missing day and month
  - 01 January will be assigned to the missing fields.
- Missing day only
  - The first day of the month will be assigned to the missing day.

17.6.2 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
  - The day, month and year of the last date on study 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 last date on study, then the day and month of the last date on study will be assigned to the missing fields.

  - If the year of the incomplete stop date is not the same as the year of the last date on study, then 31 December will be assigned to the missing fields.

- Missing day only

  - If the month and year of the incomplete stop date are the same as the month and year of the last date on study, then the day of the last date on study will be assigned to the missing day.

  - If the month and year of the incomplete stop date are not the same as the month and year of the last date on study, then the last day of the month will be assigned to the missing day.

17.7 Missing Date Information for Adverse Events

17.7.1 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 day, month and year of the date of the first dose of investigational 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 01 January will be assigned to the missing fields.

- 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 dose of investigational product, then the first day of the month will be assigned to the missing day.

17.7.2 Incomplete Stop Date

No imputation is needed for AE stop dates.

17.8 Missing Severity Assessment for Adverse Events

If the severity is missing for an AE starting before the date of the first dose of the investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of the investigational product, then a severity of "Severe" 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.

17.9 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.

17.10 Character Values of Clinical Laboratory Variables

If a character value collected from the CRF contains ">" sign, the numeric value used in the analysis will be calculated from the numeric part of the collected value times 2. For example, given a collected clinical laboratory result of "> 75", the numeric value used in the analysis will be 150.

If a character value collected from the CRF contains "<" sign, the numeric value used in the analysis will be calculated from the numeric part of the collected value divided by 2. For example, given a collected clinical laboratory result of "< 120", the numeric value used in the analysis will be 60.

17.11 Handling Missing HAE Attack Data

If there are incomplete attack start/end dates in the collected data, the following imputations will be performed in a sequential order of the incomplete dates within each subject. This is to ensure that multiple identical incomplete dates will be imputed as separate attacks.

- Imputation of start date for an attack:

- If the attack start day is unknown and there is no previous attack in the same month, the first day of the month will be assigned to the missing field.

- If the attack start day is unknown and there is at least one previous attack in the same month, the previous attack end date + 1 will be assigned to the missing field.

- Imputation of end date for an attack:

  The imputation of end date for an attack will follow one of the following 3 rules, whichever is the earliest:

- The start date of the current attack + 6 if attack end date is partially or completely missing.

- The start date of the next attack – 2 if attack end date is partially or completely missing.

- The last day of the month if attack end date is partially missing with missing day only.

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

The Mock TFLs will be provided in a separate document.

19. APPENDIX

19.1 Derivations of efficacy endpoints related to angioedema attacks

The derivations of efficacy endpoints are demonstrated using the following hypothetical 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 3 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 over the 9 days with symptoms yields a Cumulative Daily Severity of 19. 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	19

For the secondary efficacy variables of Cumulative Attack Severity, Cumulative Daily Severity, Number of attack-free days during a treatment period, Number of angioedema attacks requiring acute treatment during a treatment period and 98-day AAS, the normalized numbers (per month) calculated by following steps will be used in the analyses.

19.2 Derivation of normalized efficacy endpoints

Any subject who completes a treatment period should provide data with which to derive efficacy scores. Thus, for each individual treatment period, the normalized efficacy scores are calculated as below:

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*, (the normalized score expressed as score per **Month**), which is calculated as $(Y_i / X_i) * 30.4$

19.3 Angioedema Quality of Life Questionnaire – American English Version 2012

Instructions for evaluation of the AE-QoL

The structure of AE-QoL

AE-QoL consists of four dimensions and a total score

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

Fatigue/Mood
6. Difficulties of falling asleep
7. Waking up during the night
8. Feeling tired during the day
9. Difficulties in concentrating

10. Feeling downhearted

Fears/Shame
12. Feeling burdened at having swellings
13. Fear of new suddenly appearing swellings
14. Fear of increased frequency of swellings
15. Ashamed to visit public places
16. Embarrassed by the apppearence of swellings
17. Fear of long term negative drug effects

Nutrition
5. General limitations in foods and eating
11. Limitations in the selection of food and beverages

Total Score
Items 1 to 17

How to calculate AE-QoL scales and the AE-QoL total score

AE-QoL is meant to be evaluated by using its four individual dimensions (profile instrument) but is can also be used to determine a total score (index instrument):

The AE-QoL dimension scores as well as the AE-QoL total score are calculated by using the following formula:

(Σ items – min Σ items / max Σ items – min Σ items) x 100
Example:
Dimension "Functioning":
Item 1: answer 3
Item 2: answer 2
Item 3: answer 4
Item 4: answer 5
Σ items: (3+2+4+5) = 14
min Σ items: (1+1+1+1) = 4
max Σ items: (5+5+5+5) = 20
Enter values in formula: (14 - 4 / 20 – 4) x 100 = 62.5%

The AE-QoL dimension scores correspond to the mean of the items within each dimension. If some items are missing, the total of the items within the dimension is divided by the number of the non missing items.

The same holds for the AE-QoL total score.

An AE-QoL dimension score should not be calculated if more than one item is missing in that dimension.

The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are missing.

Please note that only calculating the raw dimension scores (mean of the item scores within each scale) and the raw total score score (mean of all item scores) would be easier than the above described procedure. However, in case of missing answers, an interindividual as well as an intraindividual comparison of AE-QoL results would be limited. The above described linear transformation of all raw scores into percentage scores (indicating the location of the raw scores in relation (in percent) to its maximum possible score) solves this problem and makes it possible to judge and compare AE-QoL results even when single items are missing. The linear transformation of raw scores results in minimal and highest possible scale and total scores of 0 and 100, respectively.

19.4 Major Protocol Deviations

The following protocol deviations are classified as major protocol deviations that may affect the primary efficacy endpoint. Subjects who satisfy these protocol deviations will be excluded from the Per-protocol Set.

1. Subject <12 years and subject was randomized into the study (I1)
2. Subject was NOT diagnosed by a physician to have HAE (Type I or II) and subject was randomized into the study (I2)
3. Subject was NOT diagnosed by a physician to have a functional C1 inhibitor (C1 INH) level less than 50% of normal and subject was randomized into the study (I2)
4. Adult subject currently receiving prophylactic therapy with C1 INH, NOT having a history of ≥2.0 angioedema attacks per month (average) during the 3 consecutive months prior to starting prevention therapy and subject was randomized into the study (I3)
5. Subject (>12 years of age) not receiving prophylactic therapy with C1 INH, NOT having a history of ≥2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit and subject was randomized into the study (I3)
6. Adult subject currently receiving a stable dose of attenuated androgens, NOT having a history of ≥2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit and subject was randomized into the study (I3).
7. Adults (>18 years of age) receiving prophylactic IV CINRYZE that exceeds the approved dosing regimen of 1000 U every 3 or 4 days (receiving a weekly dose >2000 U). (E1)
8. Adolescents (>12 and <18 years of age) currently receiving prophylactic therapy with C1 INH. (E2)

9. Have received any C1 INH therapy or any blood product for the treatment or prevention of angioedema attacks within 3 calendar days prior to the first dose of investigational product in Treatment Period 1. (E4)

10. If female, have started or changed the dose of any hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen/progestin containing products) within 2 months prior to the screening visit. (E5)

11. Have a history of hypercoagulability (abnormal blood clotting) or other predisposition for thromboembolism. (E6)

12. Have a diagnosis of acquired angioedema or known presence of anti-C1 INH antibodies. (E7)

13. Have a history of allergic reaction to C1 INH products, including CINRYZE (or any components of CINRYZE), or other blood products. (E8)

14. Be pregnant or breastfeeding. (E9)

15. Have received an investigational drug within 30 days prior to the first dose of investigational product in Treatment Period 1. (E10)

16. Have, as determined by the investigator and/or the sponsor's medical monitor, any surgical or medical condition that could interfere with the administration of investigational product or interpretation of study results. (E11)

17. Subject administered "damaged" IP (e.g., IP with unapproved temperature excursion)

18. Calculated study drug compliance of <85% among subjects whose treatment duration is at least 6 weeks in the treatment period.

19. Subject missed ≥ 3 consecutive doses

20. Subject was randomized but did not receive study drug

21. Investigator did not complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject eDiary.

22. Concomitant use of Use of C1 INH therapy (other study drug) for prophylaxis against angioedema attacks after randomization upto 1 wk FU period

23. Initiation of long term therapy (including IV C1-INH, Transexamic acid or androgen therapy) after randomization upto the last dose

24. Change in dose of hormonal contraceptive regimen or hormone replacement therapy (ie, estrogen/progestin containing products) after randomization

25. Study drug is restarted later than 30 days of the temporary interruption after a Thrombotic/Thrombo-embolic event

26. Accidental Unblinding

27. Subject receiving 3 or more consecutive doses of incorrect treatment assigned by IXRS

28. Study drug exposed to temperature excursion (deemed unusable by Shire) dispensed to subject with reported AEs being associated with the exposed drug in the opinion of the PI.

HRQoL STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP616-300
Project No.:	0238-0431
Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults with Hereditary Angioedema: Assessment of Health-related Quality of Life (HRQoL)
Drug:	SHP616, C1 esterase inhibitor [human] liquid for injection
Sponsor:	Shire Development LLC and International Affiliates 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date:	Version 0.6, Date 22 August 2017

Version No:	Document History Description of Update	Author(s)	Effective Date
0.1	Original Draft	PPD, PPD	20 Oct 2016
0.2	Review and comments	PPD PPD, PPD,	8 May 2017
0.3	Revisions	PPD, PPD	19 May 2017

Version No:	Document History Description of Update	Author(s)	Effective Date
0.4	Revisions	PPD, PPD, PPD	7 July 2017
0.5	Revisions	PPD, PPD, PPD	21 Aug 2017
0.6	Revisions	PPD	22 Aug 2017

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LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AAS	Angioedema Activity Score
AE-QoL	Angioedema Quality of Life (questionnaire)
AUC	Area Under the Curve
EQ-5D-5L	EuroQol 5-Dimensional 5-Level Descriptive System
EQ-VAS	EuroQol Visual Analogue Scale
HAE	Hereditary Angioedema
HRU	Healthcare Resource Utilization
HRUA-HAE	Healthcare Resource Utilization Assessment related to HAE
HRQoL	Health Related Quality of Life
MCID	Minimal Clinical Important Difference
MDC_{95}	Minimal Detectable Change with 95% confidence
NNA	Normalized Number of Attacks
PRO	Patient Reported Outcome
RD	Responder Definition
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SEM	Standard Error of Measurement
VAS	Visual Analogue Scale
WPAI-GH	Work Productivity and Activity Impairment - General Health (questionnaire)

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the analyses to be conducted on the Patient Reported Outcome (PRO) data for Study SHP616-300: A Phase 3, randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study to evaluate the efficacy and safety of subcutaneous (SC) administration of 2000 IU of C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks in adolescents and adults with hereditary angioedema (HAE). Specifications for PRO tables and figures will be provided in a separate document.

The primary efficacy endpoint in SHP616-300 is the normalized number of angioedema attacks (NNA) during a treatment period, measured as observed. The impact of treatment on health related quality of life (HRQoL), health status, work, and activity impairment due to health, disability, and disease symptoms were assessed as secondary endpoints using several PROs: Angioedema Quality of Life Questionnaire (AE-QoL), EuroQol 5-dimensional 5-level (EQ-5D-5L) descriptive system, and the EuroQol Visual Analogue Scale (EQ-VAS), Work Productivity and Activity Impairment Questionnaire - General Health (WPAI-GH), Sheehan Disability Scale (SDS), and Angioedema Activity Score (AAS). Healthcare resource utilization (HRU) data are also collected as part of the study. This document outlines the analyses to be conducted on the PRO and HRU data.

2. STUDY DESIGN

2.1 Study Design Overview

Data will be collected in Study SHP616-300, a phase 3, randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study to evaluate the efficacy and safety of SC administration of 2000 IU of C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks in adolescents and adults with HAE. The trial uses a partial Balaam's cross-over study design with two periods (each lasting 14 weeks), two treatments (active and placebo), and three treatment sequence groups (Exhibit A). The Study Design Flow Chart is shown in Exhibit B.

This multicenter study is being conducted at approximately 40 sites globally (North America and EMEA). The study aims to screen 75 subjects, enroll 66, and ensure that 54 subjects complete both study periods. Treatment sequence groups 1 (AB) and 2 (BA) will each contain 26 subjects, with treatment sequence 3 (AA) containing 14 subjects.

Exhibit A: Treatment Sequences

Treatment Sequence	Treatment Period 1	Treatment Period 2	Approximate Number of Subjects Randomized
1 (AB)	A	B	26
2 (BA)	B	A	26
3 (AA)	A	A	14

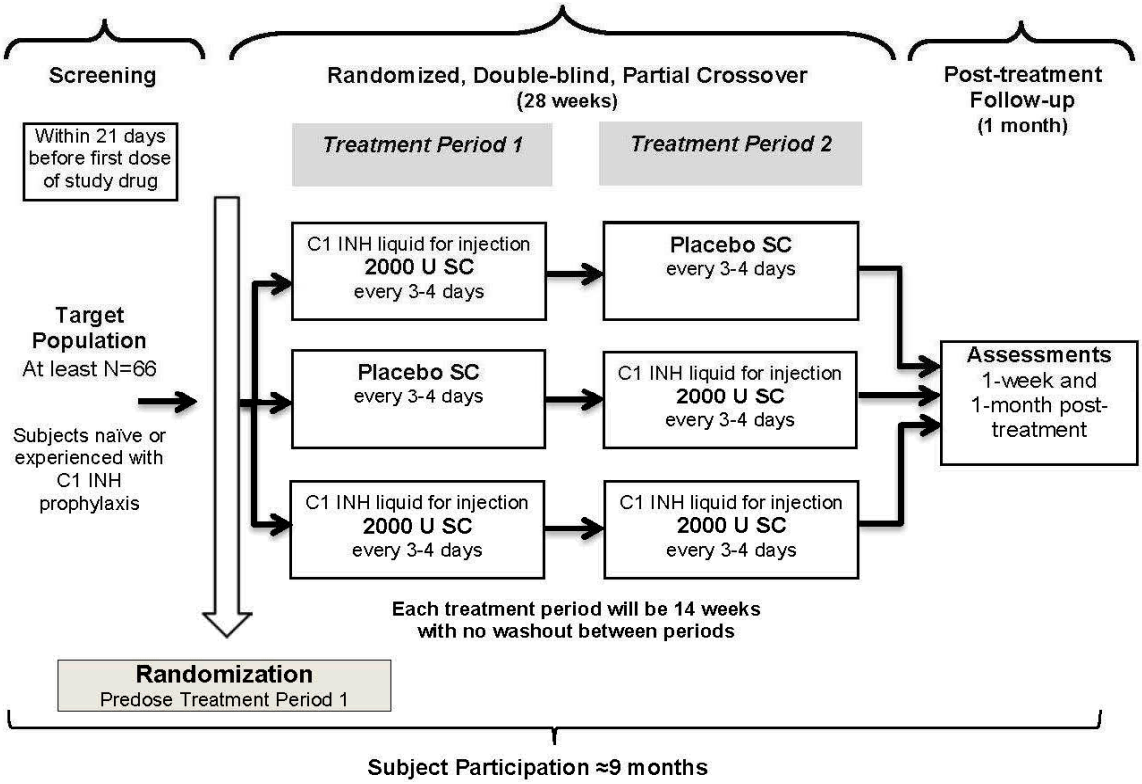
Treatment A: 2000 IU (4.0 mL) C1 esterase inhibitor [human] liquid for injection administered SC twice weekly (every 3 or 4 days) for 14 weeks.
Treatment B: Placebo (4.0 mL) administered SC twice weekly (every 3 or 4 days) for 14 weeks.

2.2 The Cross-over Design

A cross-over design is one in which the effects of different treatments (here C1 esterase inhibitor [human] liquid for injection and placebo) are compared on the same subject during different study periods. This study design was chosen as the best way to jointly address the protocol objectives of establishing efficacy (relative to placebo) and safety (i.e., adequate numbers of subjects for precision of estimation in detecting potential safety signals). An advantage of such a design is that a comparison of treatments on the same subject is expected to be more precise than a comparison between subjects and therefore to require fewer subjects for the same precision.

The simple analysis of a cross-over trial assumes that the effect of treatment is the same during each study period, i.e., that the effect of any treatment given during the second period is not influenced by the treatment received in the first. This assumption, no interaction between treatment and period, can be tested. Hills and Armitage (1979) provide a comprehensive overview of the fundamentals of cross-over trial design and analysis.

Exhibit B: Study Design Flow Chart



2.3 Study Design Considerations

The present trial uses a partial Balaam's cross-over study design with two periods (each lasting 14 weeks), two treatments (active and placebo), and three treatment sequence groups: AB, BA, AA (Exhibit A). Balaam (1968) proposed a design-based approach to assess the problem of carry-over effects, by pointing out that if the AB/BA design were extended to include the sequences AA and BB, then within-subject estimates of a direct treatment effect could be obtained even in the presence a carryover effect. However, Balaam's design was able to achieve this because it assumed a particular model for the carryover effect which no longer enjoys wide support (Senn, 2002). The Balaam's design is typically chosen to when it is hypothesised that there is a self-carryover effect, i.e., the response during the second period on the same treatment is affected by the response during the first study period, or when there is a treatment by period interaction. In this study, a partial Balaam's design is used, in the absence of a BB sequence group; the Balaam's design is not completely balanced. The Balaam's design is particularly relevant since there will be no washout between the 2 study periods, each of 14 weeks. The omission of a washout period is to minimize the duration that subjects will be without active treatment.

In this trial, there are six-sequence by period means, two in each treatment sequence group (AB, BA, and AA). The five resulting degrees of freedom can be decomposed into 2 for sequence, 1 for treatment, 1 for period, and 1 for carryover. In the trial, the primary efficacy endpoint will be analyzed (in the subjects in the Full Analysis Set randomised to the AB/BA groups) by using a

mixed effect linear model with period, sequence, stratification factor (use of prophylactic therapy with C1 INH, which was derived by long-term prevention with C1 INH at randomization), and treatment as fixed effects, and subject nested within sequence as a random effect. The mean treatment difference ($\mu_{\text{C1 INH}} - \mu_{\text{placebo}}$) will be estimated with a 95% CI provided. The main analytic approach for the analysis of the PRO data will be similar and include only subjects randomised to the AB/BA groups, unless specified in the analyses section.

(Note: The Full Analysis Set is all subjects who have taken at least 1 dose of investigational product (the Safety Set) who have at least 1 post baseline (e.g., randomization) primary efficacy assessment.)

The trial was powered to demonstrate superior efficacy even in the presence of carryover effects. To assess any carryover effect, a sensitivity analysis excluded from the evaluation of the NNA any attacks occurring within the first 2 weeks of Study period 2 for both sequences when carryover is suspected to be maximal. Since carryover should occur only with the A/B treatment sequence, its effect (if present) will be to spread C1 esterase inhibitor [human] liquid for injection efficacy into the placebo study period, thereby diluting the efficacy of C1 INH and favouring the null hypothesis of the primary efficacy analysis; it is not anticipated that any placebo effect will similarly benefit C1 esterase inhibitor [human] liquid for injection within the B/A treatment sequence.

3. ANALYSIS OBJECTIVES

3.1 Analysis of PRO data

The main objectives of the analyses of the PRO data collected in SHP616-300 are:

1. To describe AE-QoL, WPAI-GH, SDS, and AAS scores by treatment and period (absolute, change and percentage change from baseline at each scheduled visit for AB, BA, and AA sequences) and assess differences between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA) (change and percentage change).
2. To describe and estimate whether the effect of an attack on EQ-5D-5L index and EQ-VAS scores differs between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA).
3. To describe and assess differences in the proportion of subjects achieving the responder definition (RD) in AE-QoL and AAS scores from baseline to final assessment between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA).

The exploratory objective is:

1. To explore the relationship between efficacy (as defined in the protocol) and scores on the AE-QoL, WPAI-GH, SDS, and AAS (Hypothesis: Subjects with improved efficacy also have improved scores).

3.2 Analysis of HRUA-HAE data

The main objective of the analysis of the HRUA-HAE data collected in SHP616-300 is:

1. To describe HRUA-HAE (absolute values) according to treatment, study period (1 or 2) and sequence (AB, BA).

4. STUDY MEASURES

4.1 Responder Definition (RD)

A RD is the absolute change value, at an individual patient level, which indicates that a meaningful change in a PRO instrument score has occurred.

When no RD has been estimated, it has been proposed that a one-standard error measurement (one-SEM) criterion, or equivalently 0.5 standard deviations (SDs) when the reliability of the instrument is ≥0.75, can be used as a proxy for minimal change (Norman et al., 2003). This distribution-based method provides the smallest change which, for an individual, is likely to be beyond the measurement error of the instrument, thus understood to represent true change. However, it is not known whether this change is clinically relevant. While not acceptable as a RD in itself, this distribution-based approach provides boundary information as any value proposed as a RD will need to be at least as large to rule out the possibility of responder classification occurring by chance.

In the absence of any known RDs in the HAE, or any other population, RDs for minimal change will be estimated using one-half a SD in the study baseline (Visit 1a) AE-QoL, EQ-5D-5L and AAS scores. It is reasonable to assume that these instruments have reliabilities of ≥0.75. This estimate is based on the distributional characteristics of the sample under study. In addition, a number of pre-defined values (based on existing estimates for the minimal clinically important difference (MCID) or RD) will be applied in a sensitivity type analysis.

4.2 PRO Measures and Scoring

4.2.1 Angioedema Quality of Life (AE-QoL) Questionnaire

The AE-QoL questionnaire is a self-administered validated angioedema disease-specific quality of life instrument (Weller et al., 2012). Each of the 17 items has a five-point response scale ranging from 1 (Never) to 5 (Very Often). The questionnaire will be scored according to the developers' guidelines (Weller et al., 2012) to produce a total score and four domain scores (functioning, fatigue/mood, fear/shame, nutrition). Raw domain scores (mean of the item scores within each scale) and the raw total score (mean of all item scores) will be rescaled using linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score, where the higher the score the greater the QoL impairment. The minimal clinically important difference (MCID) for the total score is 6 (Weller et al., 2016). However, there is no evidence on the MCID/RD for the AE-QoL *domain* scores. Therefore, in addition to applying the

value of 6 for the total score, the method of using 0.5 SD in baseline domain scores will be used to determine the RD:

- Rescaled AE-QoL total score = 6, Baseline SD*0.5
- Rescaled AE-QoL functioning domain score = 6, Baseline SD*0.5
- Rescaled AE-QoL fatigue/mood domain score = 6, Baseline SD*0.5
- Rescaled AE-QoL fear/shame domain score = 6, Baseline SD*0.5
- Rescaled AE-QoL nutrition domain score = 6, Baseline SD*0.5

4.2.2 EuroQol 5-dimensional 5-level (EQ-5D-5L) descriptive system and EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L is a standardized measure of health status comprised of a descriptive system including five health-related quality of life states (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS of overall health. Each dimension is rated on a 5-point response scale indicating severity of problems, where 1 is "no problems" and 5 is "extreme problems". The five questions are scored and together contribute to the EQ-5D-5L index (utility) score between 0 and 1 (1 being perfect health), which will be calculated using the developers' algorithm based on country-specific reference score sets (Van Hout et al., 2012). Score sets are available for Denmark, France, Germany, Japan, Netherlands, Spain, UK, US and Zimbabwe. For countries in which no score set exists (Canada, Hungary, Israel, Romania, and Sweden) the closest neighboring country will be used as a proxy (EuroQol Group, 2015).

The EQ-VAS is a measure of overall self-rated health status, used and analyzed separately from the index score. The EQ-VAS records the subject's self-rated health on a 20-cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine". The EQ-VAS score ranges from 0 to 100, with higher scores indicative of better overall health.

4.2.3 Work Productivity and Activity Impairment – General Health (WPAI-GH)

The WPAI-GH is a 6-item questionnaire assessing work and activity impairment due to health problems during the past 7 days. It will be scored for each assessment according to the scoring guidelines listed below (Reilly et al., 1993). The instrument elicits four main scores in relation to general health specifically: absenteeism (the percentage of work time missed because of one's health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past seven days) (Reilly et al., 1993). The domains are calculated as follows:

1. Absenteeism (work time missed = (Q2/(Q2+Q4))*100)
2. Presenteeism (impairment at work or reduced on-the-job effectiveness = (Q5/10)*100)
3. Work productivity loss (overall work impairment/absenteeism plus presenteeism = (Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)])*100)
4. Activity Impairment = ((Q6/10)*100)

The scores are percentages with higher values indicating greater percentage impairment.

4.2.4 Sheehan Disability Scale (SDS)

The SDS is a 5-item, self-rated questionnaire designed to measure the extent to which a person's disability due to an illness or health problem interferes with each of the following three dimensions: work/school, social life/leisure activities, and family life/home responsibilities (Sheehan, 1983). Three items ask subjects to rate the extent to which three aspects of daily life are impaired by his or her symptoms using a 10-point scale. Two items ask subjects how many days have been lost or unproductive in the last week. A total global functioning impairment score is calculated as the sum of the three individual dimensions, ranging from 0 (unimpaired) to 30 (highly impaired), with higher scores indicative of greater impairment. The raw numerical scores will also be rescaled to a percentage of the maximum score (Sheehan, 1983). Higher scores show greater impairment.

4.2.5 Angioedema Activity Score (AAS)

The AAS collects information of disease activity in the last 24 hours. The following items are assessed: experience of swelling, severity of the swelling, timing of the swelling, extent of discomfort due to the swelling, extent that the swelling caused limitations in daily life, and feelings of being disfigured by the swelling. The instrument uses a binary response option for the first item and a three-point response scale for the 5 items thereafter. Total scores range between 0 and 15 points (Weller et al., 2013). The total disease activity score for the duration of an entire study period is the sum of each daily score post-treatment in each 14-week study period – the 98-day AAS. The weekly average daily disease activity scores will also be calculated for each study week, and compared with the baseline day score, for each study period. An overall daily average AAS score will also be calculated for each study period.

The MID for a 7-day total score is 8 (Weller et al., 2013). This is equivalent to a MID of 64 for a 14-week study period and around 1 for an average daily score. In the absence of known MCIDs or RDs for the AAS in HAE, the MID will be used as well as one-half of the SD of baseline scores as an MCID/RD estimate:

- AAS Index Score = 1, Baseline SD*0.5
- AAS VAS Score = 1, Baseline SD*0.5

4.2.6 Healthcare Resource Utilization Assessment related to HAE (HRUA-HAE)

The usage of healthcare resources related to HAE in the last month (HRUA-HAE) is assessed (every four weeks) with a 5-item questionnaire collecting:

i. Number of hospital admissions
ii. Number of healthcare provider visits
iii. Number of tests required
iv. Number of emergency medicine unit or out-of-hours care clinic visits
v. Number of days of home care

The total number of hospital admissions, healthcare provider visits, tests required, emergency/out-of-hours clinic visits, and days of home care will be calculated, using the information collected in the HRUA-HAE, for the duration of each study period by summing all of the responses to each individual item during each period.

4.3 Study Assessments

The administration of study measures for each study period will follow the schedule of assessments provided in the study protocol (see Table 1 and Table 2). The PRO measures will be completed using the electronic subject diary and will be assessed as follows:

AE-QoL: Administered every 4 weeks on weeks 1 (prior to treatment administration), 5, 9, and 13, of each study period. It will also be administered at the early discontinuation visit, if applicable, and at the 1-week post-treatment visit.

EQ-5D-5L: Administered on weeks 1 (prior to treatment administration), and 12, of each study period, and on each day subjects experience signs or symptoms of AE attack. It will also be administered at the early discontinuation visit, if applicable, and at the 1-week post-treatment visit.

WPAI-GH: Administered on week 1 (prior to treatment administration) and once a week, for the duration of each study period. It will also be administered at the early discontinuation visit, if applicable, and at the 1-week post-treatment visit.

SDS: Administered on week 1 (prior to treatment administration) and once a week, for the duration of each study period. It will also be administered at the early discontinuation visit, if applicable, and at the 1-week post-treatment visit.

AAS: Administered daily. It will also be administered at the early discontinuation visit, if applicable, and at the 1-week post-treatment visit.

HRUA-HAE: Administered on weeks 1 (prior to treatment administration), 4, 8, and 12, of each study period. It will also be administered at the 1-month post-treatment visit.

Table 1: Schedule of Assessments – Study period 1

		STUDY PERIOD 1 (BY STUDY WEEK)																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		DOSING VISITS (1a to 28a)																											
Procedures	**Screen[a]**	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**	**18a**	**19a**	**20a**	**21a**	**22a**	**23a**	**24a**	**25a**	**26a**	**27a**	**28a**
Informed consent	✔																												
Medical history	✔																												
Inclusion/Exclusion criteria	✔	✔ [c]																											
Adverse events[b]	✔	✔ ---------- ✔																											
Randomization (predose)		✔ [c]																											
Physical examination	✔	✔ [c]							✔								✔								✔				✔
Prior/concomitant meds	✔	✔ [c]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Height and body weight	✔																												
Vital signs (BP, pulse)[d, e]	✔	✔	✔	✔	✔				✔								✔								✔				✔
12-lead ECG[d]	✔																												
Safety labs[f]	✔	✔ [c]							✔								✔								✔				✔
UA with microscopy		✔ [c]																											✔
Virology screening[g]	✔																												
Pregnancy testing[h]	✔	✔ [c]																											
IP injection		✔ [i]	✔	✔	✔	✔	✔	✔	✔ [i]	✔	✔	✔	✔	✔	✔	✔	✔ [i]	✔	✔	✔	✔	✔	✔	✔	✔ [i]	✔	✔	✔	✔ [i]
ISR assessment[j]		✔	✔	✔	✔	✔	✔	✔	✔ [j]	✔	✔	✔	✔	✔	✔	✔	✔ [j]	✔	✔	✔	✔	✔	✔	✔	✔ [j]	✔	✔	✔	✔ [j]
Acceptability survey[k]																													✔
Self-administration survey[k]																													✔
Angioedema attack monitoring[k, l]		✔ ---------- ✔																											
AAS[k]		✔ ---------- ✔																											
AE-QoL questionnaire[k]		✔ [c]								✔								✔								✔			
EQ-5D-5L[k, m,]		✔ [c]																							✔				
WPAI-GH and SDS[k]		✔ [c]		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔	
HRUA-HAE		✔ [c]							✔								✔								✔				
Anti-C1 INH antibodies		✔ [c]							✔ [c]								✔ [c]								✔ [c]			✔ [c,n]	✔ [c,n]
PK/PD sampling	**See protocol**																												

Table 1: Schedule of Assessments – Study period 1

		STUDY PERIOD 1 (BY STUDY WEEK)																									
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		DOSING VISITS (1a to 28a)																									
Procedures	**Screen[a]**	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**	**18a**	**19a**	**20a**	**21a**	**22a**	**23a**	**24a**	**25a**	**26a**	**27a**	**28a**

AAS=angioedema activity score; AE-QoL=angioedema quality of life; aPPT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 esterase inhibitor; CRF=case report form; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; HAE=hereditary angioedema; HIV=human immunodeficiency virus; HRUA=health resource utilization assessment; INR=international normalized ratio; IP=investigational product; ISR=injection site reaction; PD=pharmacodynamic; PK=pharmacokinetic; PT=prothrombin time; SDS=Sheehan Disability Scale; UA=urinalysis; WPAI-GH=Work Productivity and Activity Impairment General Health Questionnaire

[a] All subjects will have a screening evaluation within 21 days prior to the first dose of investigational product (Visit 1a=Dosing Day 1).

[b] Adverse events will be collected from the time of informed consent through 7 days after the last dose of investigational product.

[c] Specified procedures should be performed prior to investigational product administration.

[d] Vital signs and ECGs will be measured using standard methods at each study site. Additional vital signs measurements and ECGs may be performed during the study if clinically indicated.

[e] On dosing days, vital signs should be measured ≤30 min before the start of the injection, ≤10 min after the end of the injection, and then between 30 min and 1 h after the end of the injection.

[f] Biochemistry, hematology, and coagulation (aPPT, PT, INR, D-dimer). In addition, D-dimer should be evaluated in any subject who presents at a study visit with signs and symptoms consistent with suspected venous thromboembolism.

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

[h] Female subjects of childbearing potential; serum pregnancy test at screening and urine pregnancy test at all other time points.

[i] Investigational product will be administered by qualified personnel at the investigational site at Dosing Visits 1a, 8a, 16a, 24a, and 28a.

[j] Injection site reaction assessments will be performed 15 min, 30 min, and 1 h after the end of the injection. At Visits 8a, 16a, 24a, and 28a an overall assessment of injection site severity (mild, moderate, and severe as defined in Section 11.1 in main study SAP) and the overall duration of the injection site reactions will be captured in the CRF.[k] In the electronic subject diary.

[l] The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary.

[m] In addition to the scheduled time points, subjects should complete the EQ-5D-5L on each day that they experience signs or symptoms of an angioedema attack.

[n] Collection of blood sample for the immunogenicity assessment should coincide with the subject's PK/PD sampling schedule and will occur at either Visit 27a or Visit 28a (see Table 5 in main study SAP).

Table 2: Schedule of Assessments – Study period 2

Procedures	STUDY PERIOD 2 (BY STUDY WEEK)																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	DOSING VISITS (1b to 28b)																											
	1b	2b	3b	4b	5b	6b	7b	8b	9b	10b	11b	12b	13b	14b	15b	16b	17b	18b	19b	20b	21b	22b	23b	24b	25b	26b	27b	28b
Adverse events[a]	✔ ----------																										✔	
Physical examination	✔[b]							✔								✔								✔				✔
Concomitant medications	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Body weight	✔																											
Vital signs (BP, pulse)[c]	✔	✔	✔	✔				✔								✔								✔				✔
Safety labs[d]	✔[b]							✔								✔								✔				✔
UA with microscopy	✔[b]																											✔
Pregnancy testing[e]	✔[b]																											
IP injection	✔[f]	✔	✔	✔	✔	✔	✔	✔[f]	✔	✔	✔	✔	✔	✔	✔	✔[f]	✔	✔	✔	✔	✔	✔	✔	✔[f]	✔	✔	✔	✔[f]
ISR assessment[g]	✔	✔	✔	✔	✔	✔	✔	✔[g]	✔	✔	✔	✔	✔	✔	✔	✔[g]	✔	✔	✔	✔	✔	✔	✔	✔[g]	✔	✔	✔	✔[g]
Acceptability survey																												✔
Self-administration survey[h]																												✔
Angioedema attack monitoring[h, i]	✔ ----------																										✔	
AAS[h]	✔ ----------																										✔	
AE-QoL questionnaire[h]	✔[b]								✔								✔								✔			
EQ-5D-5L[h, j]	✔[b]																							✔				
WPAI-GH and SDS[h]	✔[b]		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔		✔	
HRUA-HAE	✔[b]							✔								✔								✔				
Anti-C1 INH antibodies	✔[b]							✔[b]								✔[b]								✔[b]				✔[b]
PK/PD sampling	**See protocol**																											

AAS=angioedema activity score; AE-QoL=angioedema quality of life; aPPT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 esterase inhibitor; CRF=case report form; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; HAE=hereditary angioedema; HRUA=health resource utilization assessment; INR=international normalized ratio; IP=investigational product; ISR=injection site reaction; PD=pharmacodynamic; PK=pharmacokinetic; PT=prothrombin time; SDS=Sheehan Disability Scale; UA=urinalysis; WPAI-GH=Work Productivity and Activity Impairment-General Health Questionnaire

Note: ECGs may be performed during Study period 2 if clinically indicated, using standard methods at each study site.

[a] Adverse events will be collected from the time of informed consent through 7 days after the last dose of investigational product.

[b] Specified procedures should be performed prior to investigational product administration.

[c] Vital signs will be measured using standard methods at each study site. Additional vital signs measurements may be performed during the study if clinically indicated. On dosing days, vital signs should be measured ≤30 min before the start of the injection, ≤10 min after the end of the injection, and then between 30 min and 1 h after the end of the injection.

[d] Biochemistry, hematology, and coagulation (aPPT, PT, INR, D-dimer). In addition, D-dimer should be evaluated in any subject who presents at a study visit with signs and symptoms consistent with suspected venous thromboembolism.

[e] Urine pregnancy test for female subjects of childbearing potential.

[f] Investigational product will be administered by qualified personnel at the investigational site at Dosing Visits 1b, 8b, 16b, 24b, and 28b.

Table 2: Schedule of Assessments – Study period 2

Procedures	STUDY PERIOD 2 (BY STUDY WEEK)																									
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	DOSING VISITS (1b to 28b)																									
	1b	2b	3b	4b	5b	6b	7b	8b	9b	10b	11b	12b	13b	14b	15b	16b	17b	18b	19b	20b	21b	22b	23b	24b	25b	26b	27b	28b

[g] Injection site reaction assessment will be performed 15 min, 30 min, and 1 h after the end of the injection. At Visits 8b, 16b, 24b, and 28b an overall assessment of injection site severity (mild, moderate, and severe as defined in Section 11.1 in the main study SAP) and the overall duration of the injection site reactions will be captured in the CRF. [h] In the electronic subject diary.

[i] The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary.

[j] In addition to the scheduled time points, subjects should complete the EQ-5D-5L on each day that they experience signs or symptoms of an angioedema attack.

5. DATA MANAGEMENT

5.1 Data Handling Considerations

5.1.1 Data Analysis Populations

The analyses will use data from the full analysis data set: all enrolled subjects randomized to treatment sequence AB or BA who completed at least the baseline data collection. Subjects enrolled in the AA sequence will be included in the analyses where stated.

5.1.2 Baseline data

For analyses using mixed models, a common baseline will be taken as visit 1a. For other analyses, as appropriate, the baseline visit will be the baseline for each specific study period: visit 1a will be the baseline visit for period 1, and visit 1b will be the baseline visit for period 2.

5.1.3 Missing Data

Frequencies will be used to evaluate missing data and measures will be scored in accordance with the instrument developers' recommendations listed below:

- AE-QoL: Domains can be calculated if no more than 1 item is missing and the total score if no more than 25% of items (> 4 items) are missing (Weller et al., 2012).
- EQ-5D-5L: Index scores cannot be calculated if any of the five dimensions is missing (Simons et al., 2015).
- EQ-VAS: EQ-VAS score cannot be calculated if the EQ-VAS is not completed at an assessment.
- WPAI GH: Scores cannot be calculated if there is a missing response to a corresponding item (Reilly Associates, 2002).
- SDS: No established conventions exist but since the Global functioning impairment score is comprised of only three items, the score will not be calculated if at least one of the three dimensions is missing.
- AAS: Total scores can be calculated so long as no more than a week (7 days) of data are missing (Weller et al., 2013).

Imputation of missing data will be limited to end of treatment data used in the calculation of change scores. In the event that a subject is missing end of treatment data, the closest available score to the period end or discontinuation will be used so long as the value was obtained a minimum of 9 weeks past the period start date. If not available, no change score will be calculated. No other missing data will be imputed.

5.2 Variables

The relevant variables from Study SHP616-300 to be used in the analyses are shown in Exhibit C.

Exhibit C: Variables to be used in the analyses

Variable	Type
Subject ID	Categorical variable
Age	Continuous variable
Gender	Dichotomous variable
Prophylaxis use	Dichotomous variable
Treatment	Dichotomous variable
Sequence	Categorical variable
Period	Dichotomous variable
Carry-over effect	Dummy variable
Time point	Ordinal variable
AE-QoL total score	Continuous variable
AE-QoL functioning score	Continuous variable
AE-QoL fatigue/mood score	Continuous variable
AE-QoL fear/shame score	Continuous variable
AE-QoL nutrition score	Continuous variable
EQ-5D-5L index score	Continuous variable
EQ-VAS score	Continuous variable
WPAI-GH absenteeism	Continuous variable
WPAI-GH presenteeism	Continuous variable
WPAI-GH work productivity loss	Continuous variable
WPAI-GH activity impairment	Continuous variable
Rescaled SDS work/school score	Continuous variable
Rescaled SDS social life/leisure activities score	Continuous variable

Exhibit C: Variables to be used in the analyses

Variable	Type
Rescaled SDS family life/home responsibilities score	Continuous variable
Rescaled SDS total global functioning score	Continuous variable
AAS activity score – daily	Continuous variable
AAS activity score – weekly daily average	Continuous variable
AAS activity score – overall total	Continuous variable
AAS activity score – overall average	Continuous variable
Number of hospital admissions	Continuous variable
Number of healthcare provider visits	Continuous variable
Number of tests required	Continuous variable
Number of emergency medicine unit/out-of-hours care clinic visits	Continuous variable
Number of days home care	Continuous variable

6. STATISTICAL ANALYSIS

6.1 Distributional Considerations

Normality will be assessed visually by examination of frequency distributions and histograms, with superimposed normal curves, and statistically using values of skewness and kurtosis and their standard errors (SEs, with the population assumed to be normal if the SE is > ½ the value) and Shapiro-Wilk's tests. Based on the results of these analyses appropriate descriptive and inferential analyses (statistical tests) will be conducted (detailed below).

6.2 Descriptive Statistics

Data will be summarised using descriptive statistics. Continuous variables will be presented as mean and standard deviation (SD) for normally distributed variables, and as median and interquartile range for non-normally distributed variables. Categorical variables will be presented as frequencies (n) and percentages (%).

6.3 Statistical Tests

Statistical tests used throughout will correspond to the data distribution. If the data are not normally distributed, the majority of tests conducted will be non-parametric: either chi-squared (χ^2) or McNemar's tests for testing associations between unpaired and paired categorical data, respectively, Spearman's correlation coefficients for testing associations between variables of at least ordinal scale, Mann-Whitney U tests for comparing median scores between two groups, Kruskal-Wallis tests for comparing median scores between three or more groups, Wilcoxon matched pairs tests for comparing paired data, and Friedman tests for comparing groups of paired data. If parametric tests are undertaken (e.g., Pearson's r instead of Spearman correlation coefficients; independent sample t-tests instead of Mann-Whitney tests; ANOVAs instead of Kruskal-Wallis tests; paired t-tests instead of Wilcoxon tests; repeated measures ANOVAs instead of Friedman tests), consideration will be given to transformations to achieve a normal distribution first. Significance will be taken at the 5% level ($p<0.05$, two-tailed) throughout, with 95% confidence intervals (CIs) used to express the uncertainty in the data.

6.4 Data Analysis

The analyses will be undertaken using SAS v9.4. The analysis will be performed on the Full Analysis Set according to the steps outlined below.

6.4.1 Analysis of PRO data

Objective 1: To describe AE-QoL, WPAI-GH, SDS, and AAS scores by treatment and period (absolute, change and percentage change from baseline at each scheduled visit for AB, BA, and AA sequences) and assess differences between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA) (change and percentage change).

Descriptive statistics (i.e. mean and SD, range, plus median and interquartile range if required based on the distribution of the data) will be used to summarize AE-QoL, WPAI-GH, SDS, and AAS scores at each assessment. The data will be presented for each subject group (AB, BA, AA), treatment and period, in terms of absolute score, absolute change (end of treatment minus baseline), and percentage change (end of treatment minus baseline as a percentage of baseline) scores for each treatment (A or B) within each study period (1 or 2). For the AE-QoL, the absolute scores for each visit by treatment will be taken from the main SAP analyses. For the other measures, only item-level information is presented in the main SAP analyses and thus score level data are required. Summary results for each PRO measure will be tabled in a form similar to that shown below:

Study Period	Sequence A/B		Sequence B/A		Sequence A/A		Total	
	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Period 1: Placebo (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	Period 1: 2000 IU Cinryze (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	2000 IU Cinryze (N=xx)	Placebo (N=xx)
Study Period #								
Absolute Scores								

Study Period	Sequence A/B		Sequence B/A		Sequence A/A		Total	
	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Period 1: Placebo (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	Period 1: 2000 IU Cinryze (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	2000 IU Cinryze (N=xx)	Placebo (N=xx)
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Change in Scores								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Percentage Change								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

For each PRO measure the data presented will be as follows:

Measure	Absolute	Change	Percentage change
AE-QoL	1a/1b (baseline) 9a/9b (week 5) 17a/17b (week 9) 25a/25b (week13) Mean post baseline	- Week 5 – baseline week 9 – baseline week 13 – baseline	- Week 5 – baseline week 9 – baseline week 13 – baseline
EQ-5D-5L -5L utility and VAS	1a/1b (baseline) 24a/b (week 12)	- Week 12 – baseline	- Week 12 – baseline
WPAI-GH and SDS	1a/1b (baseline) 3a/3b (week 2) 5a/5b (week 3) 7a/7b (week 4) 9a/9b (week 5) 11a/11b (week 6) 13a/13b (week 7) 15a/15b (week 8) 17a/17b (week 9) 19a/19b (week 10) 21a/21b (week 11) 23a/23b (week 12) 25a/25b (week13) 27a/27b (week 14) Mean post baseline	- week 2 – baseline week 3 – baseline week 4 – baseline week 5 – baseline week 6 – baseline week 7 – baseline week 8 – baseline week 9 – baseline week 10 – baseline week 11 – baseline week 12 – baseline week 13 – baseline week 14 – baseline	- week 2 – baseline week 3 – baseline week 4 – baseline week 5 – baseline week 6 – baseline week 7 – baseline week 8 – baseline week 9 – baseline week 10 – baseline week 11 – baseline week 12 – baseline week 13 – baseline week 14 – baseline
AAS – 7-day daily average	1a/1b (baseline) 3a/3b (week 2) 5a/5b (week 3) 7a/7b (week 4) 9a/9b (week 5) 11a/11b (week 6) 13a/13b (week 7) 15a/15b (week 8) 17a/17b (week 9) 19a/19b (week 10) 21a/21b (week 11) 23a/23b (week 12) 25a/25b (week13) 27a/27b (week 14) Total score Average daily score	- week 2 – baseline week 3 – baseline week 4 – baseline week 5 – baseline week 6 – baseline week 7 – baseline week 8 – baseline week 9 – baseline week 10 – baseline week 11 – baseline week 12 – baseline week 13 – baseline week 14 – baseline	- week 2 – baseline week 3 – baseline week 4 – baseline week 5 – baseline week 6 – baseline week 7 – baseline week 8 – baseline week 9 - baseline week 10 – baseline week 11 – baseline week 12 – baseline week 13 – baseline week 14 – baseline

The AE-Qol, WPAI-GH, SDS, and AAS data will be presented in Table 1.1.1, Table 1.1.2, Table 1.1.3, Table 1.1.4, Table 1.1.5, Table 1.1.6, and Table 1.1.7; Table 1.2.1, Table 1.2.2, Table 1.2.3, Table 1.2.4, Table 1.2.5, and Table 1.2.6; Table 1.3.1, Table 1.3.2, Table 1.3.3, Table 1.3.4, Table 1.3.5, and Table 1.3.6; and Table 1.4.1, Table 1.4.2, Table 1.4.3, and Table 1.4.4, respectively. The data will also be depicted graphically. These graphs will be simple line plots of mean scores with standard errors in each subject group at each visit (Figure 1.1.1, Figure 1.1.2, Figure 1.1.3, Figure 1.1.4, and Figure 1.1.5; Figure 1.2.1, Figure 1.2.2, Figure 1.2.3, and Figure 1.2.4; Figure 1.3.1, Figure 1.3.2, Figure 1.3.3, and Figure 1.3.4; and Figure 1.4.1).

These tables and figures will allow informal assessment of whether there is a) a treatment effect, b) a sequence effect, c) a period effect, and d) and treatment by period interaction. A treatment by period interaction occurs when the effect of the treatment/placebo depends on the period in which it was administered. For example, if there is a carry-over effect of active treatment (the effect of the treatment persisting beyond the period in which it was administered), then the placebo effect would be expected to be larger in period 2, when it follows the active treatment, than in period 1 when it precedes it.

Separate mixed effects regression models will be used to assess the effect of treatment on *change* in each of the PRO measure scores (for AAS scores, the change from baseline to the weekly average daily score in the final week of the study period will be considered). The dependent variable will be the change in score across the study period from baseline to the last visit at which the measure was administered. Treatment group will be a fixed effect (AB, BA). Additional fixed effects will be included to control for baseline score (visit 1a or 1b), age, gender, country, prophylaxis use, period, sequence, and carry-over effects. Random effects will be included comprising random intercepts of subject crossed with treatment. The results of the models will be shown in Table 1.1.8, Table 1.1.9, Table 1.1.10, Table 1.1.11, and Table 1.1.12; Table 1.2.7, Table 1.2.8, Table 1.2.9, and Table 1.2.10; Table 1.3.7, Table 1.3.8, Table 1.3.9, and Table 1.3.10; and Table 1.4.5.

Objective 2: To describe and estimate whether the effect of an attack on EQ-5D-5L index and EQ-VAS scores differs between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA).

The change in EQ-5D index and EQ-VAS scores from the previous assessment to the first attack during a study period will be summarised using appropriate descriptive statistics (e.g. mean and SD, range, median, and interquartile range). The EQ-5D-5L index and EQ-VAS scores at subsequent attacks will also be described. All data will be presented for each subject group (AB, BA, AA), for each treatment (A or B) within each study period (1 or 2). The data will be presented in Table 2.1.1 and Table 2.1.2.

These tables for the AB and BA subject groups will allow informal assessment of whether there is a) a treatment effect, b) a sequence effect, c) a period effect, and d) and treatment by period interaction. A treatment by period interaction occurs when the effect of the treatment/placebo depends on the period in which it was administered. For example, if there is a carry-over effect of active treatment (the effect of the treatment persisting beyond the period in which it was

administered), then the placebo effect would be expected to be larger in period 2, when it follows the active treatment, than in period 1 when it precedes it.

Objective 3: To describe and assess differences in the proportion of subjects achieving the responder definition (RD) in AE-QoL and AAS scores from baseline to final assessment between treatments (A or B), controlling for study period (1 or 2) and sequence (AB, BA).

Frequencies and percentages will be used to summarize the proportion of subjects achieving the RD on the AE-QoL and AAS from baseline to end of each study period. For the AAS this will be the change from baseline to the average daily score during the last 7 days of the study period. The data will be presented for each subject group (AB, BA, AA), presenting the frequencies for each treatment (A or B) within each study period (1 or 2). Results will be tabled in a form similar to that shown below:

PRO Measure	Sequence A/B		Sequence B/A		Sequence A/A		Total	
	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Period 1: Placebo (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Placebo (N=xx)	Placebo (N=xx)
AE-QoL								
n	xx	xx	xx	xx	xx	xx	xx	xx
Percent	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
AAS								
n	xx	xx	xx	xx	xx	xx	xx	xx
Percent	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%

The AE-Qol and AAS data will be presented in Table 3.1.1, Table 3.1.2, Table 3.2.1, and Table 3.2.2, respectively. The data will also be presented graphically. These graphs will be bar charts showing the frequency in each treatment group in each period (Figure 3.1.1, Figure 3.1.2, and Figure 3.2).

These tables and figures will allow informal assessment of whether there is a) a treatment effect, b) a period effect, and c) and treatment by period interaction. A treatment by period interaction occurs when the effect of the treatment/placebo depends on the period in which it was administered. For example, if there is a carry-over effect of active treatment (the effect of the treatment persisting beyond the period in which it was administered), then the placebo effect would be expected to be larger in period 2, when it follows the active treatment, than in period 1 when it precedes it.

Mixed effects logistic regression models will be constructed for each of the PRO measure scores. The dependent variable will be a binary variable created for whether a subject achieved the RD in each study period (for AAS scores, the change from baseline to the weekly average daily score in the final week of the study period will be considered). Treatment group will be a fixed effect

(AB, BA). Fixed effects will be included to control for baseline score (visit 1a or 1b), age, gender, country, prophylaxis use, period, sequence, and carry-over effects. Random effects will be included comprising subject crossed with treatment. Results of models will be shown in Table 3.1.3a, Table 3.1.3b, Table 3.1.4a, Table 3.1.4b, Table 3.1.5a, Table 3.1.5b, Table 3.1.6a, Table 3.1.6b, Table 3.1.7a, Table 3.1.7b, Table 3.2.3, and Table 3.2.4.

Exploratory Objective 1: To assess the relationship between efficacy (as defined in the protocol) and scores on the AE-QoL, WPAI-GH, SDS, and AAS scores (Hypothesis: Subjects with improved efficacy also have improved scores).

Efficacy will be defined as normalized number of attacks (NNA), per the study protocol. NNA is expressed as the number of attacks per month (i.e., 30.4 days) of exposure:

NNA = 30.4 x (number of attacks during study period)/ (days of study period).

If a subject discontinues during the study period, the denominator of the NNA will be the days on treatment for that subject; this is equivalent to the last observation carried forward imputation method to impute the missing information following the subject's discontinuation.

Separate mixed effects regression models will be used to assess the effect of NNA on *change* in each of the PRO measure scores (for AAS scores, the change from baseline to the weekly average daily score in the final week of the study period will be considered). The dependent variable will be the change in score across the study period from baseline to the last visit at which the measure was administered. NNA will be a fixed effect. Additional fixed effects will be included to control for treatment group, baseline score (visit 1a or 1b), age, gender, country, prophylaxis use, period, sequence (AB, BA), and carry-over effects. An interaction between treatment and NNA will also be tested. Random effects will be included comprising random intercepts of subject crossed with treatment. Results of the models will be shown in Table 5.1.1, Table 5.1.2, Table 5.1.3, Table 5.1.4, Table 5.1.5, Table 5.2.1, Table 5.2.2, Table 5.2.3, Table 5.2.4, Table 5.3.1, Table 5.3.2, Table 5.3.3, Table 5.3.4, and Table 5.2.

6.4.2 Analysis of HRUA-HAE data

Objective 1: To describe HRUA-HAE (absolute values) according to treatment, study period (1 or 2) and sequence (AB, BA).

Descriptive statistics (i.e. mean and SD, or median and interquartile range) will be used to summarize HRUA-HAE values at each assessment. The data will be presented for each subject group (AB, BA, AA) in terms of absolute values for each treatment (A or B) within each study period (1 or 2). Results will be shown in a similar way to that shown below:

Study Visit	Sequence A/B		Sequence B/A		Sequence A/A		Total	
	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Period 1: Placebo (N=xx)	Period 2: 2000 IU Cinryze (N=xx)	Period 1: 2000 IU Cinryze (N=xx)	Period 2: Placebo (N=xx)	Placebo (N=xx)	2000 IU Cinryze (N=xx)
Study Visit #								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

The data will be presented in Table H1, Table H2, Table H3, Table H4, and Table H5. These tables will allow informal assessment of whether there is a) a treatment effect, b) a sequence effect, c) a period effect, and d) and treatment by period interaction. A treatment by period interaction occurs when the effect of the treatment/placebo depends on the period in which it was administered. For example, if there is a carry-over effect of active treatment (the effect of the treatment persisting beyond the period in which it was administered), then the placebo effect would be expected to be larger in period 2, when it follows the active treatment, than in period 1 when it precedes it.

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8. LIST OF TABLES

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8.5 HRUA-HAE Analyses

Objective 1

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10. PROGRAMMING CONVENTIONS

10.1 Study Measure Scoring

10.1.1 Angioedema Quality of Life (AE-QoL) Questionnaire

The questionnaire will be scored according to the developers' guidelines (Weller et al., 2012) to produce a total score and four domain scores (functioning, fatigue/mood, fear/shame, nutrition). Raw domain scores (mean of the item scores within each scale) and the raw total score (mean of all item scores) will be rescaled using linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score, where the higher the score the greater the QoL impairment.

Final variables for analysis (per time-point and per study period):

1. Rescaled AE-QoL total score
2. Rescaled AE-QoL functioning domain score
3. Rescaled AE-QoL fatigue/mood domain score
4. Rescaled AE-QoL fear/shame domain score
5. Rescaled AE-QoL nutrition domain score

10.1.2 EuroQol 5-dimensional 5-level (EQ-5D-5L) Descriptive System and EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L index score will be calculated using the developers' algorithm based on country-specific reference score sets developed (Van Hout et al., 2012). Score sets are available for Denmark, France, Germany, Japan, Netherlands, Spain, UK, US and Zimbabwe. For countries in which no score set exists (Canada, Hungary, Israel, Romania, and Sweden) the closest neighboring country will be used as a proxy (EuroQol Group, 2015).

The EQ-VAS is a measure of overall self-rated health status, used and analyzed separately from the index score. The EQ-VAS ranges from 0 to 100, with higher scores indicative of better overall health.

Final variables for analysis (per time-point and per study period):

1. EQ-5D-5L index score
2. EQ-VAS score

10.1.3 Work Productivity and Activity Impairment – General Health (WPAI-GH)

The WPAI-GH will be scored for each assessment according to the scoring guidelines listed below (Reilly et al., 1993):

1. Absenteeism (work time missed = (Q2/(Q2+Q4))*100)
2. Presenteeism (impairment at work or reduced on-the-job effectiveness = (Q5/10)*100)
3. Work productivity loss (overall work impairment/absenteeism plus presenteeism = (Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)])*100)
4. Activity Impairment = ((Q6/10)*100)

Final variables for analysis (per time-point and per study period):

1. Absenteeism score
2. Presenteeism score
3. Work productivity loss score
4. Activity impairment score

10.1.4 Sheehan Disability Scale (SDS)

The raw scores for impairment in work/school, social life/leisure activities, and family life/home responsibilities will be rescaled to a percentage of the maximum possible score (maximum score is 10). A total global functioning impairme7nt score is calculated as the sum of the three raw work/school, social life/leisure activities, and family life/home responsibilities scores. This is also rescaled to a percentage of the maximum possible score (maximum score is 30) (Sheehan, 1983).

Final variables for analysis (per time-point and per study period):

1. Rescaled SDS total global functioning score
2. Rescaled SDS work/school score
3. Rescaled SDS social life/leisure activities score
4. Rescaled SDS family life/home responsibilities score

10.1.5 Angioedema Activity Score (AAS)

The final AAS daily score is the sum of the five items (Weller et al., 2013). This is calculated for each day the instrument is administered.

The following summary scores will be calculated:

1. The total disease activity score for the full duration of a study period = the sum of each final daily score post-baseline in each 14-week study period.
2. The overall average for the full duration of a study period = the mean of all the final daily scores post-baseline in each 14-week study period.
3. The weekly average daily disease activity scores = the mean of all the final daily scores post-baseline in each week individually.

Final variables for analysis:

1. Daily final AAS score (per day and per study period)
2. Weekly daily average final AAS score (per week and per study period)
3. Overall total AAS score (per study period)
4. Overall average AAS score (per study period)

10.1.6 Healthcare Resource Utilization Assessment related to HAE (HRUA-HAE)

The raw values are used. The total values for the entire treatment period are calculated by summing the responses to all assessments during that period for each item separately.

Final variables for analysis (per time-point and total, and per study period):

1. Number of hospital admissions
2. Number of healthcare provider visits
3. Number of tests required
4. Number of emergency medicine unit or out-of-hours care clinic visits
5. Number of days of home care

10.2 Calculating Change in Scores

Change in scores will be calculated as follows for each visit and each study period separately:

- Study period 1:
    - Follow up visit x score - baseline (visit 1a) score
- Study period 2:
    - Follow up visit x score - baseline (visit 1b) score

Change in AAS scores will be calculated as follows:

- Study period 1:
    - Weekly average daily scores for the each week of follow up - baseline (visit 1a) daily score
- Study period 2:
    - Weekly average daily scores for the each week of follow up - baseline (visit 1b) daily score

The overall change score is always the final follow up visit minus the baseline visit, for each study period separately. For AAS scores, it is change from baseline to the weekly average daily score in the final week, for each study period separately.

Imputation of missing data will be limited to end of treatment data used in the calculation of change scores. In the event that a subject is missing end of treatment data, the closest available score to the period end or discontinuation will be used so long as the value was obtained a minimum of 9 weeks past the period start date. If not available, no change score will be calculated. No other missing data will be imputed.

10.3 Responder Definition Variables

A RD binary variable will be created for each relevant PRO measure (AE-QoL, and EQ-5D-5L) and score. Each person will receive a 0 if they did NOT reach the MCID or estimated distribution-based RD for the PRO measure and score in the relevant study period, and they will receive a 1 if they did.

- AE-QoL
    - Rescaled AE-QoL total score = 6, Baseline SD*0.5
    - Rescaled AE-QoL Functioning domain score = 6, Baseline SD*0.5
    - Rescaled AE-QoL Fatigue/mood domain score = 6, Baseline SD*0.5

  - Rescaled AE-QoL Fear/shame domain score = 6, Baseline SD*0.5
  - Rescaled AE-QoL Nutrition domain score = 6, Baseline SD*0.5

- EQ-5D-5L
  - EQ-5D-5L Index Score = 0.05, 0.075, 0.10, 0.125, Baseline SD*0.5
  - EQ-VAS Score = 5, 7.5, 10, Baseline SD*0.5

- AAS
  - Average daily scores = 1, Baseline SD*0.5.

10.4 Dummy Variable for Carry-over Effect

A dummy variable will be created in order to control for carry-over effect. The study protocol states that carry-over effect is possible when the active treatment was given in the first period, and may extend over the first two weeks of the second period.

If the data are in wide format, a 1 for carry-over will be given in period 2 if the active treatment was administered in period 1. In all other cases, a 0 will be given. If the data are in long format, a 1 for carry-over will be given for the time-points over the first two weeks of period 2 if the active treatment was administered in period 1. In all other cases, a 0 will be given.

10.5 Explanation of the Standard Deviation Rule

- The standard deviation rule is half of the standard deviation.

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PK AND PD ANALYSIS PLAN

A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults with Hereditary Angioedema

Sponsor Protocol No.: SHP616-300 (Amendment 3)
Investigational Product: SHP616 (CINRYZE®)

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