



PROTOCOL: SHP616-300

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

IND: 16516

EUDRACT NO.: 2015-002478-19

SPONSOR:

Shire ViroPharma, Inc.
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INVESTIGATORS: Multicenter

PROTOCOL HISTORY: Amendment 4: 08 Feb 2017
Amendment 3: 11 Jan 2016
Amendment 2: 03 Sep 2015
Amendment 1: 22 Jul 2015
Original Protocol: 28 May 2015

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08 Feb 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire ViroPharma, Inc.) Approval

Signature:

[Redacted Signature]

Date:

[Redacted Date]

[Redacted Title] MD, PhD

Investigator's Acknowledgement

I have read this protocol for Shire ViroPharma Study SHP616-300.

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.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:

(please hand print or type)

Signature: _____

Date: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Amendment 4 to Protocol SHP616-300 incorporates the following major changes:

- Added 2 key secondary efficacy endpoints to assess efficacy excluding the first 2 weeks of each treatment period. The primary and existing key secondary endpoints are not affected. The new key secondary endpoints provide additional efficacy assessments while allowing the investigational product to attain steady-state levels and reducing potential carryover effects. Corresponding updates were made to the key secondary study objectives. In addition, revised description of multiplicity adjustments to account for the 2 new key secondary efficacy endpoints.
- Harmonized country-specific protocol requirements into this global amendment.
- Updates were made to some study procedures (eg, reporting period for all angioedema attacks and concomitant medications is now through 1-month post-treatment, blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays).

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency, clarity, or format) are not reflected in the summary of changes.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 4	Amendment Date 08 Feb 2017	Global/Country/Site Specific Global
Description of Change and Rationale		Section(s) Affected by Change
The Sponsor's Medical Monitor has changed to PPD MD, PhD.		Protocol Signature Page, Emergency Contact Information
Clarified that at least 75 subjects will be screened and at least 66 subjects will be enrolled and randomized to support all efficacy and safety objectives.		Synopsis
Added 2 key secondary efficacy endpoints to assess efficacy excluding the first 2 weeks of each treatment period, to allow the investigational product to attain steady-state levels and reduce potential carryover effects. Corresponding updates were made to the key secondary study objectives. In addition, revised description of multiplicity adjustments to account for the 2 new key secondary efficacy endpoints.		Synopsis , Section 2.2.2 , Sections 9.8.1 and 9.8.2.1
Revised inclusion criteria to only allow enrollment of adult (≥ 18 years) HAE patients in Germany and Israel.		Synopsis , Section 4.1
Added "not applicable to Germany and Israel" to the exclusion criterion for adolescent subjects and rescue medications allowed in adolescent subjects.		Synopsis , Section 4.2 , Section 5.2.1
Revised exclusion criteria to exclude subjects positive for hepatitis B, hepatitis C, or HIV infection; alcohol, drug, or medication abuse within 1 year before screening; or mental condition rendering the subject or		Synopsis , Section 4.2

parent(s)/legal guardian unable to understand the nature, scope of the study, and possible consequences of the study. Also excluding subjects with a relationship to study staff or sponsor (including people accommodated in an institution as well as people who are dependent on the sponsor, CRO, site or the investigator).	
Added that blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays.	Synopsis , Table 4 , Section 7.2.4.1 , Section 9.10.1
Revised to clarify that the reporting period for all angioedema attacks and concomitant medications is from the first dose of investigational product through to the 1-month post-treatment visit and to indicate the subject diary should be completed on the day of discontinuation and/or at the 1-week and 1-month post-treatment visits, as applicable.	Table 3 , Section 5.2 , Sections 7.1.4 and 7.1.5
Noted that double-barrier methods are not an acceptable form of female contraception in Germany.	Section 4.3.1
Added that mandatory discontinuation of investigational product would occur if the sponsor became aware of conditions that were unexpected, were significant, or posed an unacceptable risk to patients.	Section 4.4
Added that in Germany, if a subject discontinues investigational product for a mandatory reason, this must be specified in the subject's CRF.	Section 4.4.1
Added that for subjects participating in Germany, if a thrombotic/thromboembolic event occurs in any subject, investigational product administration for that subject will be discontinued.	Section 4.4.4 , Appendix 4 , Appendix 5
Added that for subjects who experience a laryngeal attack, they should inject icatibant and proceed immediately to the nearest medical care facility.	Section 5.2.1
Revised to include the date and time of complete resolution of angioedema attack symptoms should be recorded for each attack.	Section 7.2.2.2
Added a section to define adverse events of special interest for CINRYZE. Adverse events of special interest will be summarized as a part of the safety analyses.	Section 8.1.8 , Section 9.9
Removed paragraph describing the study's enrollment goal as it was not needed in this section for the sample size calculation and power considerations. Corrected typographical errors.	Section 9.6
Editorial revisions to clarify planned pharmacokinetic/pharmacodynamic analyses.	Synopsis , Section 9.10.1
Clarified that the sponsor may suspend or terminate the study if conditions arise which indicate that the clinical investigation should be halted due to an unacceptable patient risk.	Section 10.1.4

See [Appendix 6](#) for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover) and are provided below.

US and Canadian Sites

Fax: PPD [REDACTED]

Email: PPD [REDACTED]

EU/ROW Sites

Fax: PPD [REDACTED]

Email: PPD [REDACTED]

For protocol- or safety-related issues, the investigator must contact the Shire ViroPharma Medical Monitor:

PPD [REDACTED], MD, PhD, Clinical Development

Office phone: PPD [REDACTED]

Mobile phone: PPD [REDACTED]

Fax: PPD [REDACTED]

Email: PPD [REDACTED]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire ViroPharma product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please report all Product Quality Complaints to:

PPD

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ABBREVIATIONS

AAS	Angioedema Activity Score
AE	adverse event
AE-QoL	angioedema quality of life (questionnaire)
ATE	arterial thromboembolism
AUC _{last}	area under the curve from the time of dosing to the last measurable concentration
AUC _{0-∞}	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
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
EQ-5D-5L	EuroQol 5-dimensional 5-level descriptive system
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAE	hereditary angioedema
β-hCG	beta human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRUA	health resource utilization assessment
ICH	International Conference on Harmonisation

IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
λ_z	first order rate constant associated with the terminal (log-linear) portion of the curve
NNA	normalized number of attacks
PD	pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetics
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDS	Sheehan Disability Scale
$t_{1/2}$	terminal half-life
T/TE	thrombotic/thromboembolic
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
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VTE	venous thromboembolism
WPAI-GH	Work Productivity and Activity Impairment-General Health (questionnaire)

STUDY SYNOPSIS

Protocol number: SHP616-300	Drug: C1 esterase inhibitor [human] liquid for injection
Title of the study: 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.	
Number of subjects (total and for each treatment arm): At least 75 subjects will be screened At least 66 subjects will be enrolled and randomized to support all efficacy and safety objectives At least 26 subjects will be randomized to the treatment sequence 1 or 2, and at least 14 subjects will be randomized to the treatment sequence 3	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 40 sites globally (North America and Europe)	
Study period (planned): 2015-2017	Clinical phase: 3
Objectives: Primary: To demonstrate the superior efficacy of subcutaneous (SC) administration of 2000 IU C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks relative to placebo based on the normalized number of attacks (NNA) during a treatment period. Key Secondaries: 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: <ol style="list-style-type: none"> 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 period. 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: <ul style="list-style-type: none"> • 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 in the 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 pharmacokinetics (PK) and pharmacodynamics (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

Rationale:

Shire ViroPharma has developed a new, ready-to-use liquid formulation of CINRYZE® for SC administration. This product, C1 esterase inhibitor [human] liquid for injection, obviates the need for reconstitution by the patient or health care provider and, owing to its higher concentration, affords the opportunity for more rapid administration of the drug and may improve tolerability, without an expected change or compromise in efficacy. Subcutaneous administration represents a convenient alternative method of administering prophylaxis to hereditary angioedema (HAE) patients overall and for whom accessing peripheral veins is difficult or in patients where placement of central venous catheters are contraindicated, as well as a means to minimize the potential adverse effects of intravenous (IV) administration.

Investigational product, dose, and mode of administration:

- C1 esterase inhibitor [human] liquid for injection is supplied in clear glass vials containing 1000 IU of C1 INH in 2 mL of sterile liquid. Two (2) vials, a total 4 mL, are required per 2000 IU dose. The solution also contains the following inactive ingredients: sodium phosphate, sorbitol, glycine, and water for injection. No reconstitution or dilution is required. Vials must be stored at 2–8°C (36–46°F) and protected from light.
- Placebo is supplied in the identical 2 mL presentation as the active investigational product minus the C1 INH protein. Two (2) vials, a total 4 mL, are required per dose. The inactive ingredients in the 2 mL solution are the same as the active product: sodium phosphate, sorbitol, glycine, and water for injection. No reconstitution or dilution is required. Vials must be stored at 2–8°C (36–46°F) and protected from light.

Blinded investigational product (Treatments A or B: 2000 IU C1 esterase inhibitor [human] liquid for injection or placebo) will be administered twice weekly (every 3 or 4 days) for 14 weeks in each of 2 separate treatment periods. Each dose of investigational product will be administered in the subject's abdomen as a single 4 mL SC injection.

Commercial icatibant labeled for clinical trial use will be supplied as rescue medication for the treatment of acute angioedema attacks.

Methodology:

This is a randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study. This design was chosen as the best way to jointly address the protocol objectives of establishing efficacy (relative to placebo) and safety (ie, enrolling an adequate number of subjects for precision of estimation in detecting potential safety signals). Additionally, this design maximizes the number of subjects exposed to C1 esterase inhibitor [human] liquid for injection and minimizes subject exposure to placebo, while having adequate subject exposure to placebo to assess efficacy.

Subjects will be screened within 21 days prior to randomization. Subjects are required to have a history (based on subject recall and medical records) of ≥ 2 attacks per month on average per inclusion criterion #3. 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 using interactive response technology (see table below). Randomization of subjects will be stratified by use of prophylactic therapy with C1 INH at the time enrollment.

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.

Each treatment period will be 14 weeks, without a washout between the 2 periods. The omission of a washout period is to minimize the duration that subjects will be without active treatment. It is recommended that the twice weekly dosing schedule (every 3 or 4 days) be maintained between the last dose of investigational product in Treatment Period 1 and the first dose of investigational product in Treatment Period 2. Every effort should be made to complete scheduled dosing and to avoid situations where investigational product is not received. In order to prevent a missed dose, a less than 3-day interval may occur, with the recommendation of allowing at least 24 hours between doses.

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

Subjects will remain outpatients throughout the study. Investigational product will be administered at the investigational site for Dosing Visits 1, 8, 16, 24, and 28 during both treatment periods. Other doses may be administered by qualified blinded personnel at the investigational site or at the subject's home or other agreed upon location or self-administered by the subject (adolescent or adult) with or without supervision (qualified home health professional and/or study site personnel), after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering the investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver after receiving appropriate training, will be allowed to administer the investigational product to an adolescent subject with or without supervision.

Throughout the study, an electronic subject diary will be used to record specific information regarding the subject's symptoms of HAE and details on self-administration. This will include signs and symptoms of angioedema attacks, location (including whether mucosal or non-mucosal), triggers for angioedema attacks, medications used for the acute treatment of angioedema attacks, elective procedures, and interruptions in activities of daily living due to an angioedema attack. Additionally, quality of life questionnaires and surveys on SC administration of the investigational product will be also subject evaluated. Note: For adolescent subjects, a parent/legal guardian/caregiver is allowed to assist the subject in completing the electronic subject diary, including the quality of life questionnaires.

Adverse events will be recorded from the time the informed consent is signed through 7 days after the last dose of investigational product. This includes events occurring during the screening phase of the study, regardless of whether or not the investigational product is administered. In addition, the investigator will report all SAEs that occur through 30 days after the last dose of investigational product to Shire Pharmacovigilance and the respective Independent Reviewing Authority according to local reporting requirements.

A post-treatment visit will be performed at the investigative site 1 week (± 1 day) after the last dose of investigational product in Treatment Period 2 for follow-up safety assessments. In addition, subjects will have blood samples collected for PK/PD and C1 INH antibody testing at 1 month (± 2 days) after the last dose of investigational product.

If a subject prematurely discontinues investigational product, early discontinuation visit procedures (Table 3) are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-week and 1-month post-treatment visits.

The schedules of study procedures are provided immediately following the study synopsis:

- **Table 1:** Clinical study assessments – Treatment Period 1 (Visits 1a to 24a).
- **Table 2:** Clinical study assessments – Treatment Period 2 (Visits 1b to 24b).
- **Table 3:** Clinical study assessments – Early discontinuation visit, 1-week post-treatment and 1-month post-treatment visits.
- **Table 4:** Blood sample collection schedule – PK/PD assessments.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. Be ≥ 12 years of age, or in Germany and Israel, be ≥ 18 years of age.
2. Have a diagnosis of HAE (Type I or II) and a functional C1 inhibitor (C1 INH) level less than 50% of normal.
3. Meet one of the following criteria (attack rate may be based on subject recall in conjunction with the subject's medical records):
 - If subject is adult (≥ 18 years of age) and currently receiving prophylactic therapy with C1 INH, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to starting prevention therapy.
 - OR**
 - If subject is adolescent (≥ 12 and < 18 years of age) or adult and not receiving prophylactic therapy with C1 INH, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit.
 - OR**
 - If subject is adult (≥ 18 years of age) and currently receiving a stable dose of attenuated androgens, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit.
4. For subjects ≥ 18 years of age, be willing to receive treatment with icatibant for any angioedema attacks that occur during the study that, in the opinion of the healthcare care provider, requires medical intervention. Note: For subjects ≥ 12 to < 18 years of age, standard of care therapy per local protocols should be provided.
5. Agree to adhere to the protocol-defined schedule of assessments.
6. If female, must have a negative serum beta human chorionic gonadotrophin (β -hCG) pregnancy test at the screening visit and must have a negative urine pregnancy test prior to the first dose of investigational product (Visit 1a), and agree to comply with any applicable contraceptive requirements of the protocol.
7. If male, be surgically sterile or agree to follow an acceptable method of birth control (eg, abstinence, barrier control) from the screening visit through 2 months after the last dose of investigational product.
8. If an adult (≥ 18 years of age), be informed of the nature of the study and provide written informed consent before any study-specific procedures.

OR

If a child (< 18 years of age), have a parent(s)/legal guardian who is informed of the nature of the study provide written informed consent for the child to participate in the study before any study-specific

procedures are performed (with assent from the child when appropriate). Alternatively, certain sites/Independent Reviewing Authorities may permit adolescents who are <18 years of age to be informed of the nature of the study and provide written informed consent without consent from a parent(s)/legal guardian.

Exclusion Criteria:

1. 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).
2. Adolescents (≥ 12 and <18 years of age) currently receiving prophylactic therapy with C1 INH (not applicable to Germany and Israel).
3. Have had signs or symptoms of an angioedema attack within 2 days prior to the first dose of investigational product in Treatment Period 1.
4. 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.
5. 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.
6. Have a history of hypercoagulability (abnormal blood clotting) or other predisposition for thromboembolism.
7. Have a diagnosis of acquired angioedema or known presence of anti-C1 INH antibodies.
8. Have a history of allergic reaction to C1 INH products, including CINRYZE (or any components of CINRYZE), or other blood products, or Firazyr (icatibant).
9. Be pregnant or breastfeeding.
10. Have received an investigational drug within 30 days prior to the first dose of investigational product in Treatment Period 1.
11. Have, as determined by the investigator and/or the sponsor's medical monitor, any surgical or medical condition (including positive for hepatitis B, hepatitis C, or HIV infection; alcohol, drug, or medication abuse within 1 year before screening; or mental condition rendering the subject or parent(s)/legal guardian unable to understand the nature, scope of the study, and possible consequences of the study), or relationship to study staff or sponsor (including people accommodated in an institution as well as people who are dependent on the sponsor, CRO, site or the investigator) that could interfere with the administration of investigational product or interpretation of study results.

Maximum duration of subject involvement in the study:

Individual participation from the screening visit through the 1-month post-treatment visit will be approximately 9 months.

- Planned duration of screening period: Up to 21 days
- Planned duration of enrollment period: 6 months
- Planned duration of treatment period: Treatment Periods 1 and 2 are 14 weeks each (total 28 weeks) with no washout between periods
- Planned duration of follow-up: 1 month follow-up in total, with safety assessments at both 1-week and 1-month post-treatment

Endpoints and statistical analysis:

Primary Efficacy Endpoint: The NNA recorded during each treatment period. The NNA is computed as the number of attacks per month (ie, 30.4 days) of exposure ($NNA = 30.4 \times [\text{number of attacks during treatment period}] / [\text{days of treatment period}]$). 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.

The primary analysis of the primary efficacy endpoint will test against the null hypothesis that the NNA of C1 esterase inhibitor [human] liquid for injection is greater than or equal to the NNA of placebo ($H_0: \mu_{C1\text{ INH}} - \mu_{\text{placebo}} \geq 0$; $H_1: \mu_{C1\text{ INH}} - \mu_{\text{placebo}} < 0$). The primary efficacy endpoint will be analyzed by using a linear mixed effect model with period, sequence, stratification factor (use of prophylactic therapy with C1 INH), and treatment as fixed effects, and subject nested within sequence as a random effect. The mean treatment difference ($\mu_{C1\text{ INH}} - \mu_{\text{placebo}}$) will be estimated with a 95% confidence interval (CI).

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.

Key Secondary Efficacy Endpoints:

1. The proportion of subjects meeting the criterion of at least a 50% 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% 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 endpoints 1 and 3 are defined as achieving a $\geq 50\%$ reduction in the NNA (P_R) during the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period. Key secondary endpoints 1 and 3 will be analyzed as the proportion of subjects meeting criterion P_R . 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. The proportion meeting criterion 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.

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

Other Secondary Efficacy Endpoints:

- To determine the proportions of subjects achieving at least a 50% reduction in the NNA during a treatment period relative to the pretreatment assessment.
- Cumulative attack severity. This score is the sum of the maximum symptom severity recorded for each angioedema attack in a treatment period.
- Cumulative daily severity. This score is the sum of the severity scores recorded for every day of reported symptoms in a treatment period.
- Number of attack-free days during a treatment period.
- Number of angioedema attacks requiring acute treatment during a treatment period.
- Disease activity as measured by the 98-day AAS. This score is the sum of the daily AAS during a treatment period, where the daily AAS is the sum of AAS items per day.
- Results of the Angioedema Quality of Life (AE-QoL) questionnaire.
- Determine the response to icatibant when administered as treatment for an acute angioedema attack by:
 - Time to subject-assessed initial symptom improvement (TISI).
 - Time to subject-assessed complete symptom resolution (TCSR).

Subjects in the Full Analysis Set (Section 9.7) will be used to evaluate the efficacy of SC administration of C1 esterase inhibitor [human] liquid for injection. The treatment differences in clinical responder rate, both of which are defined within treatments, will be analyzed using McNemar's test for testing equality of proportions of responders within treatments. All other secondary endpoints will be analyzed using a linear mixed effect model with period, sequence, stratification factor (use of prophylactic therapy with C1 INH), and treatment as fixed effects, and subject nested within sequence as a random effect. The results of all secondary efficacy

analyses will be summarized by the point estimate of within-subject treatment differences or response rates and the corresponding 95% CI. Descriptive statistics (n, median, 25% and 75% quartiles, and range) will be provided to summarize icatibant-related efficacy endpoints (TISI and TCSR) by treatment and icatibant-treated angioedema attack for all subjects in the Full Analysis Set. Where appropriate (for subjects ≥ 12 to < 18 years of age) other rescue medications used to treat acute angioedema attacks will also be summarized using descriptive statistics. In addition, angioedema attacks will be summarized by the maximum symptom severity and treatment for all subjects in the Full Analysis Set.

Safety Endpoints:

- Number of subjects experiencing AEs, including severity and causality. AEs will also be assessed by time of onset (eg, during administration of investigational product or within 24 hours after the end of injection of investigational product).
- Clinical laboratory tests (hematology, chemistry, and coagulation), vital signs, and ECG findings will be summarized by treatment and visit. Potentially clinically important findings will also be summarized or listed.
- Incidence, severity (mild, moderate, severe), overall impact on daily living, and duration of SC injection site reactions.
- Results of C1 INH antibody testing will be reported for individual subjects and summarized.
- Tolerability of icatibant therapy for acute angioedema attacks will be summarized.

PK/PD Endpoints: Plasma concentrations of C1 INH antigen, functional C1 INH activity, and complement C4 and C1q for individual subjects will be determined using validated bioanalytical methods. Results will be summarized using descriptive statistics for values at each time point. C1q concentrations will only be assessed at baseline (ie, pre-injection, Dosing Visit 1a).

Pharmacokinetic/pharmacodynamic (PK/PD) parameters will be calculated using observed and baseline-corrected concentration-vs-time data using non-compartmental analysis for C1 INH antigen, functional activity, and C4 levels (as appropriate), and results will be summarized using descriptive statistics. The PK/PD properties of SC C1 esterase inhibitor [human] liquid for injection will be characterized by population PK/PD modeling, and exposure-response will be explored.

Blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays.

Other Endpoints:

- Results of the EuroQol 5-dimensional 5-level descriptive system (EQ-5D-5L) health status instrument will be presented in accordance with the EQ-5D-5L user guide (Version 2.0).
- Results of the Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire will be summarized.
- Results of the Sheehan Disability Scale (SDS) will be summarized.
- Results of the survey of subject acceptability of SC administration of investigational product will be summarized.
- Results of the survey of subject experience with self-administration of investigational product will be summarized.

STUDY SCHEDULES

Table 1 **Schedule of Assessments – Treatment Period 1**

Procedures	Screen ^a	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)																											
		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 ^t		✓ ^c		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	
HRUA-HAE		✓ ^c							✓								✓									✓			
Anti-C1 INH antibodies		✓ ^c							✓ ^c								✓ ^c									✓ ^c			✓ ^{c, n}
PK/PD sampling		A detailed blood sample collection schedule for PK/PD assessments is provided in Table 4																											

Table 1 Schedule of Assessments – Treatment Period 1

Procedures	Screen ^a	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)																											
		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. 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 (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 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 4](#)).

Table 2 Schedule of Assessments – Treatment Period 2

Procedures	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)																											
	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 4																											

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

^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 (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.

^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

Table 2 Schedule of Assessments – Treatment Period 2

Procedures	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)																											
	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

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.

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

Table 3 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 ^e	✓	✓	✓
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; aPPT=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

^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 (aPPT, 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 and/or at the 1-week and 1-month post-treatment visits, as applicable.

^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.

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.

Table 4 Blood Sample Collection for PK/PD Analyses

TREATMENT PERIOD 1	
Visit / Dose #	Blood Sampling Time Points^a
	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 <u>or</u> 28a / Dose 27 or 28 ^d	Predose 27 <u>or</u> 28 (within 15 min)
	48 hours postdose 27 <u>or</u> 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.

Note: Blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a gene mutation on chromosome 11 that results in a quantitative or functional deficiency of C1 esterase inhibitor (C1 INH) protein (Bernstein 2011). C1 INH is produced mainly by hepatocytes and acts as a “suicide inhibitor” by forming complexes with target serine proteases that result in their inactivation and the consumption of C1 INH. C1 INH regulates the activity of several components of the complement, contact (bradykinin-forming), and fibrinolytic systems (Kaplan 2010). Dysregulation of these cascades (particularly the contact system) due to C1 INH deficiency causes the uninhibited production of bradykinin, which promotes inflammation through increased vascular permeability and excessive accumulation of fluid in body tissues (Kaplan and Joseph 2010). Thus, patients with HAE are susceptible to recurrent episodes of debilitating swelling throughout the body. During acute angioedema attacks, the plasma levels of bradykinin in HAE patients can increase from 2 to 12 times (18.0–90.0 pM) the upper limit of normal (0.2–7.1 pM; Cugno et al. 2003). Serum concentrations of C1 INH in patients with HAE are 5% to 30% of normal (Cicardi et al. 1987), thus necessitating C1 INH replacement therapy to prevent manifestations of the disease.

The diagnosis of a C1 INH deficiency is suggested by a history that includes recurrent attacks of angioedema, characterized by non-itching swelling of the skin or mucosa. Serum C4, C1 INH antigen, and functional C1 INH levels can be measured to assist with the diagnosis of HAE. There are 2 main types of HAE: Type I HAE (85% of cases), characterized by a low level of C1 INH antigen, and Type II HAE (15% of cases), characterized by “normal” levels of functionally deficient C1 INH protein (Frank et al. 1976). There is no clinical difference between Type I and Type II HAE. A third form of HAE, where patients have normal C1 INH levels, was initially described and referred to as Type III (Bork et al. 2000a). Patients with this type of HAE, more frequently women, have normal complement levels (including normal C1 INH), but a well-defined history of angioedema in the absence of concurrent urticaria (Zuraw and Christiansen 2009; Bernstein 2011). Mutations in the gene for coagulation factor XII (F12) have been identified in a minority of affected families (Bork et al. 2007). There are subtle phenotypic differences between patients with HAE due to C1 INH deficiency and those with normal C1 INH levels, including age at symptom onset, attack location(s), period of disease-free intervals, and inheritance pattern (Zuraw et al. 2012). The pathogenesis of HAE with normal C1 INH remains to be fully elucidated.

Hereditary angioedema with C1 INH deficiency can present as early as the first year of life (Ohela 1977; Farkas et al. 2002), however, the median age at onset of initial symptoms is between 9 and 12 years (Farkas et al. 2007). Nearly all affected individuals experience symptoms of the disease; however, the symptoms vary in both their frequency and severity throughout a patient’s lifetime (Gompels et al. 2005; Zuraw 2003). Angioedema attacks may or may not have a triggering event. Trauma, medical or dental procedures, psychological stress, menstruation, infections, oral contraceptive use, and the use of other medications, such as angiotensin-converting enzyme inhibitors have been identified as possible triggers (Georgy and Pongracic 2012; Bowen et al. 2010). Angioedema attacks can affect the face, tongue, larynx,

gastrointestinal tract, genitourinary system, and extremities (Zuraw 2008). Laryngeal swelling can occlude the airway and cause death by asphyxiation, and these attacks primarily account for the mortality risk associated with C1 INH deficiency (Agostoni and Cicardi 1992; Bork et al. 2000b). Gastrointestinal involvement can mimic an acute surgical emergency, and misdiagnosis often results in unnecessary procedures to remove normal appendices and gallbladders (Weis 2009). Hence, angioedema attacks require prompt treatment, often in an emergency room.

In addition to the impact on physical and mental health, the burden of illness in patients with HAE is considerable with respect to missed educational and career opportunities, work productivity, and a substantial economic burden for the cost of treatment (Lumry et al. 2010; Aygören-Pürsün et al. 2014). Hereditary angioedema not only causes short-term disability associated with attacks, but patients endure long-term effects on their daily lifestyle, emotional health, family life, and it may also affect caregivers' quality of life (Bygum et al. 2015). Effective management of HAE, including optimization of therapy, may reduce the clinical burden and have an overall favorable impact on the quality of life for individual HAE patients and their families (Banerji 2013; Caballero et al. 2014).

1.2 Product Background and Clinical Information

CINRYZE[®] (C1 esterase inhibitor [human]) was developed by the sponsor for the management of HAE. CINRYZE is a highly purified, viral-inactivated, nanofiltered concentrate of C1 INH produced from human plasma. The manufacturing process includes 3 virus inactivation/removal steps: polyethylene glycol precipitation, pasteurization, and nanofiltration. CINRYZE is a normal human plasma protein that is not subject to cytochrome P450 metabolism, excretion, or pharmacokinetic (PK) drug-drug interactions exhibited by low molecular weight compounds.

Intravenous (IV) administration of 1000 U of CINRYZE every 3 or 4 days is approved for routine prevention (prophylaxis) of angioedema attacks in patients with HAE in the United States (2008), European Union (2011), Australia (2012), Canada (2012), and Switzerland (2013). In several of these countries, CINRYZE is also approved for the acute treatment and preprocedure prevention of angioedema attacks.

The clinical efficacy of CINRYZE for the prevention of angioedema attacks in patients with HAE was demonstrated in 1 randomized, double-blind, placebo-controlled study (LEVP 2005-1/B) and 1 open-label study (LEVP 2006-4). Study LEVP 2005-1/B demonstrated that preventive therapy with CINRYZE resulted in both a statistically significant and clinically meaningful decrease in the rate, severity, and duration of acute attacks compared to placebo/on-demand therapy. Therapy with CINRYZE also increased antigenic C1 INH and functional C1 INH levels. These results were supported by Study LEVP 2006-4 (that provided data for longer periods of preventive therapy across a wider age range of subjects), which demonstrated a reduction in the frequency of attacks while on CINRYZE compared to a historical baseline. The open-label study also demonstrated that the efficacy of CINRYZE for the prevention of angioedema attacks did not diminish over time periods of at least 1 year.

The sponsor initiated a clinical development program for subcutaneous (SC) administration of CINRYZE for prevention of angioedema attacks using the same lyophilized formulation as that approved for IV injection. The initial program focused on safety, tolerability, and relative

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bioavailability of SC administration of CINRYZE (Studies 0624-100 and 0624-200). Preliminary assessments confirmed that CINRYZE can be absorbed after SC administration. However, because the exposure profile differed from that following IV administration, it was not known whether or to what extent SC administration would confer efficacy for the management of HAE.

Based on results from nonsponsor studies conducted with recombinant human hyaluronidase (rHuPH20) and other injectable protein products, it was hypothesized that co-administration with rHuPH20 would increase dispersion and absorption of subcutaneously injected CINRYZE. Subsequently, the development program evaluated the safety, tolerability, PK/pharmacodynamics (PD), and efficacy of SC administration of CINRYZE with rHuPH20 (Studies 0624-101, 0624-102, 0624-204, and 0624-206). However, in August 2013, the FDA directed the sponsor to stop administration of rHuPH20 in the ongoing Phase 2 study (0624-206) of CINRYZE with rHuPH20 due to the development of anti-rHuPH20 antibodies in some patients. Dosing was also terminated in an ongoing Phase 1 healthy volunteer study (0624-102) of CINRYZE with rHuPH20. Because the combination product (CINRYZE with rHuPH20) was being studied in these 2 trials, administration of CINRYZE was also discontinued. The FDA encouraged the sponsor to further the clinical development of CINRYZE alone administered via SC injection. Hence the evolution of the clinical development program with the new low volume, ready-to-use liquid formulation (C1 esterase inhibitor [human] liquid for injection) for SC administration.

C1 esterase inhibitor [human] liquid for injection has been evaluated in an in vitro hemocompatibility assay using human blood and plasma, a tissue irritation study in New Zealand White rabbits, and a 14-day repeat-dose toxicity study in Sprague Dawley rats. Incubation with whole blood at a concentration of 225 IU/mL C1 esterase inhibitor [human] liquid for injection did not elicit hemolysis nor did the same concentration induce flocculation, precipitation, or coagulation. In the tissue irritation study in rabbits, microscopic examination of the injection sites showed minimal to mild inflammation that was most pronounced for perivascular injection route, followed by SC and then IV injection routes. In the 14-day repeat-dose study in rats, doses of 0 (sodium phosphate, glycine, and sorbitol), 200, 400, and 1000 IU/kg/day were administered subcutaneously once a day, while a fifth group of rats received 1000 IU/kg/day intravenously. The only signs of toxicity were related to the expected immunogenic response to a human protein. Therefore, the no observed adverse effect level is considered to be 1000 IU/kg/day of C1 esterase inhibitor [human] liquid for injection for both the SC and IV routes of administration. Therefore, the toxicity profile for this ready-to-use liquid formulation is generally comparable to the lyophilized product even when a higher dose of the new formulation was tested.

An initial clinical assessment of the new liquid formulation was conducted in a Phase 1 study in healthy volunteers (SHP616-103). This study evaluated the safety, tolerability, and relative bioavailability of the SC administration of 1000 IU and 2000 IU C1 esterase inhibitor [human] liquid for injection compared with the marketed formulation of CINRYZE (1000 U IV). This single-center, open-label study consisted of a single-dose IV administration of CINRYZE (lyophilized formulation) in Treatment Period 1 followed by a randomized, open-label, 2x2 crossover design (Treatment Periods 2 and 3) to evaluate SC C1 esterase inhibitor [human] liquid for injection. The safety and pharmacokinetic results from Study SHP616-103 are presented in Sections 1.2.1.1 and 1.2.2.2, respectively.

High-level summaries of the clinical experience with SC administration of both CINRYZE (CINRYZE alone and CINRYZE + rHuPH20) and C1 esterase inhibitor [human] liquid for injection are provided below. Always refer to the latest version of the CINRYZE investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of CINRYZE and C1 esterase inhibitor [human] liquid for injection.

1.2.1 Safety and Efficacy Data From Clinical Studies with SC CINRYZE and with SC C1 Esterase Inhibitor [Human] Liquid for Injection

Studies that evaluated SC administration of CINRYZE alone and CINRYZE with rHuPH20 provided valuable data that informed key elements of this Phase 3 study of C1 esterase inhibitor [human] liquid for injection. Both programs enrolled healthy volunteers and subjects with HAE; 86 healthy volunteers (215 doses administered) and 72 subjects with HAE (1321 doses administered) have received 1 or more doses of SC CINRYZE in the development program to date (Table 5).

Table 5 Exposure to SC CINRYZE

Program Study Number	Total Number of Subjects Exposed	Number of SC Doses Administered			
		500 U	1000 U	2000 U	Total Doses
Healthy Volunteers					
CINRYZE Alone					
Study 0624-100 ^a	9	1	0	14	15
Study 0624-102 ^b	37	0	37	0	37
CINRYZE with rHuPH20					
Study 0624-101	24	0	0	47	47
Study 0624-102 ^b	51	0	116	0	116
Healthy Volunteers Total	86	1	153	61	215
Subjects with HAE					
CINRYZE Alone					
Study 0624-200	25	0	52	48	100
CINRYZE with rHuPH20					
Study 0624-204	12 ^c	0	24	24	48
Study 0624-206	47	0	578	595	1173
Subjects with HAE Total	72	0	654	667	1321
OVERALL TOTAL	158	1	807	728	1536

HAE=hereditary angioedema; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous

^a CINRYZE via SC infusion and SC injection.

^b A total of 53 subjects were enrolled in Study 0624-102 and received SC CINRYZE either alone (N=37) or co-administered with rHuPH20 (N=51).

^c These 12 subjects received SC CINRYZE alone in Study 0624-200 and SC CINRYZE with rHuPH20 in Study 0624-204.

1.2.1.1 Clinical Safety

Across the 2 studies of SC CINRYZE alone (Studies 0624-100 and 0624-200), 9 healthy adults and 25 subjects with HAE received CINRYZE doses of 1000 U and/or 2000 U. In healthy adult subjects, a single dose of 2000 U CINRYZE administered via the SC route was associated with mild injection/infusion site discomfort; however, no subjects were discontinued from study drug due to an AE. In HAE subjects, multiple doses of CINRYZE (1000 U or 2000 U) administered via the SC route were associated with generally mild to moderate injection site reactions, most notably pain, which was commonly characterized as burning or stinging. No subjects were discontinued from study drug due to an injection site reaction. No SAEs occurred during either SC study, and no subjects experienced a TEAE that was thrombotic or thromboembolic in nature. In addition, in both studies of SC CINRYZE, results of clinical laboratory evaluations and vital signs measurements were generally unremarkable and did not suggest any treatment-emergent abnormalities related to the administration of CINRYZE.

Across the 4 studies of SC CINRYZE + rHuPH20 (Studies 0624-101 0624-102, 0624-204 and 0624-206), 77 healthy adults and 59 subjects with HAE received CINRYZE doses of 1000 U and/or 2000 U. No SAEs occurred, no subjects were discontinued due to an AE, and no subjects experienced a TEAE that was thrombotic or thromboembolic in nature. The most commonly reported AEs were mild-moderate injection site reactions (eg, erythema, swelling, pain). Other safety parameters (clinical laboratory evaluations and vital signs measurements) were generally unremarkable and did not suggest any treatment-emergent abnormalities related to the administration of SC CINRYZE + rHuPH20.

In Study 0624-206, a total of 21 (45%) subjects had detectable anti-rHuPH20 antibodies during the study, with 15 (32%) of the 21 subjects having a post-baseline titer of >1:20. All samples from these subjects were determined to be negative for rHuPH20-neutralizing activity. As requested by the FDA, the sponsor followed subjects who had treatment-emergent titers of $\geq 1:20$ for 1 year post-treatment. There were no clinical sequelae observed in any subject and all titers declined during longitudinal follow-up. Three subjects in Study 0624-102 had reportable anti-rHuPH20 antibodies at a titer $\geq 1:20$; however, in all 3 cases, subjects had antibodies to rHuPH20 present at baseline (prior to the first dose of study drug). Subjects were not asked to participate in longitudinal follow-up, as anti-rHuPH20 antibody titers remained at or below the baseline level for each subject by the end of the study.

In Study SHP616-103, a total of 26 healthy volunteers were enrolled in the study. Twenty-three (23) subjects received a single SC dose of both 1000 and 2000 IU, and 1 subject only received a single SC dose of the 1000 IU C1 esterase inhibitor [human] liquid for injection. Therefore 24 unique subjects have been exposed to 47 doses of C1 esterase inhibitor [human] liquid for injection.

Subcutaneous administration of 1000 IU and 2000 IU C1 esterase inhibitor [human] liquid for injection was generally well tolerated and the clinical safety data were consistent with previous CINRYZE IV or SC studies. Overall 19 (73.1%) of the 26 subjects reported at least 1 TEAE in the study: 62% (16/26), 29% (7/24), and 44% (10/23) of subjects administered 1000 U IV CINRYZE, 1000 IU and 2000 IU of SC C1 esterase inhibitor [human] liquid for injection, respectively.

With regard to the local tolerability of SC administration of 1000 IU and 2000 IU C1 esterase inhibitor [human] liquid for injection, there was no clear difference in the overall incidence of injection site reactions with respect to dose (1000 IU versus 2000 IU). Twenty-three of 24 (95.8%) subjects reported injection site reactions, all were mild (58.3%) to moderate (37.5%) in severity, and the majority resolved within 2 hours postdose. The majority of reported reactions were erythema (mild or moderate) and a warm sensation (all mild).

1.2.1.2 Clinical Efficacy

The Phase 2 dose-ranging, crossover Study 0624-206 was designed to determine if there was a difference in efficacy between 2 SC doses of CINRYZE (1000 U and 2000 U co-administered with rHuPH20). The study was terminated before enrollment was complete (at the request of FDA due to the detection of anti-rHuPH20 antibodies in some subjects). Of the 47 subjects enrolled, 22 completed both treatment periods. Thus, due to the early termination of the study, the final sample size of the intent-to-treat efficacy population was smaller than planned (22/47, 47%). Regardless, the statistical advantage of a crossover study is that patients serve as their own control and the relative effect of the experimental treatments can be determined most efficiently with respect to within-patient differences.

The experimental results favored twice weekly SC administration of CINRYZE 2000 U + 48,000 U rHuPH20 compared with CINRYZE 1000 U + 24,000 U rHuPH20 for the primary and all secondary efficacy endpoints during treatment, most notably in the within-subject treatment comparison.

An analysis of primary and secondary efficacy endpoints during treatment was performed for the mean difference between treatments (2000 U – 1000 U SC CINRYZE), within subjects in a treatment sequence and overall, as shown below in [Table 6](#).

For the primary endpoint of normalized number of angioedema attacks during treatment, a treatment effect favoring the 2000 U compared with the 1000 U SC CINRYZE dose was observed for the within-subject treatment comparison; the overall mean difference (95% confidence interval [CI]) between treatments was -0.61 (-1.23, 0.01) and achieved borderline significance ($p=0.0523$).

With regard to secondary efficacy endpoints, statistically significant ($p<0.05$) treatment effects favoring the 2000 U compared with the 1000 U SC CINRYZE dose were observed for the within-subject treatment comparisons for both cumulative attack severity and for the number of attacks requiring acute treatment, with overall mean differences between treatments of -1.33 ($p=0.0277$) and -0.56 ($p=0.0315$), respectively.

No sequence effect was observed for the mean difference between the 2000 U and 1000 U SC CINRYZE doses within subjects in Sequences A/B or B/A for the primary or for any secondary endpoint (p -value for sequence effect across endpoints: ≥ 0.6290).

These findings indicated that CINRYZE at a dose of 2000 U SC was superior to a dose of 1000 U in terms of clinical efficacy improvement. The results are more compelling in light of their arising from truncated enrollment and consequently, an underpowered study.

Table 6 Primary and Secondary Efficacy Endpoints During Treatment by Sequence (Within-Subject Treatment Comparison) – ITT-E Population (Study 0624-206)

Endpoints (Normalized)	Sequence A/B Difference: B-A N=12	Sequence B/A Difference: B-A N=10	Overall Difference: B-A N=22	Treatment Comparison p-value ^a
Primary				
Number of angioedema attacks	-0.72 (-1.71, 0.27)	-0.48 (-1.36, 0.40)	-0.61 (-1.23, 0.01)	0.0523
Secondary				
Cumulative attack severity	-1.53 (-3.41, 0.35)	-1.09 (-2.74, 0.57)	-1.33 (-2.49, -0.16)	0.0277
Cumulative daily severity	-1.53 (-4.42, 1.36)	-2.19 (-6.06, 1.69)	-1.83 (-3.98, 0.32)	0.0912
Cumulative symptomatic days	-0.95 (-2.64, 0.74)	-0.87 (-3.35, 1.62)	-0.91 (-2.23, 0.41)	0.1660
Number of attacks requiring acute treatment	-0.67 (-1.20, -0.14)	-0.43 (-1.47, 0.62)	-0.56 (-1.06, -0.05)	0.0315

CI=confidence interval; ITT-E=intent-to-treat efficacy; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous

Note: Data are presented as the mean (95% CI). Treatment A=1000 U SC CINRYZE + 24,000 U rHuPH20; Treatment B=2000 U SC CINRYZE + 48,000 U rHuPH20. Subjects who were dosed but did not have any attacks in the period were assigned a value of zero for each of the efficacy parameters. Only subjects who completed both treatment periods are included in the ITT-E population.

^a p-value for paired t-test.

1.2.2 Pharmacokinetics of CINRYZE and C1 Esterase Inhibitor [Human] Liquid for Injection

1.2.2.1 Population PK/PD Modeling and a PK/PD Exposure-Response Analysis of CINRYZE

Population PK and PK/PD modeling of C1 INH and C4 were developed based on data collected in 10 clinical studies with healthy volunteers and HAE patients who received IV or SC administrations of CINRYZE. Exposure-response analyses were performed based on 2 studies for the use of CINRYZE for the prophylactic treatment to prevent HAE.

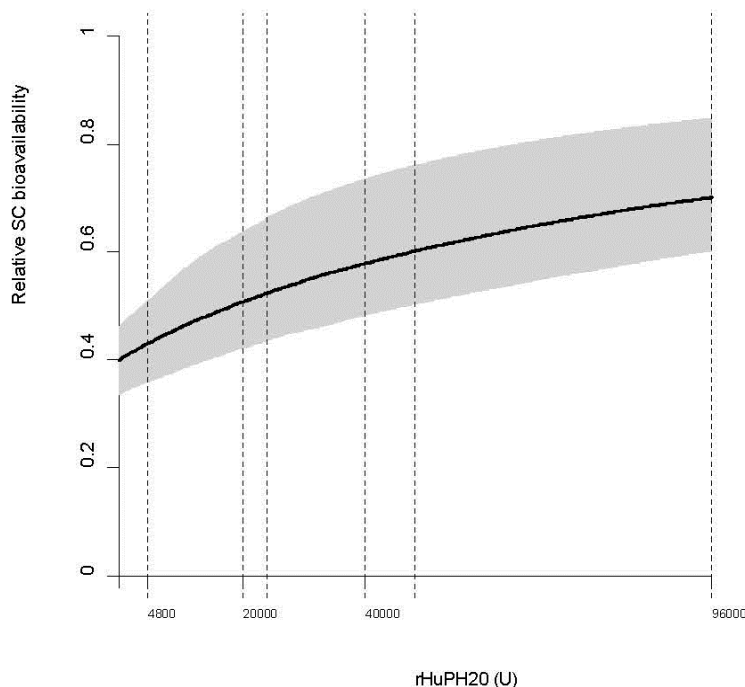
The final population PK model of C1 INH was a 1-compartment model with endogenous C1 INH levels. The absorption of CINRYZE following SC dosing was characterized with a first-order rate and relative absorption fraction (Frel). Based on the population PK model, the relative bioavailability of CINRYZE following SC dosing without rHuPH20 was 38.8%. Typical CL of C1 INH was 0.0864 L/h (1.44 mL/min) in HAE patients with a typical body weight of 70 kg. The $t_{1/2}$ of C1 INH in a typical 18.0, 36.6, and 80.0-year-old patient weighing 70 kg were 32.0, 29.0, and 26.0 hours, respectively.

The effect of rHuPH20 on the rate and extent of absorption of C1 INH was included in the model. The use of rHuPH20 with SC administration appears to have little to no improvement on C1 INH exposure. This was illustrated in the Phase 1 study with healthy volunteers (Study 0624-102) where CINRYZE 1000 U SC administered with 200, 2000, or 20,000 U rHuPH20 was not

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statistically different in C_{\max} and AUC_{last} compared with CINRYZE alone. In addition, the population PK model estimated only a 10% increase in bioavailability with rHuPH20, which reached saturation with increasing rHuPH20 concentrations as presented in Figure 1.

Figure 1 The Effect of Increasing rHuPH20 Concentration on Relative SC Bioavailability of C1 INH Functional Activity

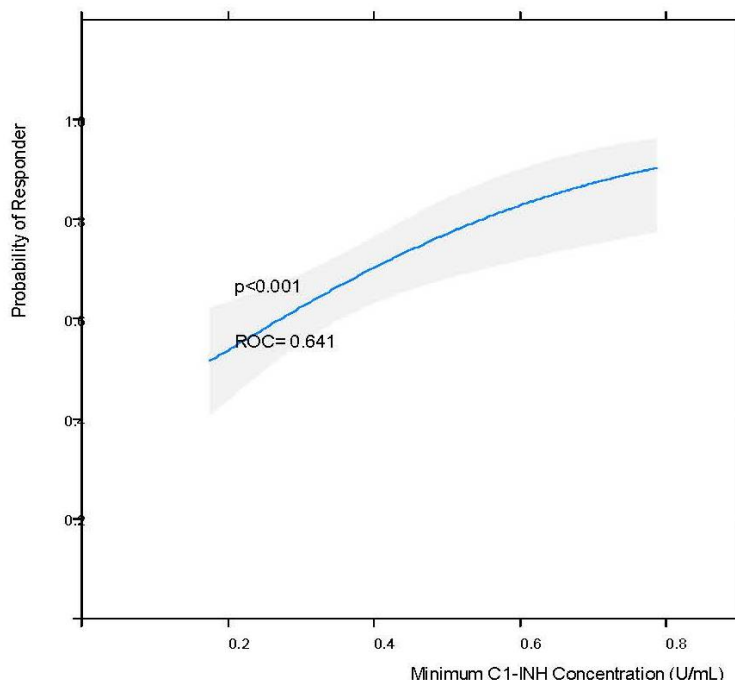


C1 INH=C1 esterase inhibitor; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous

The population PK model was used to support the assessment of the exposure-response relationship of CINRYZE during prophylactic treatment of angioedema attacks for C1 INH and C4. The response criterion originally used in Study 0624-400 was used to define responder status, whereby a response was defined as ≤ 1 angioedema attack/month, since this criterion has been deemed clinically meaningful by both expert clinicians and patients with HAE. A logistic regression model was used to link C_{\min} values of C1 INH (continuous) with the probability of response (binary) following IV dosing of 1000 U of CINRYZE in studies LEVP 2005-1/B and LEVP 2006-4 (Section 1.2). The exposure-response relationship of C_{\min} values of C1 INH following IV dosing of CINRYZE is presented in Figure 2.

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Figure 2 Exposure-response Relationship Following IV Dosing of CINRYZE (Probability of ≤ 1.0 Angioedema Attack/Month)



C1 INH=C1 esterase inhibitor; ROC=receiver-operating characteristic

Higher C_{min} values of C1 INH were associated with a higher probability of response in patients with HAE ($p < 0.001$). The above exposure-response relationship was to be used to predict the probability of response for any C_{min} values of C1 INH in subjects with HAE. For example, typical C_{min} values of 0.207, 0.289, 0.380, and 0.556 U/mL (corresponding to first, second, third, and fourth quartiles of C_{min} of C1 INH, respectively) would be expected to result in response probabilities of 54.4%, 61.5%, 68.8%, and 80.5%, respectively. Typical C1 INH plasma functional activity levels in HAE patients range from 5–30% of normal (0.05–0.3 U/mL) ([Cugno et al. 1990](#)).

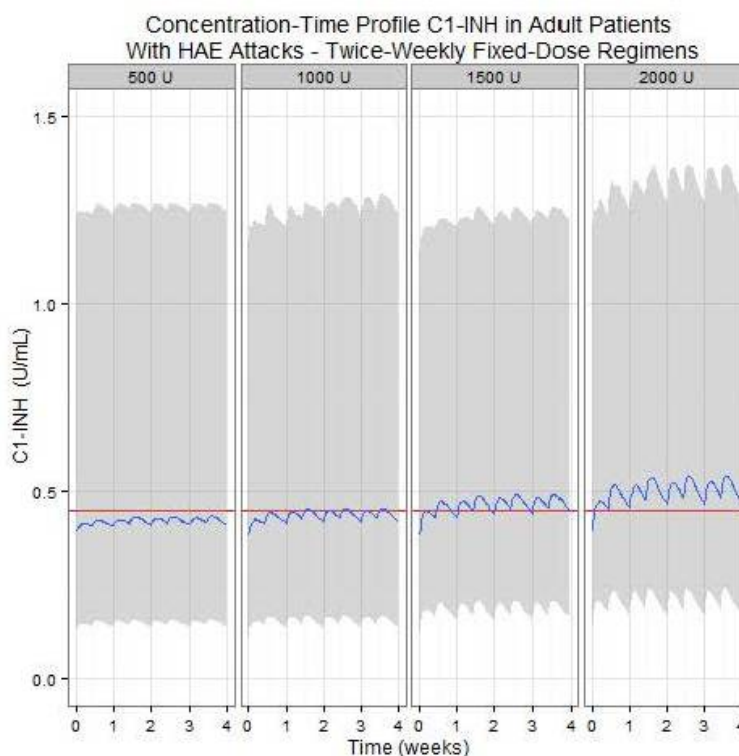
Receiver-operating characteristic analysis was used to identify an optimal C_{min} cutoff of C1 INH that would optimize the probability of avoiding an angioedema attack. Based on data from study LEVP 2006-4 with IV administration of 1000 U CINRYZE approximately twice weekly, the optimal C_{min} cutoff was 0.479 U/mL. When considering a 2-week period of delay, the optimal C_{min} cutoff was 0.433 U/mL. Based on the above ROC analyses, a targeted C1 INH C_{min} value of 0.45 U/mL was used to determine the expected response following SC dosing of 2000 U of CINRYZE. Based on the exposure-response model, a C1 INH C_{min} value of >0.45 U/mL would achieve at least a 70% probability of success (≤ 1 angioedema attack/month).

No statistically significant relationship was observed between minimum C4 concentrations and the probability of response.

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The combination of the population PK model and exposure-response relationship model was used to simulate C1 INH C_{min} following SC dosing of CINRYZE to support the dosing rationale and improve the likelihood of success at achieving an efficacious dose in patients with HAE (Figure 3).

Figure 3 Simulated Concentration-time Profiles of C1 INH in Adult Patients with HAE – Twice-weekly Dose Regimen



C1 INH=C1 esterase inhibitor; HAE=hereditary angioedema

From these simulations, results show that a dose of 2000 U would maintain mean (blue line) functional C1 INH C_{min} values above the targeted level of 0.45 U/mL (red horizontal line).

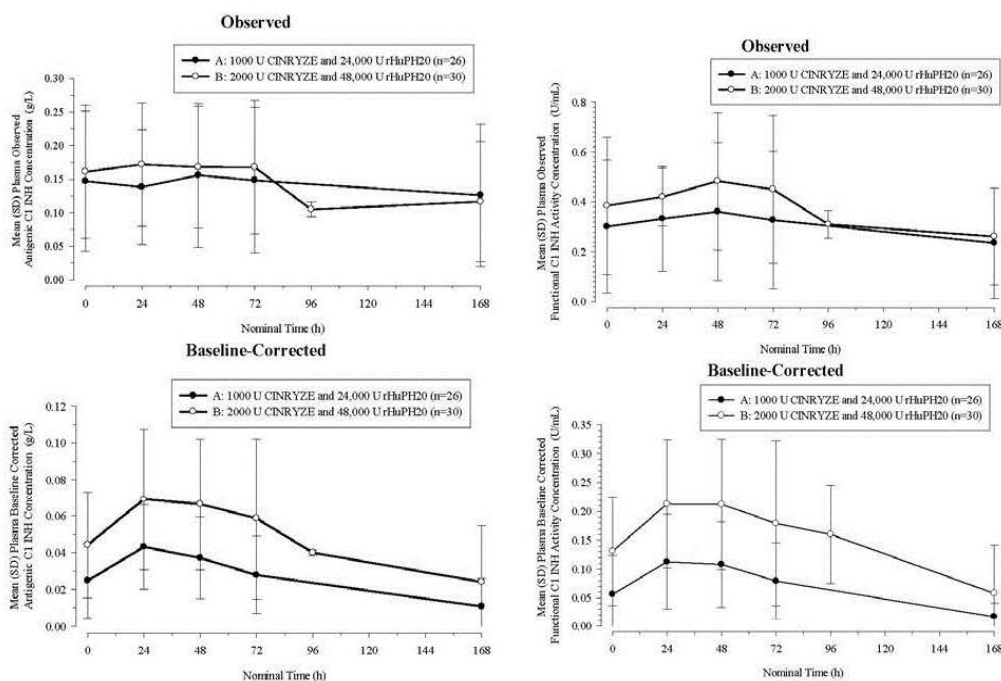
In studies LEVP 2005-1/B and LEVP 2006-4, in which subjects with HAE received IV doses of 1000 U CINRYZE approximately twice weekly, mean pre-infusion functional C1 INH concentrations ranged from 0.38-0.41 U/mL and 0.37-0.52 U/mL, respectively, during the treatment period.

In the recent Phase 2 clinical study 0624-206, in which subjects with HAE received twice weekly SC doses of 1000 U CINRYZE with 24,000 U rHuPH20 or 2000 U CINRYZE with 48,000 U rHuPH20 in two 8-week crossover periods, higher exposure with the 2000 U CINRYZE dose was observed (Figure 4). The mean baseline-corrected C_{max} and AUC_{0-168} of antigenic C1 INH for 2000 U SC CINRYZE + 48,000 U rHuPH20 were 1.8- and 2.3-fold higher, respectively, compared to those observed for 1000 U SC CINRYZE + 24,000 U rHuPH20. The mean baseline-corrected

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C_{max} and AUC_{0-168} of functional C1 INH activity for 2000 U SC CINRYZE + 48,000 U rHuPH20 were 2.0- and 2.6 fold higher, respectively, compared to their respective means for 1000 U SC CINRYZE + 24,000 U rHuPH20. The observed mean minimum concentration (C_{min}) of functional C1 INH activity at steady-state for the 2000 U dose of SC CINRYZE with rHuPH20 was above the physiologically relevant level of 0.4 U/mL compared with 1000 U dose of SC CINRYZE with rHuPH20 (0.408 and 0.319 U/mL, respectively).

Figure 4 Mean (\pm SD) Steady-State (Week 8) Plasma Concentrations of C1 INH Antigen (left) and Functional C1 INH Activity (right) vs. Time after SC Administration of CINRYZE with rHuPH20 in Subjects with HAE (Protocol 0624-206)



1.2.2.2 Pharmacokinetic Analysis of C1 Esterase Inhibitor [Human] Liquid for Injection

In Study SHP616-103, new bioanalytical assays were developed and validated for the quantitative determination of C1 INH protein and functional binding of C1 INH in human plasma. These assays differed from those used in previous Cinryze SC studies to determine plasma concentrations of C1 INH antigen and functional C1 INH activity.

Following SC administration of 1000 IU and 2000 IU C1 esterase inhibitor [human] liquid for injection, injected C1 INH was slowly absorbed with median t_{max} ranging from 36–48 hours for both C1 INH antigen and functional C1 INH binding. Mean baseline-corrected C_{max} and AUC_{last} PK parameters for both C1 INH antigen and functional C1 INH binding after IV and SC administration are shown in Figure 5 and Figure 6, respectively.

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Figure 5 Individual and Mean (\pm SD) Baseline-corrected C_{\max} Across Treatments for C1 INH Antigen and Functional C1 INH Binding (Study SHP616-103)

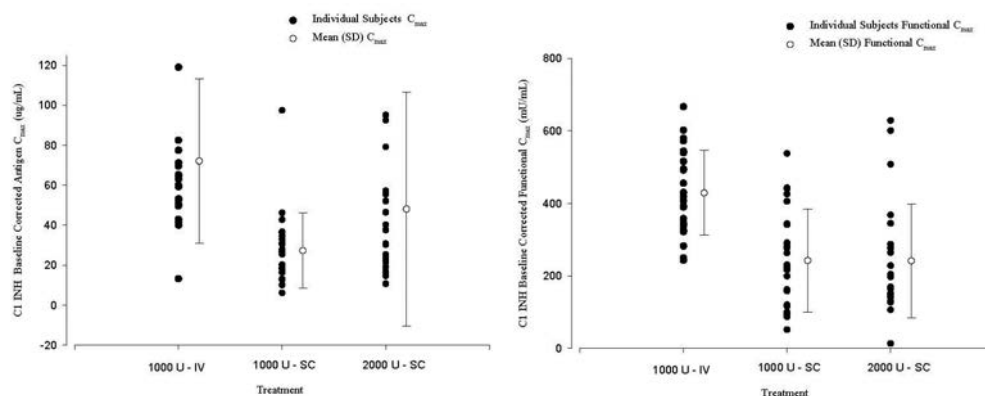
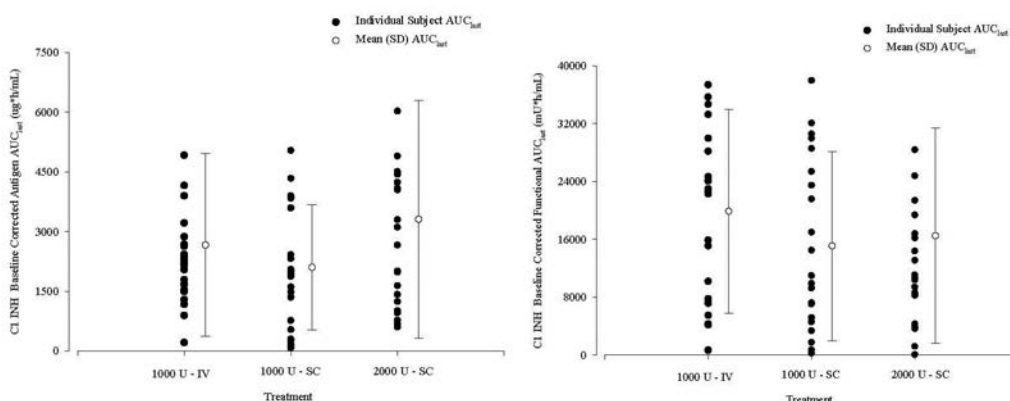


Figure 6 Individual and Mean (\pm SD) Baseline-corrected AUC_{last} Across Treatments for C1 INH Antigen and Functional C1 INH Binding (Study SHP616-103)



Subcutaneous administration of C1 esterase inhibitor [human] liquid for injection was less than dose proportional, with a 2-fold increase in dose resulting in 1.76- and 1.58-fold increase in C_{\max} and AUC_{last} respectively for C1 INH antigen, and 0.99- and 1.09-fold increase in C_{\max} and AUC_{last} respectively for functional C1 INH binding.

The baseline-corrected point estimates of the AUC_{last} ratios and 90% confidence intervals for C1 INH antigen and functional C1 INH binding was used to determine the relative bioavailability of 1000 and 2000 IU C1 esterase inhibitor [human] liquid for injection with 1000 U IV CINRYZE. The relative bioavailabilities for the 1000 IU and 2000 IU SC dose of C1 esterase inhibitor [human] liquid for injection were approximately 69% (44–110%) and 60% (38–95%) respectively for C1 INH antigen, and 67% (34–130%) and 39% (20–77%) respectively for C1 INH functional binding (in non-HAE subjects).

1.2.2.3 Dose Selection

The approach for preventative therapy in HAE patients is to provide enough CINRYZE to achieve or exceed a threshold C1 INH functional activity concentration in plasma that has a >70%

likelihood of preventing an angioedema attack. The combined data from prior SC CINRYZE studies (including the evaluation of bioavailability) along with the demonstration of similar bioavailability achieved in the completed Phase 1 single dose study of C1 esterase inhibitor [human] liquid for injection, support dose selection of 2000 IU C1 esterase inhibitor [human] liquid for injection for further evaluation in a Phase 3 study.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The sponsor has developed a new, ready-to-use liquid formulation of CINRYZE (C1 esterase inhibitor [human]). The CINRYZE liquid product (C1 esterase inhibitor [human] liquid for injection) is intended for the same indication as the licensed, lyophilized powder formulation of CINRYZE: routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE. The route of administration will be SC injection, and the dosing regimen will be 2000 IU every 3 or 4 days. Shire ViroPharma anticipates that patients will benefit from the inherent advantages of SC administration, as well as the ready-to-use liquid, lower volume product compared with one requiring reconstitution. In addition, the CINRYZE liquid product is more concentrated than the licensed CINRYZE product (500 vs 100 U/mL), which should enable more rapid administration of the drug and may improve tolerability, without an expected change or compromise in efficacy.

The sponsor has selected 2000 IU of C1 esterase inhibitor [human] liquid for injection as the appropriate active dose for this Phase 3 study. This dose is based on the results of a recently completed Phase 2, randomized, double-blind, dose-ranging, crossover study that evaluated SC administration of CINRYZE with rHuPH20 (a dispersing agent) for the prevention of angioedema attacks in adolescents and adults with HAE (Study 0624-206). Results revealed greater clinical benefit with 2000 U of CINRYZE compared with 1000 U. In addition, the 2000 IU dose is supported by PK results from Study 0624-206, by the results of population PK and exposure-response modeling, and by PK data from a Phase 1 study (0624-102) that demonstrated the minimal influence of rHuPH20 on functional C1 INH activity when co-administered with CINRYZE (Section 1.2.2.1). Finally, the 2000 IU dose is further supported by the PK and bioavailability data from the Phase 1 study of C1 esterase inhibitor [human] liquid for injection (Protocol SHP616-103).

The study design was chosen as the best way to jointly address the protocol objectives of establishing efficacy (relative to placebo) and safety (ie, adequate numbers of subjects for precision of estimation in detecting potential safety signals). Additionally, this design maximizes the number of patients exposed to C1 esterase inhibitor [human] liquid for injection and minimizes patient exposure to placebo while having adequate patient exposure to placebo to assess efficacy. Thus, the proposed study is described as a “partial” crossover because 2 treatment sequences involve crossing over to the other experimental agent and the third sequence does not. All subjects will receive active treatment during this study and will have an overall two-thirds probability to be randomized to active drug in any treatment period.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of this study is 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 normalized number of attacks (NNA) during a treatment period.

2.2.2 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 a 50% 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 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 in the 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

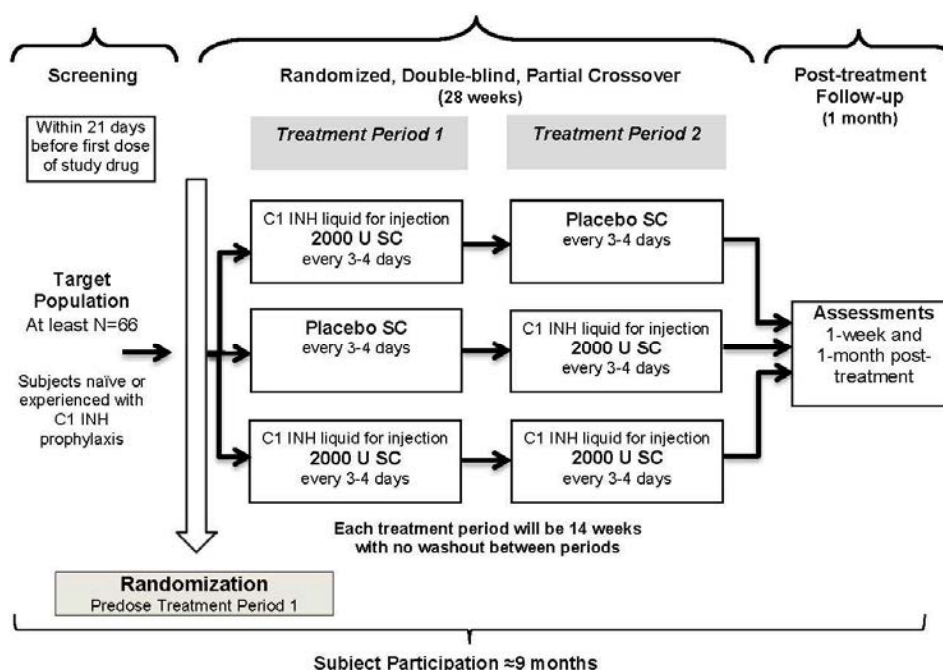
3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study (Figure 7). The design was chosen to optimally address the joint protocol objectives of establishing efficacy (relative to placebo) and safety (ie, enrolling an adequate number of subjects to have precision of estimation to detect or rule out safety signals). Additionally, this design maximizes the number of subjects exposed to C1 esterase inhibitor [human] liquid for injection and minimizes subject exposure to placebo, while having adequate subject exposure to placebo to assess efficacy.

Subjects will be screened within 21 days prior to randomization. Subjects are required to have a history (based on subject recall and medical records) of ≥ 2 attacks per month on average per inclusion criterion #3. 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 (ie, Dosing Day 1a) using interactive response technology (IRT). Randomization of subjects will be stratified by use of prophylactic therapy with C1 INH at the time enrollment.

Figure 7 Study Design Flow Chart



Each treatment period will be 14 weeks, without a washout between the 2 periods. The omission of a washout period is to minimize the duration that subjects will be without active treatment. It is recommended that the twice weekly dosing schedule (every 3 or 4 days) be maintained between the last dose of investigational product in Treatment Period 1 and the first dose of investigational product in Treatment Period 2. Every effort should be made to complete scheduled dosing and to avoid situations where investigational product is not received. In order to prevent a missed dose, a less than 3-day interval may occur, with the recommendation of allowing at least 24 hours between doses.

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

Subjects will remain outpatients throughout the study. Investigational product will be administered at the investigational site for Dosing Visits 1, 8, 16, 24, and 28 during both treatment periods. Other doses may be administered by qualified blinded personnel at the investigational site or at the subject's home or other agreed upon location or self-administered by the subject (adolescent or adult) with or without supervision (qualified home health professional or study site personnel), after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering the investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver after receiving appropriate training, will be allowed to administer the investigational product to an adolescent subject with or without supervision.

Throughout the study, an electronic subject diary will be used to record specific information regarding the subject's symptoms of HAE and details on self-administration as described in Sections 7.2.2.2 and 6.5.1 respectively. Additionally, quality of life questionnaires and surveys on SC administration of the investigational product will be also subject evaluated. Note: For adolescent subjects, a parent/legal guardian/caregiver is allowed to assist the subject in completing the electronic subject diary, including the quality of life questionnaires.

Adverse events will be recorded from the time the informed consent is signed through 7 days after the last dose of investigational product. This includes events occurring during the screening phase of the study, regardless of whether or not the investigational product is administered. In addition, the investigator will report all SAEs that occur through 30 days after the last dose of investigational product to Shire Pharmacovigilance and the respective Independent Reviewing Authority according to local reporting requirements.

A post-treatment visit will be performed at the investigative site 1 week (± 1 day) after the last dose of the investigational product in Treatment Period 2 for follow-up safety assessments. In addition, subjects will have blood samples collected for PK/PD and C1 INH antibody testing at 1 month (± 2) days after the last dose of the investigational product.

If a subject prematurely discontinues investigational product, regardless of the reason, the early discontinuation visit safety procedures listed in Table 3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-week and 1-month post-treatment visits.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 9 months. The study will be completed in approximately 15 months.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

Approximately 40 sites globally (North America and Europe) are expected to participate in this study.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Be ≥ 12 years of age, or in Germany and Israel, be ≥ 18 years of age.
2. Have a diagnosis of HAE (Type I or II) and a functional C1 INH level less than 50% of normal.
3. Meet one of the following criteria (attack rate may be based on subject recall in conjunction with the subject's medical records):
 - If subject is adult (≥ 18 years of age) and currently receiving prophylactic therapy with C1 INH, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to starting prevention therapy.
 - OR**
 - If subject is adolescent (≥ 12 and < 18 years of age) or adult and not receiving prophylactic therapy with C1 INH, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit.
 - OR**
 - If subject is adult (> 18 years of age) and currently receiving a stable dose of attenuated androgens, have a history of ≥ 2.0 angioedema attacks per month (average) during the 3 consecutive months prior to the screening visit.
4. For subjects ≥ 18 years of age, be willing to receive treatment with icatibant for any angioedema attacks that occur during the study that, in the opinion of the healthcare care provider, require medical intervention. Note: For subjects ≥ 12 to < 18 years of age, standard of care therapy per local protocols should be provided.

5. Agree to adhere to the protocol-defined schedule of assessments.
6. If female, must have a negative serum beta human chorionic gonadotrophin (β -hCG) pregnancy test at the screening visit and must have a negative urine pregnancy test prior to the first dose of investigational product (Visit 1a), and agree to comply with any applicable contraceptive requirements of the protocol.
7. If male, be surgically sterile or agree to follow an acceptable method of birth control (eg, abstinence, barrier control) from the screening visit through 2 months after the last dose of investigational product.
8. If an adult (≥ 18 years of age), be informed of the nature of the study and provide written informed consent before any study-specific procedures.

OR

If a child (< 18 years of age), have a parent(s)/legal guardian who is informed of the nature of the study provide written informed consent for the child to participate in the study before any study-specific procedures are performed (with assent from the child when appropriate). Alternatively, certain sites/Independent Reviewing Authorities may permit adolescents who are < 18 years of age to be informed of the nature of the study and provide written informed consent without consent from a parent(s)/legal guardian.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. 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).
2. Adolescents (≥ 12 and < 18 years of age) currently receiving prophylactic therapy with C1 INH (not applicable to Germany and Israel).
3. Have had signs or symptoms of an angioedema attack within 2 days prior to the first dose of the investigational product in Treatment Period 1.
4. 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.
5. 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.
6. Have a history of hypercoagulability (abnormal blood clotting) or other predisposition for thromboembolism.
7. Have a diagnosis of acquired angioedema or known presence of anti-C1 INH antibodies.
8. Have a history of allergic reaction to C1 INH products, including CINRYZE (or any components of CINRYZE), other blood products, or Firazyr (icatibant).
9. Be pregnant or breastfeeding.

10. Have received an investigational drug within 30 days prior to the first dose of investigational product in Treatment Period 1.
11. Have, as determined by the investigator and/or the sponsor's medical monitor, any surgical or medical condition (including positive for hepatitis B, hepatitis C, or HIV infection; alcohol, drug, or medication abuse within 1 year before screening; or mental condition rendering the subject or parent(s)/legal guardian unable to understand the nature, scope of the study, and possible consequences of the study), or relationship to study staff or sponsor (including people accommodated in an institution as well as people who are dependent on the sponsor, CRO, site or the investigator) that could interfere with the administration of investigational product or interpretation of study results.

4.3 Reproductive Potential

4.3.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception, as described below. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

Female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and aged ≥ 51 years)
- Surgically sterile (having undergone 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization
- Females of childbearing potential with a negative serum β -hCG pregnancy test at the Screening Visit and a negative urine pregnancy test prior to randomization (predose at Visit 1a). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam) (Note: double-barrier methods are not an acceptable form of contraception in Germany)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 2 months prior to the Screening Visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to a hormonal contraceptive for 30 days.

4.3.2 Male Contraception

Male subjects will be required to use a condom in conjunction with spermicidal gel, foam, cream, film, or suppository from time of dosing until 2 months after the last dose of investigational product.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible. If the sponsor discovers conditions arising during the study that are unexpected, are significant, or pose an unacceptable risk to patients, mandatory discontinuation of the investigational product will occur.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Early Discontinuation Visit (Section 7.1.4) are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-week and 1-month Post-treatment visits. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the case report form (CRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is discontinued for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow up
- Lack of efficacy
- Other (specify; in Germany, must indicate if mandatory reason [see Section 4.4])

4.4.2 Subjects 'Lost to Follow up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of

these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

4.4.3 Anaphylactic Reaction

If an anaphylactic reaction occurs in any subject, investigational product will be discontinued, and the subject will follow the schedule of assessments for early discontinuation ([Table 3](#)). Subjects already enrolled will continue with study drug administration and procedures.

4.4.4 Thrombotic or Thromboembolic Event

If a thrombotic/thromboembolic (T/TE) event occurs in any subject, no further enrollment will occur pending a complete review of all available data. Already enrolled subjects will continue with investigational product administration and study procedures. Following a safety review of the T/TE event, study enrollment may be restarted if the medical monitor determines that the event was unrelated or unlikely to be related to investigational product or other C1 inhibitors, which may have been administered for an angioedema attack. Unblinding of the randomization code for that subject may be required (see below).

If a T/TE event occurs in any subject, investigational product administration for that subject will be discontinued (in Germany) or interrupted (in other countries); however, other study procedures will continue, as clinically appropriate. Diagnosis and management of all suspected T/TE events should be per local standard of care; [Appendix 4](#) and [Appendix 5](#) present a suggested medical algorithm for diagnosis and management of such conditions. Investigators must also comply with all reporting and/or procedures for AEs/SAEs as indicated in the suggested algorithm. Following a complete medical review by the sponsor in conjunction with the investigator, and if determined safe to do so, dosing with investigational product may be resumed (in all countries except Germany) to complete a total of 28 doses in the treatment period that was interrupted. Study procedures, including PK/PD testing, will resume relative to dosing. If investigational product cannot be restarted within 30 days of the temporary interruption, the subject will be discontinued from treatment and will follow the schedule of assessments for early discontinuation ([Table 3](#)). If unblinding is required, a physician external to the study will review relevant safety information, including the subject's assigned treatment. The unblinded physician will relay his or her findings and recommendations to the medical monitor, exercising caution not to reveal the subject's randomization to anyone associated with the conduct of the study.

5. PRIOR AND CONCOMITANT TREATMENT

Prior and concomitant medications that will be recorded on the appropriate CRF page include prescription medications, blood products (eg, albumin, packed red blood cells, whole blood, fresh frozen plasma, platelets), dietary supplements/vitamins, electrolyte supplementation, and over-the-counter medications. Topical medications (non-prescription) will be recorded only if used as treatment for an AE.

5.1 Prior Treatment

Any therapy received during the 12 months prior to randomization for the management of angioedema attacks should be recorded, including overall start and stop dates if known, and the HAE indication (ie, acute treatment, long-term prevention, short-term [preprocedural] prevention).

In addition, all medications taken within 1 week prior to Day 1 of Treatment Period 1 will be entered into the CRF.

5.2 Concomitant Treatment and Medical/Surgical Procedures

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the 1-month post-treatment visit, inclusive. All prescription and over-the-counter medications being taken by subjects during this time period are regarded as concomitant treatments. For any medication that is administered, the investigator will document the drug name, amount, route of administration, frequency, and duration administered, as well as the reason for administering the medication on the appropriate CRF page.

Elective procedures should be postponed, where possible. Medical/surgical procedures performed during the study will be recorded on the CRF, along with the date, time, and reason for the procedure. Pre-procedure prophylaxis may be provided (and documented as outlined above) if medically indicated and according to local standard of care.

5.2.1 Management of Angioedema Attacks

If a subject (≥ 18 years of age) experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, icatibant should be administered to treat the attack. Commercial icatibant labeled for clinical trial use will be supplied in a single-dose pre-filled glass syringe delivering 3 mL of solution containing 30 mg icatibant and should be stored at or below 25°C (must not be frozen). Icatibant is to be administered by the SC route in the abdominal area. The entire volume in the syringe should be administered and the injection should occur over at least 30 seconds. If response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of at least 6 hours. Do not administer more than 3 injections in 24 hours. The subject will be allowed to self-administer icatibant if already trained by a health care provider or after receiving instructions on the use and appropriate training by study site personnel or a qualified home health professional. If a laryngeal attack occurs (ie, swelling of the airways), the subject should inject icatibant and proceed immediately to the nearest medical care facility. If it is the opinion of the investigator that the subject still needs medication for his/her acute angioedema attack after icatibant administration, then other standard of care therapy (eg, C1 INH, ecallantide) may be provided per locally approved product information.

For subjects ≥ 12 to < 18 years of age (not applicable to Germany and Israel), standard of care therapy per local protocols should be provided, such as (where approved for adolescents) C1 esterase inhibitor (human), C1 esterase inhibitor (recombinant), and ecallantide.

The determination of the necessity for therapy to alleviate subject symptoms will be at the discretion of the investigator. Administration of investigational product and study procedures will continue without alteration to the protocol schedule, even if a subject receives any treatment for an angioedema attack.

For all medications (including fluids, anti-emetics, analgesics) associated with management of acute angioedema attacks, study personnel will record start/stop dates, time of administration, dose, unit, frequency, and route of administration in the subject's CRF page. Adverse events associated with medications used in the treatment of acute angioedema attacks will be captured on the AE CRF and attributed to the concomitant medication administered (Section 8.1.2).

Adult subjects receiving long-term prophylaxis with C1 INH prior to randomization may be randomized to treatment sequences that contain a placebo treatment period (ie, A/B or B/A); such subjects remain eligible for on-demand therapy as outlined above. If, after receipt of at least 3 weeks of investigational product, the subject's quality of life significantly deteriorates and interferes with daily living routines, and the subject experiences a 2-fold increase in attack frequency with greater severity (relative to the subject's baseline without prophylaxis), following discussion of the investigator with the sponsor, subject may be discontinued from the treatment.

The investigator will be responsible for entering information about the subject's discontinuation from study drug in the CRF and where applicable, perform study related procedures as outlined in Table 3. The investigator will also ensure the subject receives appropriate treatment based on the subjects past HAE treatment and according to local standard of care. Angioedema attacks will not be considered AEs; however, events satisfying the serious criteria should be recorded as a SAE and reported to Shire Pharmacovigilance (Section 8.1.4). Data on angioedema attacks will be collected separately from general reports of AEs and will be used in the evaluation of efficacy (Section 7.2.2). In addition, if applicable, subjects will record their response to icatibant therapy when used for treating an angioedema attack, as well as any associated side effects or tolerability issues. This information will be recorded in the electronic subject diary (Section 7.2.2.4).

5.2.2 Prohibited Treatment

Use of C1 INH therapy (other than investigational product) for prophylaxis against angioedema attacks is prohibited during this study (from the first dose of investigational product through the 1-month post-treatment visit).

The initiation of androgen therapy is prohibited during the study (from the first dose of investigational product through the 1-month post-treatment visit).

5.2.3 Nonpharmacologic Treatments and Procedures

To the extent possible, subjects will postpone elective procedures (eg, dental work) while participating in the study. In the event a procedure cannot be postponed, the subject will record this information in the subject diary and notify the site. Pre-procedure prophylaxis may be provided if medically indicated and according to local standard of care.

Nonpharmacologic treatments and procedures (eg, surgical, diagnostic, or dental) that occur during the treatment periods, as well as any medications associated with the procedure, will be recorded in the eCRF (see Section 5.2).

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is C1 esterase inhibitor [human] liquid for injection, which is supplied in clear glass vials containing 1000 IU of C1 INH in 2 mL of sterile liquid. The solution also contains the following inactive ingredients: sodium phosphate, sorbitol, glycine, and water for injection.

The reference product is placebo, which is supplied in an identical 2 mL presentation as the active investigational product minus the C1 INH protein. The inactive ingredients in the solution are the same as the active drug product: sodium phosphate, sorbitol, glycine, and water for injection.

No reconstitution or dilution is required for the test or reference product. Vials must be stored at 2–8°C (36–46°F) and protected from light.

Instructions for handling of investigational product and for SC injection site selection and preparation are provided in [Appendix 1](#) and [Appendix 2](#), respectively.

Commercial icatibant labeled for clinical trial use will be supplied as rescue medication for the treatment of acute angioedema attacks (Section 5.2.1).

6.2 Administration of Investigational Product

Blinded investigational product (C1 esterase inhibitor [human] liquid for injection or placebo) will be administered twice weekly (every 3 or 4 days) for 14 weeks in each of 2 separate treatment periods. Every effort should be made to complete scheduled dosing and to avoid situations where investigational product is not received. In order to prevent a missed dose, a less than 3-day interval may occur, with the recommendation of allowing at least 24 hours between doses. The contents of 2 vials of investigational products (a total volume of 4 mL) will be drawn into a silicone-free syringe for each SC injection. Following appropriate SC injection site selection and preparation ([Appendix 2](#)), the needle will be inserted in the subject's abdominal area in order to administer the SC injection as quickly as tolerated by the subject.

Investigational product will be administered at the investigational site for Dosing Visits 1, 8, 16, 24, and 28 during both treatment periods. Other doses may be administered by qualified blinded personnel at the investigational site or at the subject's home or other agreed upon location or self-administered by the subject (adolescent or adult) with or without supervision (qualified home health professional and/or study site personnel), after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if a qualified home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver after

receiving appropriate training will be allowed to administer the investigational product to an adolescent subject with or without supervision.

6.3 Allocation of Subjects to Treatment Sequence

This is a double-blind, placebo-controlled, 2-period, 3-sequence, partial crossover study. At least 66 eligible subjects will be randomized to 1 of 3 treatment sequences ([Table 7](#)) 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.

Table 7 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.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each level of use of prophylactic therapy with C1 INH across sites, the subject number is assigned to subjects according to the sequence of presentation for study participation. Subject number is unique within a protocol.

The randomization number represents a unique number corresponding to treatment sequence allocated to the subject, once eligibility has been determined. A randomization number will be assigned by the IRT at the baseline visit (predose Visit 1a) after subject eligibility has been confirmed using the randomization criteria. 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. Subjects will be randomized to the treatment sequence 1 (A/B), 2 (B/A), or 3 (A/A) in the randomization ratio of 2:2:1.

The subject's treatment sequence will be held in strict confidence. The treatment sequence for an individual subject may be broken in cases of emergency or for reasons of subject safety, as described in Section [6.4.1](#).

6.4 Blinding of Treatment

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

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To maintain the blind, C1 esterase inhibitor [human] liquid for injection and placebo will have an identical presentation, including its packaging and labeling, such that the contents of the glass vials within the prepackaged study kits will be indistinguishable from each other. As described in Section 6.6, investigational product will be identified only by a unique study drug kit number. Each prepackaged study kit will contain 2x2 mL vials of investigational product (a total volume of 4 mL), which will be required to be drawn into a silicone-free syringe for each SC injection. If possible, a different individual should draw up the investigational product into the syringe than the individual administering the SC injection to the study subject.

Knowledge of the PK/PD data would compromise the study blind. As such, the independent external laboratory performing the PK/PD analyses will keep the results in strict confidence until the study is unblinded.

Additionally, a limited number of representatives of the sponsor responsible for the IRT and product labeling will be unblinded to treatment assignment in order to review drug accountability on an ongoing basis throughout the study (Section 6.7).

6.4.1 Unblinding the Treatment Assignment

The randomization code for an individual subject may only be broken by the investigator or the sponsor for reasons of subject safety or in an emergency when knowledge of the product administered would be important for the treatment of the subject. If the blind is broken by the investigator, he/she must notify the Shire ViroPharma Medical Monitor immediately and must document the date, time, and reason for the code break in a note to file.

6.5 Treatment Compliance

Investigational product will be administered either by study site personnel or a qualified home health professional or may occur under their direct supervision for subjects (or parent/legal guardian/caregiver) who elect to self-administer during Treatment Periods 1 and 2 (Section 6.2). Therefore, full subject compliance with treatment is expected in this study.

6.5.1 Self-Administration

Instruction for subjects who elect to self-administer investigational product (or when needed, icanatib as rescue medication; see Section 5.2.1) with or without supervision (qualified home health professional and/or study site personnel), after receiving appropriate training by the investigator or designee will include:

- Transportation and recommended storage conditions of investigational product from the study site to the home location.
- Maintenance of accurate records regarding each administration of investigational product including supply identification (ie, lot/kit number), date and time of injection, and if for any reason the SC injection could not be completed as instructed.
- Retention of all used and unused vials of investigational product for drug accountability purposes.

6.6 Packaging and Labeling

C1 esterase inhibitor [human] liquid for injection and placebo will be packaged and labeled such that the products will be indistinguishable from each other by the investigator, study site personnel, home health professionals, and subjects.

Investigational product will be supplied in a prepackaged study kit. Each study kit will contain 2 vials of investigational product (C1 esterase inhibitor [human] liquid for injection or placebo). Both the vials and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number.

The investigative site will also be provided with ancillary supplies including silicone-free syringes and needles. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection.

Subjects who elect to self-administer investigational product will be provided the following supplies at the investigational site:

- 4-week supply (8 study kits) of investigational product
- Ancillary supplies, including silicone-free syringes, needles, and a container for sharps disposal
- Transport container for investigational product
- Subject accountability log to record investigational product storage conditions and administration details

All used and unused vials should be returned to the study kit cartons/boxes and transported to the site for drug accountability.

Written instructions on investigational product and self-administration procedures will be provided to subjects at the screening or first dosing visit (Visit 1a). Refer to the Pharmacy Manual for additional details on the investigational product and its administration.

6.7 Storage and Accountability

Investigational product will shipped refrigerated to the study site at 2–8°C. Vials of investigational product must be stored at 2–8°C (36–46°F) and protected from light. Do not freeze investigational product.

The disposition of all investigational product delivered to a principal investigator must be recorded on a subject-by-subject basis by completing the clinical trial material accountability log. The date and time of administration of the investigational product must be documented on the appropriate CRF.

The principal investigator, study site personnel, or qualified home health professional must ensure that all documentation regarding investigational product receipt, storage, dispensing,

loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit.

The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the sponsor or designee, if required.

6.8 Investigational Product Retention at Study Site

The process for return and destruction of investigational product must be determined and documented during the study start-up phase. If the sites do not have an investigational product returns process/policy, the sponsor or designee must provide guidelines to the sites. Sites must retain copies of these documents within the site regulatory binder.

If the investigational product is to be destroyed by the sites, sites must follow their own process/policy that describes such activities. Sites must retain copies of these documents within the site regulatory binder. Sites must ensure that the clinical trial material accountability and destruction log is complete, accurate, and ready for review and/or audit at each monitoring visit.

All manifests documenting shipments of investigational product must be retained, as well as copies of any investigational product return forms.

Refer to the Pharmacy Manual for additional details.

7. STUDY PROCEDURES

Subjects may be enrolled in the study after the nature and purpose of the protocol has been explained, written informed consent to participate has been voluntarily granted, and the eligibility criteria listed in Sections 4.1 and 4.2 have been met.

7.1 Study Schedule

Table 1 (Treatment Period 1), Table 2 (Treatment Period 2), Table 3 (early discontinuation visit, 1-week and 1-month post-treatment follow-up visits), and Table 4 (blood sample collection for PK/PD Analyses) provide the timing of all study procedures and assessments.

7.1.1 Screening Period

Informed consent must be obtained before any study-specific procedures are performed. Note that AEs will be collected from the time of informed consent through 7 days after the last dose of investigational product.

Subjects will have all screening procedures completed within 21 days prior to the first dose of investigational product (Visit 1a=Dosing Day 1) according to Table 1. The following procedures will occur:

- Informed consent/assent
- Adverse events (collection begins from the time of informed consent through 7 days after the

last dose of investigational product)

- Inclusion/exclusion criteria
- Medical history (includes HAE history with the documentation of attack rate for study entry criteria and if applicable, determination of C1 INH antigen level and/or C1 INH functional activity, Section 7.2.3.1)
- Physical examination
- Clinical laboratory testing (biochemistry, hematology, coagulation)
- Virology screening
- Vital signs
- ECG
- Height and weight
- Serum pregnancy test (in females of childbearing potential)
- Recording of prior and concomitant medications

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s). Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.2 Treatment Period 1

7.1.2.1 Visit 1a (predose)

The following procedures will be performed at the investigative site prior to the first dose of investigational product at Visit 1a:

- Collection of AEs
- Randomization
- Physical examination
- Vital signs (≤ 30 min before the start of injection)
- Clinical laboratory testing (biochemistry, hematology, coagulation)
- Urinalysis testing with microscopy
- Urine pregnancy test (in females of childbearing potential)
- Recording of concomitant medications (needed for confirmation of subject eligibility)
- PK (C1 INH antigen, C1 INH functional, [includes measurement of C1q]) and PD (C4) sampling (within ≈ 15 min)
- Immunogenicity (anti-C1 INH antibody)
- Angioedema quality of life (AE-QoL) questionnaire, EuroQol 5-dimensional 5-level

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descriptive system (EQ-5D-5L), Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire, and Sheehan Disability Scale (SDS) assessments recorded in the electronic subject diary

- Health resource utilization assessment (HRUA)-HAE

7.1.2.2 Visit 1a (postdose)

The following procedures will be performed after the administration of the first dose of investigational product at Visit 1a:

- Collection of AEs
- Recording in the electronic subject diary any symptoms or occurrences of an angioedema attack (and the subject diary is to be updated daily; Section 7.2.2.2).
- Vital signs (≤ 10 min after the end of the injection and between 30 min and 1 hour after the end of the injection)
- Injection site reaction assessment (15 min, 30 min, and 1 hour after the end of the injection)
- Recording the daily AAS in the electronic subject diary

7.1.2.3 Visit 2a through Visit 28a

The following procedures will be performed throughout Treatment Period 1 at the visits indicated below:

- All concomitant medication and AEs will be recorded at each visit (2a-28a)
- Recording in the electronic subject diary daily any symptoms or occurrences of an angioedema attack (Visits 2a-28a)
- Recording the daily AAS in the electronic subject diary (Visits 2a-28a)
- Vital signs ≤ 30 min predose; ≤ 10 min and between 30 min and 1 hour after the injection (Visits 2a, 3a, 4a, 8a, 16a, 24a, 28a). 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).
- Physical examination (Visits 8a, 16a, 24a, 28a)
- Investigational product will be administered at each visit (2a-28a); Visits 8a, 16a, 24a, and 28a must occur at the investigational site.
- Injection site reaction assessment will be performed 15 min, 30 min, and 1 hour after investigational product administration at Visits 8a, 16a, 24a, and 28a. At Visit 28a, the overall impact of injection site reactions on daily living (yes/no) and duration will be assessed.
- Clinical laboratory testing (biochemistry, hematology, coagulation) at Visits 8a, 16a, 24a, and 28a
- Urinalysis testing with microscopy at Visit 28a

- Acceptability and self-administration survey assessment (recorded in the electronic subject diary) at Visit 28a
- Quality of life assessments recorded in the electronic subject diary: AE-QoL (Visits 9a, 17a, 25a), EQ-5D-5L (Visit 24a and on each day that a subject experiences signs or symptoms of an angioedema attack), and WPAI-GH and SDS (Visits 3a, 5a, 7a, 9a, 11a, 13a, 15a, 17a, 19a, 21a, 23a, 25a, 27a)
- HRUA-HAE (Visits 8a, 16a, 24a)
- Immunogenicity (anti-C1 INH antibody) (predose Visits 8a, 16a, 24a, 27a or 28a)
- PK/PD sampling (C1 INH antigen, C1 INH functional, and C4) (predose Visits 2a, 8a, 16a, 24a, 27a or 28a [within ≈ 15 min], and 48 h postdose Visits 27a or 28a [± 3 hours]). Note: A predose Visit 2a blood sample is not required for subjects self-administering investigational product without supervision (ie, sample collection may not be possible).

7.1.3 Treatment Period 2

7.1.3.1 Visit 1b (predose)

The following procedures will be performed at the investigative site prior to the first dose of investigational product in Treatment Period 2 at Visit 1b:

- Collection of AEs
- Physical examination
- Vital signs (≤ 30 min before the start of injection)
- Clinical laboratory testing (biochemistry, hematology, coagulation)
- Urinalysis testing with microscopy
- Urine pregnancy test (in females of childbearing potential)
- Recording of concomitant medications
- PK (C1 INH antigen, C1 INH functional) and PD (C4) sampling (within ≈ 15 min)
- Immunogenicity (anti-C1 INH antibody) blood sample collection
- AE-QoL, EQ-5D-5L, WPAI-GH, and SDS assessments recorded in the electronic subject diary
- HRUA-HAE

7.1.3.2 Visit 1b (postdose)

The following procedures will be performed after the administration of investigational product at Visit 1b:

- Collection of AEs
- Recording in the electronic subject diary any symptoms or occurrences of an angioedema attack

- Vital signs (≤ 10 min after the end of the injection and between 30 min and 1 hour after the end of the injection)
- Injection site reaction assessment (15 min, 30 min, and 1 hour after the end of the injection)
- Recording the daily AAS in the electronic subject diary

7.1.3.3 Visit 2b through Visit 28b

The following procedures will be performed throughout Treatment Period 2 at the visits indicated below:

- All concomitant medication and AEs will be recorded at each visit (2b-28b)
- Recording in the subject diary daily any symptoms or occurrences of an angioedema attack (Visits 2b-28b)
- Recording the daily AAS in the subject diary (Visits 2b-28b)
- Vital signs ≤ 30 min predose; ≤ 10 min and between 30 min and 1 hour after the injection (Visits 2b, 3b, 4b, 8b, 16b, 24b, 28b). 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).
- Physical examination (Visits 8b, 16b, 24b, 28b)
- Investigational product will be administered at each visit (2b-28b); Visits 8b, 16b, 24b, and 28b must occur at the investigational site.
- Injection site reaction assessment will be performed 15 min, 30 min, and 1 hour after investigational product administration at Visits 8b, 16b, 24b, and 28b. At Visit 28b, the overall impact of injection site reactions on daily living (yes/no) and duration will be assessed.
- Clinical laboratory testing (biochemistry, hematology, coagulation) at Visits 8b, 16b, 24b, and 28b
- Urinalysis testing with microscopy at Visit 28b
- Quality of life assessments: AE-QoL (Visits 9b, 17b, 25b), EQ-5D-5L (Visit 24b and on each day that a subject experiences signs or symptoms of an angioedema attack), and WPAI-GH and SDS (Visits 3b, 5b, 7b, 9b, 11b, 13b, 15b, 17b, 19b, 21b, 23b, 25b, 27b) recorded in the electronic subject diary
- HRUA-HAE (Visits 8b, 16b, 24b)
- Acceptability survey and self-administration survey (recorded in the electronic subject diary) assessments at Visit 28b
- Immunogenicity (anti-C1 INH antibody) (predose Visits 8b, 16b, 24b, 28b)
- PK/PD sampling (C1 INH antigen, C1 INH functional, and C4) (predose Visits 2b, 8b, 16b, 24b, and 28b [within ≈ 15 min], and 24 hours (± 3 hours) (optional time point), 48 hours (± 3 hours), 72 h (± 6 hours) (optional time point), and 96 hours (± 6 hours) postdose Visit

28b). Note: A predose Visit 2b blood sample is not required for subjects self-administering investigational product without supervision (ie, sample collection may not be possible).

7.1.4 Early Discontinuation Visit

If a subject prematurely discontinues from investigational product, the following procedures are to be performed as completely as possible:

- All concomitant medications and any new or ongoing AEs will be recorded
- Recording in the electronic subject diary any symptoms or occurrences of an angioedema attack; if possible, subjects should complete the subject diary on the day of discontinuation and/or at the 1-week and 1-month post-treatment Visits, as applicable
- Recording the daily AAS in the electronic subject diary
- Vital signs
- Physical examination
- Clinical laboratory testing (biochemistry, hematology, coagulation)
- Urinalysis testing with microscopy
- Urine pregnancy testing
- Acceptability survey and self-administration survey (recorded in the electronic subject diary) assessments
- AE-QoL, EQ-5D-5L, WPAI-GH, and SDS (recorded in the electronic subject diary) assessments
- PK/PD sampling (C1 INH antigen, C1 INH functional, and C4)
- Immunogenicity (anti-C1 INH antibody)

7.1.5 Follow-up Period

A post-treatment visit will be performed at the investigative site 1 week (± 1 day) after the last dose of investigational product for follow-up safety assessments ([Table 3](#)). The following procedures will occur:

- All concomitant medications and any new or ongoing AEs will be recorded
- Recording in the electronic subject diary any symptoms or occurrences of an angioedema attack; if possible, subjects should complete the subject diary on the day of discontinuation and/or at the 1-week and 1-month post-treatment Visits, as applicable
- Recording the daily AAS in the electronic subject diary
- Vital signs
- Physical examination
- Clinical laboratory testing (biochemistry, hematology, coagulation)
- Urinalysis testing with microscopy

- Urine pregnancy testing
- AE-QoL, EQ-5D-5L, WPAI-GH, and SDS (recorded in the electronic subject diary) assessments
- PK/PD sampling (C1 INH antigen, C1 INH functional, and C4)
- Immunogenicity (anti-C1 INH antibody)

A second post-treatment visit will occur at the investigative site 1 month (± 2 days) after the last dose of investigational product. The following procedures will occur:

- All concomitant medications will be recorded
- Recording in the electronic subject diary any symptoms or occurrences of an angioedema attack; if possible, subjects should complete the subject diary on the day of discontinuation and/or at the 1-week and 1-month post-treatment Visits, as applicable
- HRUA-HAE
- PK/PD sampling (C1 INH antigen, C1 INH functional, and C4)
- Immunogenicity (anti-C1 INH antibody)

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (Section 8.1).

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 the Shire Pharmacovigilance Department.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Subject demographic details, medical history (including HAE history, Section 7.2.3.1), prior and concomitant medication data, vital signs, height, weight, physical examination, 12-lead ECG, biochemistry, hematology, coagulation, virology screening, and serum β -hCG pregnancy test will be collected at the time of enrollment at the Screening Visit.

7.2.2 Efficacy

Analyses of the efficacy endpoints in this study require documentation of specific information regarding the subject's symptoms of any angioedema attacks they may experience during the study.

7.2.2.1 Definition of an Angioedema Attack

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

- Attacks that progress from 1 site to another will be considered a single attack
- Attacks that begin to regress and then worsen before complete resolution will be considered 1 attack
- Attacks that begin, appear to resolve, and then reappear without a symptom-free calendar day reported after the appearance of resolution will also be considered 1 attack

Note: An angioedema attack does not include swelling due to trauma, arthritis, or symmetrical nonpainful swelling of the lower extremities.

7.2.2.2 Recording of Angioedema Attacks in the Electronic Subject Diary

During the study, subjects will use an electronic subject diary each day to record any symptoms or occurrences of an angioedema attack. The investigator will complete a separate angioedema attack CRF for each attack based upon their review of the data in the subject diary. Information will include the following:

- Date and time of onset and complete resolution of angioedema attack symptoms
- Characterization of whether swelling or pain is (indicate all that apply):
 - Mucosal (pharyngeal, laryngeal, gastrointestinal, genitourinary)
 - Non-mucosal (truncal, extremity, facial)
- Location (site) of the swelling or pain (indicate all that apply):
 - Upper airway (includes laryngeal or pharyngeal)
Note: Pharyngeal or oral swelling that results in airway compromise will be classified as a laryngeal attack.
 - 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])
- Severity (intensity) of the sign/symptom at each location listed:
 - Absent
 - Mild: the angioedema attack sign/symptom(s) is noticeable but is easily tolerated by the subject and does not interfere with routine activities.
 - Moderate: the angioedema attack sign/symptom(s) interferes with the subject's ability to attend work/school or participate in family life and social/recreational activities.

- Severe: the angioedema attack sign/symptom(s) significantly limits the subject's ability to attend work/school or participate in family life and social/recreational activities.
- Visual Analogue Scale (VAS) pain measurement score
- Angioedema attack trigger(s)
- Answer to the question, "Was treatment administered for the attack?" If yes, record the date, time, and name of treatment administered.

7.2.2.3 Angioedema Activity Score

Subject self-assessment of disease activity will be assessed daily by the AAS. Subjects will respond to questions in the electronic subject diary about any swelling episode that has occurred within the previous 24 hours. Each AAS item (or question) is scored between 0 and 3 points, with the minimum and maximum daily AAS ranging between 0 and 15 points ([Weller et al. 2013](#)).

7.2.2.4 Assessment of Icatibant as Therapy for Acute Angioedema Attacks

Efficacy endpoints are based on subject-assessed symptom improvement as a measure of response to icatibant therapy. When a subject receives treatment with icatibant for an acute angioedema attack, they will record the date and time of administration of the SC injection in the electronic subject diary and will monitor the following events:

Initial Symptom Improvement

- Report date and time when you feel that your symptoms start to improve.

Complete Symptom Resolution

- Report date and time when you feel that your symptoms have completely resolved.

Tolerability

- Report any side effects associated with administration of icatibant therapy.

7.2.3 Safety

The name and address of each third party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.3.1 Medical and Medication 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 will be entered into the CRF regardless of clinical relevance or presence at study start. Medical history findings that have not been present within the 5 years prior to enrollment will be recorded if deemed clinically relevant by the investigator to the conduct of the study. The medical history should include any history of allergic reactions to drugs.

HAE History

The following information associated with HAE history will be recorded in the CRF at the screening visit. If there is no documented C1 INH antigen level and/or C1 INH functional activity in the subject's medical record, a blood sample can be collected at screening and sent to a local or central laboratory (as appropriate) to confirm HAE diagnosis (Type I or II). Repeat blood sampling is allowed if the test is non-confirmatory despite a suspected diagnosis of HAE. (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 (Section 5.1)
- 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 score, estimated on a scale from 0-100, 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.

7.2.3.2 Physical Examination (Including Height and Weight)

The investigator or designee will perform physical examinations at the time points specified in Table 1, Table 2, and Table 3. General physical examinations will be performed in accordance with standard practices at the study site. Physical examination abnormalities observed prior to the screening visit will be entered into the medical history section of the CRF. Any new or worsening of pre-existing abnormalities noted at post-screening examinations should be captured as an AE on the AE CRF page, per investigator's judgment.

Body weight and height will be measured at the time points specified in Table 1 and Table 2.

7.2.3.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed (Section 8.1).

7.2.3.4 Vital Signs

Vital signs include blood pressure and pulse and will be measured at the time points specified in [Table 1](#), [Table 2](#), and [Table 3](#). During the study, additional vital signs measurements will be performed if clinically indicated. Vital signs performed on a dosing day should be obtained immediately (≤ 30 minutes) before the start of the injection of investigational product, immediately after completion of the injection of investigational product (≤ 10 minutes), and then between 30 minutes and 1 hour after completion of the injection of investigational product. Every effort should be made to measure vital signs prior to any blood sample collection. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from Baseline (predose Visit 1a) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (approximately 6 mL) for biochemistry will be taken according to [Table 1](#), [Table 2](#), and [Table 3](#). The following parameters will be assessed:

Aspartate aminotransferase (AST)	Albumin
Alanine aminotransferase (ALT)	Total protein
Alkaline phosphatase (ALP)	Glucose
Creatine phosphokinase (CPK)	Potassium
Creatinine	Sodium
Blood urea nitrogen (BUN)	Chloride
Carbon dioxide	Phosphorus

Hematology

Blood samples (approximately 2 mL) for hematology will be taken according to [Table 1](#), [Table 2](#), and [Table 3](#). The following parameters will be assessed:

Hemoglobin Red blood cell count

Hematocrit Platelet count

White blood cell count – total and differential

Coagulation

Blood samples (approximately 3 mL) for coagulation will be taken according to [Table 1](#), [Table 2](#), and [Table 3](#). The following parameters will be assessed:

International normalized ratio (INR) Prothrombin time (PT)

D-dimer^a Activated partial thromboplastin time (aPTT)

^a In addition, D-dimer should be evaluated in any subject who presents with signs and symptoms consistent with suspected venous thromboembolism.

Virology

Blood samples (approximately 6 mL) will be taken according to [Table 1](#). The following parameters will be assessed:

Human immunodeficiency virus (HIV; single assay/INNO-LIA) Hepatitis (hepatitis B surface antigen and hepatitis C antibody)

Urinalysis with microscopy

Urine samples (approximately 10 mL) will be taken according to [Table 1](#), [Table 2](#), and [Table 3](#). The following parameters will be assessed:

pH Specific gravity

Dipstick (protein, glucose, ketones, hemoglobin) Microscopic evaluation (red blood cells, white blood cells, crystals, casts, bacteria)

In addition, a local or central laboratory (as appropriate) will be used for screening C1 INH

diagnostic assessments for subjects without documented C1 INH antigen level and/or C1 INH functional activity in their medical history.

7.2.3.6 Pregnancy Test

A serum β -hCG pregnancy test is performed on all females of childbearing potential at the screening visit and a urine pregnancy test is performed thereafter according to the time points specified in [Table 1](#), [Table 2](#), and [Table 3](#). Pregnancy test results must be confirmed as negative before subjects proceed in the study.

7.2.3.7 Electrocardiogram

Subjects will have a 12-lead ECG recorded at the screening visit, as specified in [Table 1](#). During the study, additional ECGs will be performed if clinically indicated. The following ECG data will be entered into the CRF: heart rate, PR interval, QRS duration, and QT interval. The PQ interval may be used if the PR interval is not reported on the 12-lead ECG. The investigator will be responsible for providing the interpretation of all ECGs (clinically significant/not clinically significant). The subject's ECG(s) should be consistently recorded in the same position (supine).

7.2.3.8 Nonpharmacologic Treatments and Procedures

Nonpharmacologic treatments and procedures (eg, surgical, diagnostic, or dental) that occur from the first dose of investigational product through the 1-week post-treatment visit will be recorded in the CRF (Section [5.2](#)).

7.2.3.9 Thrombotic or Thromboembolic Events

Monitoring for Venous Thromboembolism or Arterial Thromboembolism

Study personnel will actively monitor subjects for possible venous thromboembolism (VTE), encompassing both deep venous thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolism (ATE) with medical history, physical examinations, review of AEs, routine coagulation laboratory testing, and/or other diagnostic tests as applicable per local standard of care at the time points specified in [Table 1](#), [Table 2](#), and [Table 3](#).

Subjects will also receive instruction on how to recognize symptoms associated with potential thrombotic events and to seek medical attention for these symptoms in addition to informing their investigator. Treatment procedures, when applicable, will be provided per local standard of care.

Suspected Venous Thromboembolism or Arterial Thromboembolism

In subjects who present with signs and symptoms that are suspicious of a possible VTE (DVT or PE) based on clinical history and physical examination, the Wells Prediction Rules ([Appendix 3](#)) in conjunction with D-dimer assessment and/or other diagnostic tests, as applicable per local standard of care, are suggested to help guide the physician. Diagnostic and/or treatment procedures, when applicable, will be provided per local standard of care.

Based on the Wells Prediction Rule scores, the following procedures are recommended:

- If the Wells Prediction DVT risk score is ≥ 1 , coagulation studies and an imaging study (eg,

lower extremity ultrasound or contrast venography) may be performed as described below.

- If the Wells Prediction PE risk score is ≥ 2 , coagulation studies and 1 or more imaging studies (eg, ventilation-perfusion scan, multidetector helical computed axial tomography, or pulmonary angiography) may be performed as described below.

In the setting of suspected VTE events, site personnel will complete the Wells Prediction Rule CRF.

Diagnosis and management of all suspected VTE and ATE events should be per local standard of care; [Appendix 4](#) and [Appendix 5](#) also presents a suggested medical algorithm for diagnosis and management of such conditions. Investigators must also comply with all reporting and/or concerning procedures for AEs/SAEs as indicated in the suggested algorithm. Confirmed diagnoses of T/TE events will be reported as SAEs (Section [8.2](#)). However, superficial thrombophlebitis and catheter-related thrombosis will be reported as either a nonserious AE or an SAE based on investigator assessment and standard AE/SAE definitions.

7.2.3.10 Injection Site Reactions

Investigational product SC injection site reactions will be captured in the local tolerability CRF. Site personnel will distinguish between injection site reactions related to the procedure (eg, will check for redness after needle is inserted and prior to investigational product administration) vs the actual investigational product. Injection site reactions that do not meet the criteria of an SAE will not need to be reported as an AE.

Subcutaneous injection site reactions will be assessed at the following post-injection time points in each treatment period: 15 minutes, 30 minutes, and 1 hour post-injection. Study personnel will examine injection sites for erythema or swelling and will question the subject to collect information on cutaneous pain, burning sensation, itching/pruritus, and warm sensation. The diameter of any erythema or swelling should be measured to obtain the severity grading. The injection site reactions will be graded as absent, mild, moderate, or severe using the scoring criteria shown in [Table 8](#). Both the severity score and the measurement of any erythema or swelling are to be captured in the CRF. In addition, the overall impact of injection site reactions on daily living (yes/no) and duration will be assessed at the last visit of each treatment period (Visits 28a and 28b).

Table 8 Severity Scoring for Injection Site Reactions

Reaction	Severity		
	Mild	Moderate	Severe
Erythema	>0 to 5 cm	>5 to 10 cm	>10 cm
Swelling	>0 to 5 cm	>5 to 10 cm	>10 cm
Cutaneous pain	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Burning sensation	Mild burning sensation, which is easily tolerated	Moderate burning sensation, causing some discomfort	Severe burning sensation, causing significant discomfort
Itching/pruritus	Mild itching/pruritus, which is easily tolerated	Moderate itching/pruritus, causing some discomfort	Severe itching/pruritus, causing significant discomfort
Warm sensation	Mild warmth to touch	Moderate warmth to touch	Significant warmth to touch

Injection site reactions resulting from the administration of icatibant (as rescue medication for acute angioedema attacks) will be reported as an AE with causality linked to icatibant.

7.2.4 Others

7.2.4.1 Clinical Pharmacology Assessments

Pharmacokinetic, Pharmacodynamic, and C1 INH Antibody Analyses

Subjects will have blood samples (7 mL) collected for the determination of plasma concentrations of C1 INH antigen, functional C1 INH, complement C4, and C1q at time points specified in [Table 4](#). Serum samples (5 mL) will be collected prior to the first dose of investigational product on Visit 1a (Dose 1 of Treatment Period 1), Visit 1b (Dose 1 of Treatment Period 2), and throughout both treatment periods for the analysis of anti-C1 INH antibodies ([Table 1](#) and [Table 2](#)). Additional blood samples for PK/PD and C1 INH antibody testing will be collected at the early discontinuation visit (if applicable) and the 1-week and 1-month post treatment visits ([Table 3](#)). Blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays.

The actual date and time of each sample collection will be recorded. Plasma samples for the determination of antigenic C1 INH, functional C1 INH activity, complement C4 and C1q concentrations, and serum samples for the evaluation of anti-C1 INH antibodies will be analyzed using validated methods. All PK/PD and immunogenicity samples will be processed according to the procedure outlined in the laboratory manual.

Selected samples may be analyzed to investigate incurred sample reproducibility of the bioanalytical methods. These analyses are only to investigate the reproducibility of the bioanalytical methods used to determine C1 INH antigen and functional C1 INH concentrations in study samples. All incurred sample reproducibility results will be reported in a separate table in the bioanalytical report. Details of disposal will be documented and maintained with the study file at the analytical laboratory.

7.2.4.2 Health-related Quality of Life Assessments

Angioedema Quality of Life Questionnaire

The AE-QoL is a questionnaire on the quality of life of patients suffering from recurrent angioedema (Weller et al. 2012). 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 AE-QoL will be completed in the electronic subject diary at the time points specified in Table 1, Table 2, and Table 3. Details about the use of the AE-QoL instrument are provided in a separate study manual.

Health-related Quality of Life Questionnaire

The EQ-5D-5L¹ 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. The EQ-5D-5L will be completed in the electronic subject diary at the time points specified in Table 1, Table 2, and Table 3, as well as on each day that a subject experiences signs or symptoms of an angioedema attack. Details about the use and administration of the EQ-5D-5L instrument are provided in a separate study manual.

Work Productivity and Activity Impairment-General Health Questionnaire

The WPAI-GH questionnaire includes 6 questions about work and activity impairment due to health problems during the past 7 days (Reilly et al. 1993). Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less work or productivity. The WPAI-GH will be completed in the electronic subject diary at the time points specified in Table 1, Table 2, and Table 3. Details about the use of the WPAI-GH instrument are provided in a separate study manual.

Sheehan Disability Scale

The 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 (Sheehan 1983). The SDS will be completed in the electronic subject diary at the time points specified in Table 1, Table 2, and Table 3.

7.2.4.3 Health Resource Utilization Assessment

Study personnel will ask subjects specific questions regarding their utilization of health care resources for the management of their HAE disease. The Health Resource Utilization Assessment (HRUA-HAE) will be completed at the time points specified in Table 1, Table 2, and Table 3. Study personnel will enter the survey responses into the appropriate CRF.

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

7.2.4.4 Survey of Acceptability of SC Administration

Study personnel will ask subjects to rate their overall experience in receiving twice weekly SC injections of investigational product at the time points specified in [Table 1](#), [Table 2](#), and [Table 3](#). For subjects who have previously received C1 INH products via IV administration, they will be asked to indicate the preferred route for medication administration. Study personnel will enter the subject's survey responses into the electronic subject diary.

In addition, investigators will be asked to indicate their preference (SC, IV, or no preference) on the route to administer medications to prevent angioedema attacks.

7.2.4.5 Self-administration Survey Assessment

After receiving appropriate training, subjects are allowed to self-administer investigational product during Treatment Periods 1 and 2 with or without direct supervision (qualified home health professional and/or study site personnel). Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver after having received appropriate training will be allowed to administer the investigational product to an adolescent subject with or without supervision. For those subjects who choose to self-administer or have a parent/legal guardian/caregiver administer the investigational product, study personnel will ask specific questions about their experience with self-administration of SC medication ([Table 2](#) and [Table 3](#)). Study personnel will enter the subject's survey responses into the electronic subject diary.

7.2.5 Volume of Blood to Be Drawn From Each Subject

Table 9 Approximate Volume of Blood to Be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
PK/PD		7	20 ^b	140
Immunogenicity (anti-C1 INH antibodies)		5	13	65
Safety	Biochemistry and β -HCG ^a	6	13	78
	Hematology	2	13	26
	Coagulation	3	13	39
Virology		6	1	6
All assessments (mL)				354

B-hCG=beta human chorionic gonadotrophin; C1 INH=C1 inhibitor; PD=pharmacodynamics; PK=pharmacokinetics

^a β -hCG testing for females of childbearing potential at the Visit 1a (predose) only.

^b Two of the 20 samples are optional as indicated in [Table 4](#).

During this study, it is expected that maximum volume of blood to be drawn from each subject will be 354 mL, as shown in [Table 9](#).

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 354 mL. When more than 1 blood assessment is done at the same time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until 7 days after the last dose of investigational product. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

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Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product and/or other study product (eg, icanitab) is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and/or other study product (eg, icanitab) and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving

- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study (angioedema attacks) should not be captured as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, events satisfying the serious criteria should be recorded as a SAE and reported to Shire Pharmacovigilance.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range (either while continuing treatment or after the end of treatment with the investigational product), and the range of variation of the respective parameter within its reference range must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section [7.1.5](#).

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire ViroPharma Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to Global Pharmacovigilance using the Shire Clinical Trial Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Serious Adverse Event Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β -hCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: This includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product higher than the protocol-specified dose.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Medication errors should be collected and reported to the sponsor for all products under investigation. The following should be considered as examples of reportable medication errors:

- The administration and/or use of the unassigned treatment
- The administration and/or use of an expired investigational product
- Violation of storage or refrigeration requirements for the investigational product

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

All investigational products administered to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

8.1.8 Adverse Events of Special Interest

In addition, the following adverse events of special interest will be closely monitored and reported throughout the study, regardless of relationship to study medication:

- Any serious anaphylactic reaction (see Section 4.4.3).

- Any serious thrombotic or thromboembolic event; stopping rules related to thrombotic or thromboembolic events are described in Section 4.4.4.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the CINRYZE Investigator's Brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Pharmacovigilance Department. A copy of the Shire Clinical Trial Serious Adverse Event Form (and any applicable follow-up reports) must also be sent to the contract research organization (CRO)/Shire ViroPharma Medical Monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A **Serious Adverse Event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions that have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as an SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or

surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.5, and must be reported to the Shire Pharmacovigilance Department and Medical Monitor within 24 hours of the first awareness of the event until 30 days after the last dose of investigational product.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

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.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject’s death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs) of related, unexpected SAEs.

In addition, the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP616 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

All statistical analyses will be performed using SAS® Version 9.1 or higher (SAS Institute, PPD PPD).

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The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or data monitoring committee in this study.

9.6 Sample Size Calculation and Power Considerations

For the primary efficacy endpoint, the NNA, a sample of 44 subjects from the crossover sequences will provide approximately 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 between-subject standard deviation of 2.0. This target is supported by the recently completed, dose-ranging, Phase 2 study with CINRYZE (0624-206).

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).

Previous communications have occurred between regulatory authorities and the sponsor regarding a Phase 3 study for the SC CINRYZE development program. The regulatory authority indicated that the Phase 3 study should be of sufficient size to have a 95% probability for detection of safety signals occurring with an incidence of 5% or greater of subjects.

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.

9.7 Study Population

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Enrolled Set** will consist of all subjects who have signed an informed consent and some study procedures have begun.

The **Randomized Set** will consist of all subjects in the Screened Set for whom a randomization number has been assigned.

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

The **Full Analysis Set** will consist of all subjects in the Safety Set who have at least 1 post-baseline (eg, randomization) primary efficacy assessment.

The **Per-protocol Set** will consist of 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.

The **Completer Set** will consist of all subjects in the Full Analysis Set who have completed the final scheduled primary assessment for the study.

The **Pharmacokinetic and Pharmacodynamic Set** will consist of all subjects in the Safety Set for whom the primary PK and PD data are considered sufficient and interpretable.

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

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

$$\text{NNA} = 30.4 \times (\text{number of attacks during treatment period}) / (\text{days of treatment period})$$

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.

The primary efficacy analysis will be conducted for the subjects in the Full Analysis Set (Section 9.7) 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 null hypothesis to be tested is 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 is that the NNA of C1 esterase inhibitor [human] liquid for injection is less than the NNA of placebo as below:

$$H_0: \mu_{\text{C1 INH}} - \mu_{\text{placebo}} \geq 0 \text{ vs}$$

$$H_1: \mu_{\text{C1 INH}} - \mu_{\text{placebo}} < 0$$

The primary efficacy endpoint will be analyzed by using a linear mixed effect model with period, sequence, stratification factor (use of prophylactic therapy with C1 INH), 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.

To assess any carryover effect, a sensitivity analysis will exclude from the evaluation of the NNA any attacks occurring within the first 2 weeks of Treatment 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]

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liquid for injection efficacy into the placebo treatment period, thereby diluting the efficacy of C1 INH and favoring 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. The study is powered to demonstrate superior efficacy even in the presence of carryover effects. Additional sensitivity analyses may be developed and included in the SAP.

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.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoints

1. The proportion of subjects meeting the criterion of at least a 50% 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% 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 $\geq 50\%$ reduction in the NNA (P_R) during the 2000 IU C1 esterase inhibitor [human] liquid for injection treatment period relative to the placebo period. Key secondary endpoints 1 and 3 will be analyzed as the proportion of subjects meeting criterion P_R . 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. The proportion meeting criterion 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 0.025 using the normal approximation to 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.

9.8.2.2 Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints to be evaluated in this study are:

- To determine the proportions of subjects achieving at least a 50% reduction in the NNA during a treatment period relative to the pretreatment assessment.
- Cumulative attack severity. This score is the sum of the maximum symptom severity recorded for each angioedema attack in a treatment period.

- Cumulative daily severity. This score is the sum of the severity scores recorded for every day of reported symptoms in a treatment period.
- Number of attack-free days during a treatment period.
- Number of angioedema attacks requiring acute treatment a treatment period.
- Disease activity as measured by the 98-day AAS. This score is the sum of the daily AAS during a treatment period, where the daily AAS is the sum of AAS items per day.
- Results of the AE-QoL questionnaire.
- Determine the response to icatibant when administered as treatment for an acute angioedema attack by:
 - Time to subject-assessed initial symptom improvement (TISI)
 - Time to subject-assessed complete symptom resolution (TCSR)

Subjects in the Full Analysis Set (Section 9.7) 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. The treatment differences in clinical responder rate, both of which are defined within treatments, will be analyzed using McNemar's test for testing equality of proportions of responders within treatments. All other secondary endpoints will be analyzed using a linear mixed effect model with period, sequence, stratification factor (use of prophylactic therapy with C1 INH), and treatment as fixed effects, and subject nested within sequence as a random effect. The results of all secondary efficacy analyses will be summarized by the point estimate of within-subject treatment differences or response rates and the corresponding 95% CI. Descriptive statistics (n, median, 25% and 75% quartiles, and range) will be provided to summarize icatibant-related efficacy endpoints (TISI and TCSR) by treatment and icatibant-treated angioedema attack for all subjects in the Full Analysis Set. Where appropriate (for subjects ≥ 12 to < 18 years of age), other rescue medications used to treat acute angioedema attacks will also be summarized using descriptive statistics. In addition, angioedema attacks will be summarized by the maximum symptom severity and treatment for all subjects in the Full Analysis Set.

9.8.3 Exploratory Efficacy Endpoints

There are no exploratory efficacy endpoints in this study.

9.9 Safety Analyses

Adverse events will be coded using the MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, preferred term, and treatment. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, AEs of special interest, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests (hematology, chemistry, and coagulation), vital signs, and ECG findings will be summarized by treatment and visit. Potentially clinically important findings will also be summarized or listed.

The incidence and severity (mild, moderate, severe) of SC injection site reactions will be summarized by treatment and visit. The overall impact of injection site reactions on daily living (yes/no) and duration will be summarized by treatment.

Results of C1 INH antibody testing will be reported for individual subjects.

The tolerability of icatibant therapy for acute angioedema attacks will be summarized.

To assess the influence of any carryover effect on adverse reporting, a sensitivity analysis may 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. In other words, C1 esterase inhibitor [human] liquid for injection may account for any TEAEs in the first 2 weeks of the placebo treatment, when the carryover effect (if present) is suspected to be maximal.

9.10 Other Analyses

9.10.1 Pharmacokinetic and Pharmacodynamic Analyses

Concentrations of C1 INH antigen, C1 INH functional, and complement C4 and C1q for individual subjects will be determined using validated bioanalytical methods. Results will be summarized using descriptive statistics (number, geometric mean, coefficient of variation, mean, standard deviation, median, minimum, and maximum) for values at each time point. C1q concentrations will only be assessed at baseline (ie, pre-injection, Dosing Visit 1a).

Pharmacokinetic/pharmacodynamic (PK/PD) parameters will be calculated using observed and baseline-corrected concentration-vs-time data using non-compartmental analysis for C1 INH antigen, functional activity, and C4 levels. The following PK/PD parameters will be calculated, as appropriate, using both unadjusted and baseline-adjusted concentrations for SC administration: C_{max} , t_{max} , and AUC_{tau} . Additional PK parameters will be calculated using only baseline-adjusted concentrations, including $t_{1/2}$, AUC_{tau} , AUC_t , and CL/F . Other PK parameters may be calculated as deemed appropriate.

Exploratory PK/PD analyses might be performed based on the correlation of plasma concentrations of C1 INH antigen, functional C1 INH, and C4 complement in conjunction with various safety parameters (eg, selected AEs, clinical laboratory results, antibodies generation, frequency, severity, or anatomic location of the angioedema attack, etc.). Correlations that will be analyzed will be determined based on observed data. The PK/PD properties of SC C1 esterase inhibitor [human] liquid for injection will be characterized by population PK/PD modeling, and exposure-response will be explored. The report of these analyses will be issued separately.

Blood samples collected from subjects for PD assessments may also be used for exploratory HAE biomarker assays. The report of these analyses, if and when conducted, will be issued separately.

9.10.2 Health-related Quality of Life Analyses

Results of the EQ-5D-5L health status instrument will be presented in accordance with the EQ-5D-5L user guide (version 2.0) by treatment.

Results of the WPAI-GH questionnaire will be summarized by treatment.

Results of the SDS will be summarized by treatment.

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

Results of the surveys for subject acceptability of SC administration and subject experience with self-administration of investigational product will be summarized.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements. These regulations and guidelines also constitute compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for conditions indicating that the clinical investigation should be halted due to an unacceptable patient risk or other reasons. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject's diary, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

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The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54.2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of

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subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form (and assent form where applicable) which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator, or for multicenter studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market C1 esterase inhibitor [human] liquid for injection; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire ViroPharma will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire ViroPharma adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire ViroPharma. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire ViroPharma products or projects must undergo appropriate technical and intellectual property review, with Shire ViroPharma agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on

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medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire ViroPharma, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

APPENDIX 1 HANDLING OF INVESTIGATIONAL PRODUCT FOR SUBCUTANEOUS INJECTION

The procedures below are provided for the handling of the investigational product. Since treatment assignment to C1 esterase inhibitor [human] liquid for injection and placebo (Treatments A and B, respectively) is to be blinded, the following instructions apply for all SC administrations in Treatment Periods 1 and 2. Always work on a clean surface and wash hands before performing the following procedures.

Handling

- Prior to administration, investigational product should be protected from light.
- No reconstitution or additional dilution of investigational product is required.
- A silicone-free syringe is to be used for withdrawal of the product from the vial and for administration.
- Important Notes: (1) when withdrawing the product from the vial, and during administration, the plunger of the syringe should be moved back and forth carefully and slowly, avoid introducing any air bubbles, and pulling the plunger past the stop on the syringe; (2) there is no need for excessive shaking of either the vial or syringe during the preparation for the SC injection.
- Investigational product should be inspected carefully for particulate matter or any discoloration prior to administration, whenever solution and container permit. The product should be colorless to slightly blue or colorless to slightly yellow and free from visible particles. Do not use if turbid or discolored.
- Any vial that has been punctured should be used promptly.
- Do not mix investigational product with other materials.
- Do not freeze.
- Do not use after expiration date.

NOTE: For this protocol, 2 vials of investigational product will be required for each SC injection (2x2 mL=4 mL total injection volume).

1. Aseptic technique should be used during handling.
2. Bring vials of investigational product to room temperature.
3. Remove caps from investigational product vials.
4. Cleanse stopper(s) with alcohol swab or germicidal solution, and allow them to dry prior to use.
5. Transfer the investigational product to a syringe for administration. Draw up the contents of 2 vials of investigational for a total volume of 4 mL.

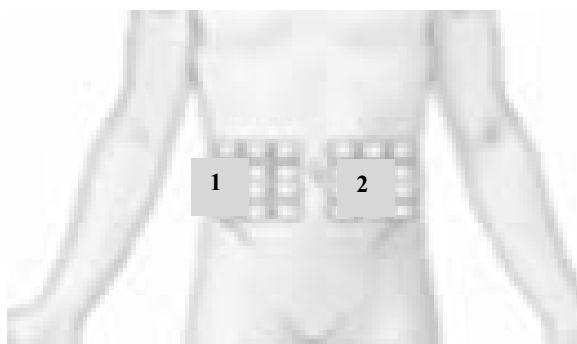
Be sure to safely dispose of the used needle and syringe.

Retain all used vials of investigational product for drug accountability purposes.

APPENDIX 2 SUBCUTANEOUS INJECTION SITE SELECTION AND PREPARATION

Subcutaneous injections of investigational product will be administered in the abdominal area. Injection sites on the abdomen are depicted in the figure below. An abdominal site that is approximately at the level of the navel (as allowed by skin condition) and approximately 15 cm (minimum 10 cm) away from the margin of the navel should be selected. The lateral portion of the abdomen is preferred over the midline area. The selected site should include fatty tissue. Administer the first injection in the right side (#1 in illustration) and the second injection in the left side (#2 in illustration). Keep alternating injection sites to the right side and then to the left side for all subsequent injection sites in Treatment Periods 1 and 2.

Illustration of Injection Sites on the Abdomen



The subject should be in a semi-reclined position during the injection (ie, semi-Fowler's position: 30-45°) and in a supine position immediately following injection for the evaluation of the injection site (ie, laying flat on back).

After the injection site for SC administration has been chosen, the investigational product will be administered as a single 4 mL SC injection as described briefly below.

- Wipe skin with alcohol to cleanse. Allow to dry.
- Gently pinch and lift the skin of the abdomen (ie, “tenting”).
- Insert the needle with bevel up close to parallel to the skin or at an angle that is $<20^\circ$. Once the needle is inserted, gently release the pinched and lifted skin (“untent the skin”). When the skin is in its normal state, the needle should have a slight upward angle of $20-30^\circ$. If the subject is obese, a steeper angle for needle insertion can be used but it is recommended keeping the angle $<45^\circ$. In practical terms, the needle placement should resemble the angle of an IV needle placement in the arm. The purpose of pinching and lifting the skin is to make sure the needle is properly inserted in the SC space and is not intradermal.
- Release the subcutaneous tissue. The needle will not back out during the injection if properly placed.
- Care should be taken to avoid inadvertent IV or IM injection.

It may be necessary to adjust the needle by pulling the needle slightly back if there appears to be a resistance to flow.

APPENDIX 3 WELLS PREDICTION RULE FOR THE DIAGNOSIS OF VENOUS THROMBEMBOLISM

Table A. Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Evaluation Table for Predicting Pretest Probability of Deep Venous Thrombosis^a

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general anesthesia or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

^a Clinical probability of deep venous thrombosis: Low= ≤0; Intermediate=1 to 2; High= ≥3. In patients with symptoms in both legs, the more symptomatic leg is used.

Data source: Qaseem et al. 2007

Table B. Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of Pulmonary Embolism^a

Clinical Characteristic	Score
Previous pulmonary embolism or deep venous thrombosis	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep venous thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3
Hemoptysis	+1
Cancer ^b	+1

^a Clinical probability of pulmonary embolism: Low=0 to 1; Intermediate=2 to 6; High= ≥7

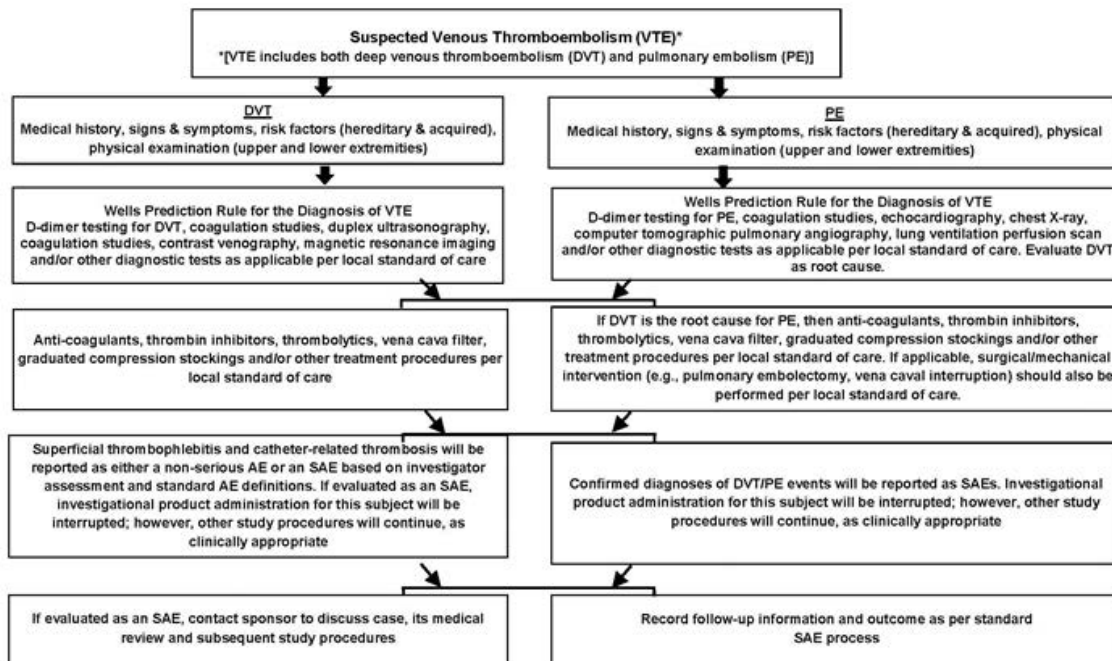
^b For the purposes of this study, cancer will include “treatment ongoing, within previous 6 months, or palliative.”

Data Source: Qaseem et al. 2007

Reference

Qaseem A, Snow V, Barry P, et al. 2007. Current diagnosis of venous thromboembolism in primary care: A clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Fam Med*; 146(6):454-58.

APPENDIX 4 ALGORITHM FOR SUSPECTED VENOUS THROMBOEMBOLISM



Note: In Germany, investigational product will be discontinued in any subject that experiences a venous thromboembolic event.

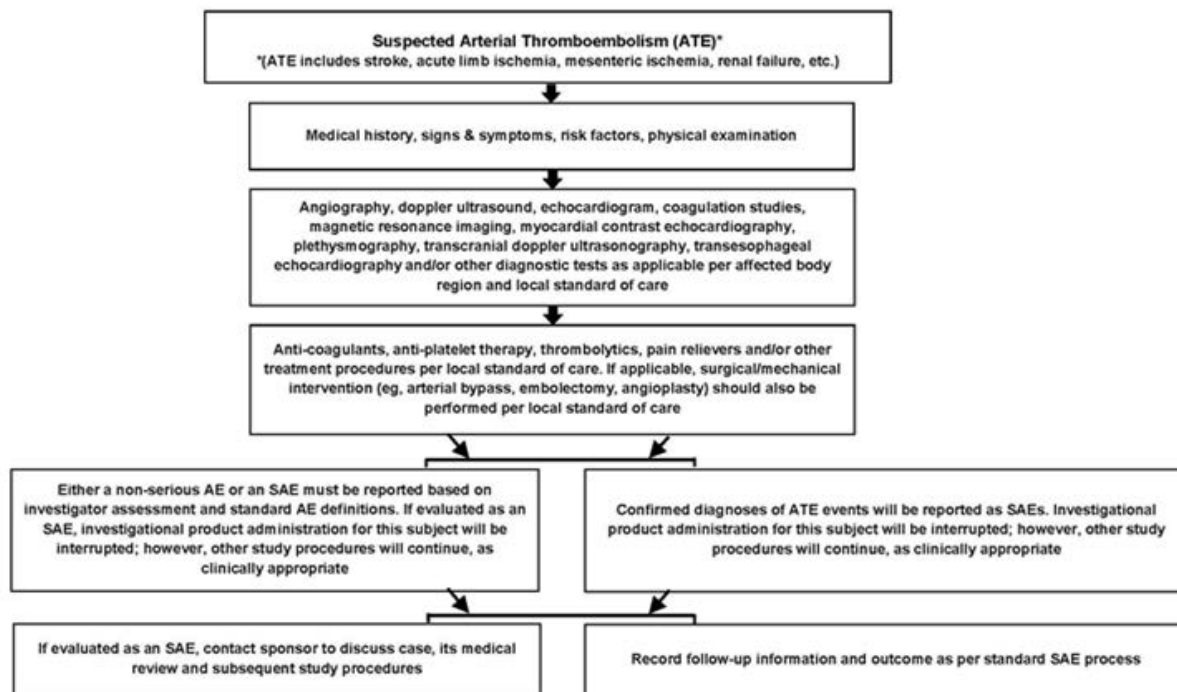
References

National Heart, Lung, and Blood Institute. Pulmonary embolism 2011. <http://www.nhlbi.nih.gov/book/export/html/4865>. Accessed May 11, 2015.

National Heart, Lung, and Blood Institute. Deep vein thrombosis 2011. <http://www.nhlbi.nih.gov/book/export/html/4871>. Accessed May 11, 2015.

Ozaki A, Bartholomew JR. Venous thromboembolism (deep venous thrombosis & pulmonary embolism). In: Carey WD, Rae-Grant A, Rimmerman C, ed. Disease Management Project. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/venous-thromboembolism>. Accessed May 11, 2015.

APPENDIX 5 ALGORITHM FOR SUSPECTED ARTERIAL THROMBOEMBOLISM



Note: In Germany, investigational product will be discontinued in any subject that experiences an arterial thromboembolic event.

References

National Library of Medicine. Arterial embolism 2014. <http://www.nlm.nih.gov/medlineplus/ency/article/001102.htm>. Accessed May 18, 2015.

Lyaker MR, Tulman DB, Dimitrova GT, Pin RH, Papadimos TJ 2013. Arterial embolism. *Int J Crit Illn Inj Sci*; 3(1): 77-87.

APPENDIX 6 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	28 May 2015	Global
Protocol Amendment 1	22 Jul 2015	Global
Protocol Amendment 2	03 Sep 2015	Global
Protocol Amendment 3	11 Jan 2016	Global
Protocol Amendment 2.1	14 Apr 2016	Country Specific (DE)
Protocol Amendment 3.1	20 Jun 2016	Country Specific (DE)

Amendment 1 to Protocol SHP616-300 incorporates the following major changes:

- Inclusion of final clinical data from Study SHP616-103, which are relevant to patient safety and the study rationale.
- The baseline angioedema attack rate required for study inclusion has been modified.
- Updates were made to some study procedures or requirements (eg, parent/legal guardian/caregiver performing and/or assisting an adolescent subject, photographs and measurements of injection site reactions, longitudinal follow-up to test for C1 INH antibody titers).

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) that have been made throughout the protocol are not reflected below.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 Jul 2015	Global/Country/Site Specific Global
Description of Change		Section(s) Affected by Change
Revised the title page to indicate that this will be a multicenter study.		Title page
Changed the baseline attack rate requirement for study entry from a history of ≥ 4 attacks per month average to ≥ 3 attacks per month average for inclusion criterion #3.		Synopsis Section 4.1
Corrected the secondary efficacy endpoint for the Angioedema Activity Score (AAS), to indicate the “98-day AAS” will be calculated in each treatment period.		Synopsis Section 9.8.2.2
Results from a statistical simulation showed that at least 25% of randomized subjects with a baseline attack rate of ≥ 4 per month average need to be included in the efficacy analysis population in order to detect a significant reduction (< 2) in NNA from baseline. This requirement was added to due the revision of the baseline attack rate from ≥ 4 to ≥ 3 in inclusion criterion #3.		Synopsis Section 3.1
A parent/legal guardian/caregiver will be allowed to administer		Synopsis

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 22 Jul 2015	Global/Country/Site Specific Global
Description of Change		Section(s) Affected by Change
investigational product to an adolescent subject during Treatment Period 2, after having received appropriate training and under the supervision of study site personnel or a qualified home health professional.		Section 3.1, Section 6.2, Section 6.5, Section 7.2.4.5
For adolescent subjects, a parent/legal guardian/caregiver is allowed to assist the subject in completing the electronic subject diary, including the quality of life questionnaires.		Synopsis Section 3.1
Updated sections to include the final clinical data (safety and pharmacokinetics) from Study SHP616-103.		Section 1.2, Section 1.2.1.1, Section 1.2.2.2
Modified the presentation of the PK results from Study 0624-206 to clarify dose selection.		Section 1.2.2.1
Modified text on dose selection and rationale for the study based on results from Study SHP616-103.		Section 1.2.2.3, Section 2.1
Clarified guidelines regarding the treatment of acute angioedema attacks with icatibant.		Section 5.2.1
Updated the details on subject randomization to specify that it will be conducted in two phases.		Section 6.3
Removed the request for subjects to participate in longitudinal follow-up for C1 INH antibody titers if they had anti-C1 INH antibodies detected in their plasma samples. If warranted, subjects may be requested to participate in follow-up of C1 INH antibody titers via a separate study protocol.		Section 7.1.5, Section 7.2.4.1
Removed the request for study personnel to obtain a digital photograph of severe injection site reactions and clarified that measurements of any erythema or swelling should be captured in the CRF.		Section 7.2.3.10
Clarified the collection period for AEs.		Section 8.1
Clarified the population of subjects (ie, those randomized to Treatment Sequence 1 [A/B] or 2 [B/A]) to be used in the evaluation of the efficacy of SC administration of C1 esterase inhibitor [human] liquid for injection compared to placebo.		Section 9.8.1, Section 9.8.2.2

Amendment 2 to Protocol SHP616-300 incorporates the following major changes:

- The inclusion and exclusion criteria regarding the attack rate and baseline prophylactic therapy was modified.
- A new exclusion criterion was added to prevent any changes of dose in hormonal products/therapies prior to study enrollment.
- Self-administration is now allowed in both treatment periods (1 and 2), under supervision and after receiving adequate training by the site or home health professional.
- Clarification added for the subjects who continue to have breakthrough attacks on the blinded investigational product despite receiving on-demand treatment for the management of angioedema attacks during the study.
- Added a section to clarify nonpharmacologic treatments and procedures.
- Added overall severity and duration assessment for injection site reactions.
- Number of subjects randomized in each of the three treatment sequences (A/B, B/A, A/A) was modified along with the statistical power calculations.
- Removed “achieving a NNA <2.0” as a secondary efficacy endpoint.

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) that have been made throughout the protocol are not reflected below.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
2	03 Sep 2015	Global
Description of Change		Section(s) Affected by Change
Revised the inclusion criterion # 3 to clarify the baseline prophylactic treatment requirement for both adults (≥ 18 yrs) and adolescents (>12 - <18 yrs).		Synopsis, Section 3.1 Section 4.1
Changed the baseline attack rate requirement for study entry from a history of ≥ 3 attacks per month average to ≥ 2 attacks per month average for inclusion criterion #3.		Synopsis, Section 3.1 Section 4.1
Exclusion criterion #1 was modified to only include adults.		Synopsis Section 4.2
Added exclusion criterion #2 for adolescents receiving prophylactic therapy with C1 INH.		Synopsis Section 4.2
Added exclusion criterion #5 to prevent females from changing the dose of any hormonal contraceptive regimen or hormone replacement therapy within 2 months prior to the screening visit.		Synopsis Section 4.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 03 Sep 2015	Global/Country/Site Specific Global
Description of Change		Section(s) Affected by Change
Authorized self-administration for subjects in both treatment periods, 1 and 2.		Synopsis, Section 3.1, Section 6.2 Section 6.5, Section 7.2.4.5
The self-administration survey was added to the assessment schedule for Treatment Period 1 for Visit 28a.		Table 1 Section 7.1.2.3
The period required for stabilization of hormonal contraceptives was revised from 30 days to 2 months prior to the screening visit.		Section 4.3.1
Added clarification on the management of angioedema attacks for subjects who continue to have breakthrough attacks on the blinded investigational product despite on-demand therapy.		Section 5.2.1
Added a section to clarify nonpharmacologic treatments and procedures and to request that subjects postpone elective procedures during the study.		Section 5.2, Section 5.2.3
Added overall assessment of severity and duration for injection site reactions, in the CRF.		Table 1, Table 2, Section 7.1.2.3, Section 7.1.3.3, Section 7.2.3.10
SAE reporting timeline was clarified to include 30 days after the last dose of investigational product.		Table 3, Section 8.2.4
Updated the new Medical Monitor for the study.		Protocol Signature Page, Emergency Contact Information section
Updated the HIV assay test from Western Blot to INNO-LIA.		Table 1, Section 7.2.3.5
Modified number of subjects randomized in each of the 3 treatment sequences (A/B, B/A, A/A).		Synopsis, Table 7, Section 6.3
Statistical power calculations were modified based on the change in the number of subjects randomized to each treatment sequence.		Section 9.6
Revised the secondary efficacy endpoint defining “clinical response to treatment” since one component (achieving a NNA <2.0) is no longer clinically meaningful given the study inclusion criterion is now ≥ 2 attacks. The corresponding secondary objective of the study has also been revised.		Synopsis, Section 2.2.2, Section 9.8.2.2

Amendment 3 to Protocol SHP616-300 incorporates the following major changes:

- Allow subjects (adolescent or adult) the option to self-administer investigational product with or without supervision after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present).
- Subjects who elect to self-administer investigational product will be instructed on investigational product transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Written instructions on investigational product and self-administration procedures will be provided to subjects at the screening or first dosing visit.
- Revised schedule for assessment of SC injection site reactions during Treatment Periods 1 and 2; the assessments will be less frequent and only occur when investigational product is administered at the investigative site. An overall assessment of the impact on daily living and duration of injection sites reaction will occur at the last visit of each treatment period.
- In order to prevent subjects from missing a scheduled dose of investigational product, additional guidance on the dosing interval has been provided.
- For subjects without documented C1 INH antigen level and/or C1 INH functional activity as part of eligibility criteria to confirm HAE diagnosis, a blood sample will be collected at screening and sent to a local or central laboratory (as appropriate).

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
3	11 Jan 2016	Global
Description of Change		Section(s) Affected by Change
Allow subjects (adolescent or adult) to self-administer investigational product with or without supervision (qualified home health professional and/or study site personnel) after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver is also allowed to administer investigational product to an adolescent subject with or without supervision.		Synopsis, Section 3.1, Section 6.2, Section 7.2.4.5
Information on self-administration of investigational product will be recorded in the electronic subject diary.		Synopsis, Section 3.1
Added Firazyr (icatibant) to exclusion criterion #8 to exclude subjects with a history of an allergic reaction to icatibant from entering the study.		Synopsis, Section 4.2
Revised schedule for assessment of SC injection site reactions to occur only when investigational product is administered at the investigative site		Table 1, Table 2, Section 7.1.2.3, Section 7.1.3.3,

(Visits 1, 8, 16, 24, and 28 in each treatment period). An overall assessment of the impact on daily living and duration of injection site reactions will occur at the last visit of each treatment period (Visit 28a and 28b).	Section 7.2.3.10
Updated safety endpoints and analyses to include the impact on daily living and duration of injection site reactions.	Synopsis, Section 9.9
In order to prevent subjects from missing a dose of investigational product (if the every 3 to 4 day interval cannot be followed), a less than 3-day interval may occur with the recommendation of allowing at least 24 hours between doses.	Synopsis, Section 3.1, Section 6.2
Vital sign measurements are not required at Visits 2, 3, and 4 in each treatment period for subjects self-administering investigational product without supervision (ie, assessment may not be possible).	Table 1, Table 2, Section 7.1.2.3, Section 7.1.3.3
A PK/PD predose blood sample at Visit 2a and 2b is not required for subjects self-administering investigational product without supervision (ie, collection of sample may not be possible).	Table 4, Section 7.1.2.3, Section 7.1.3.3
Provided details on the supply of commercial icatibant as rescue medication for the treatment of acute angioedema attacks. The product will be appropriately labeled for clinical trial use. Added recommended storage conditions for icatibant.	Section 5.2.1, Section 6.1
Subjects who self-administer investigational product (or when needed, icatibant as rescue medication) will be instructed on transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Added details on investigational product and ancillary supplies to be provided to subjects at investigational site. Written instructions on investigational product and self-administration procedures will be provided to subjects at the screening or first dosing visit (Visit 1a).	Section 6.5.1, Section 6.6
For subjects without documented C1 INH antigen level and/or C1 INH functional activity as part of eligibility criteria to confirm HAE diagnosis, a blood sample will be collected at screening and sent to a local or central laboratory (as appropriate). Repeat blood sampling is allowed if the test is non-confirmatory despite a suspected diagnosis of HAE.	Section 7.1.1, Section 7.2.3.1, Section 7.2.3.5
Clarified that injection site reactions resulting from the administration of icatibant (as rescue medication for acute angioedema attacks) will be reported as an AE with causality linked to icatibant.	Section 7.2.3.10
Added “and/or other study product (eg, icatibant)” to clarify how the relatedness of AEs is to be captured in the CRF.	Section 8.1.2
Updated product information for consistency with other patient instructions.	Appendix 1

Amendment 2.1 DE (Country-specific Amendment: Germany) to Protocol SHP616-300 incorporates the following changes:

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2.1	Amendment Date 14 Apr 2016	Global/Country/Site Specific Germany
Description of Change		Section(s) Affected by Change
Revised inclusion criteria to allow enrollment of only adult (>18 years) HAE patients.		Synopsis , Section 4.1
Added “not applicable to Germany” to exclusion criteria for adolescent subjects.		Synopsis , Section 4.2
Revised exclusion criteria to exclude subjects positive for hepatitis B, hepatitis C, or HIV infection; alcohol, drug, or medication abuse within 1 year before screening; or mental condition rendering the subject or parent(s)/legal guardian unable to understand the nature, scope of the study, and possible consequences of the study. Also excluding subjects with a relationship to study staff or sponsor (including people accommodated in an institution as well as people who are dependent on the sponsor, CRO, site or the investigator).		Synopsis , Section 4.2
Editorial revisions to clarify planned pharmacokinetic/pharmacodynamic analyses.		Synopsis , Section 9.10.1
Provided additional guidance on double-barrier methods of contraception.		Section 4.3.1
Added that mandatory discontinuation of investigational product would occur if the sponsor became aware of conditions that were unexpected, were significant, or posed an unacceptable risk to patients.		Sections 4.4 and 4.4.1
Added that if a thrombotic/thromboembolic event occurs in any subject, investigational product administration for that subject will be discontinued.		Section 4.4.4, Appendix 4 , Appendix 5
Added a section to define events of special interest for CINRYZE. Adverse events of special interest will be summarized as a part of the safety analyses.		Section 8.1.8, Section 9.9
Clarified that the sponsor may terminate the study if conditions arise which indicate that the clinical investigation should be halted due to an unacceptable patient risk.		Section 10.1.4

Other minor editorial revisions (including changes for consistency and clarity) have been made throughout the protocol.

Amendment 3.1 DE (Country-specific Amendment: Germany) to Protocol SHP616-300 incorporates the following major changes:

- Allow subjects (adolescent or adult) the option to self-administer investigational product with or without supervision after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present).
- Subjects who elect to self-administer investigational product will be instructed on investigational product transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Written instructions on investigational product and self-administration procedures will be provided to subjects at the screening or first dosing visit.
- Revised schedule for assessment of SC injection site reactions during Treatment Periods 1 and 2; the assessments will be less frequent and only occur when investigational product is administered at the investigative site. An overall assessment of the impact on daily living and duration of injection sites reaction will occur at the last visit of each treatment period.
- In order to prevent subjects from missing a scheduled dose of investigational product, additional guidance on the dosing interval has been provided.
- For subjects without documented C1 INH antigen level and/or C1 INH functional activity as part of eligibility criteria to confirm HAE diagnosis, a blood sample will be collected at screening and sent to a local or central laboratory (as appropriate).

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3.1	Amendment Date 20 Jun 2016	Global/Country/Site Specific Germany
Description of Change		Section(s) Affected by Change
Allow subjects (adolescent or adult) to self-administer investigational product with or without supervision (qualified home health professional and/or study site personnel) after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel is not present). Alternatively, a parent/legal guardian/caregiver is also allowed to administer investigational product to an adolescent subject with or without supervision.		Synopsis, Section 3.1, Section 6.2, Section 7.2.4.5
Information on self-administration of investigational product will be recorded in the electronic subject diary.		Synopsis, Section 3.1
Added FIRAZYR (icatibant) to exclusion criterion #8 to exclude subjects with a history of an allergic reaction to icatibant from entering the study.		Synopsis, Section 4.2
Revised schedule for assessment of SC injection site reactions to occur only when investigational product is administered at the investigative site (Visits 1, 8, 16, 24, and 28 in each treatment period). An overall assessment of the impact on daily living and duration of injection site reactions will occur at the last visit of each treatment period (Visit 28a and 28b).		Table 1, Table 2, Section 7.1.2.3, Section 7.1.3.3, Section 7.2.3.10
Updated safety endpoints and analyses to include the impact on daily living and duration of injection site reactions.		Synopsis, Section 9.9
In order to prevent subjects from missing a dose of investigational product (if the every 3 to 4 day interval cannot be followed), a less than 3-day interval may occur with the recommendation of allowing at least 24 hours between doses.		Synopsis, Section 3.1, Section 6.2
Vital sign measurements are not required at Visits 2, 3, and 4 in each treatment period for subjects self-administering investigational product without supervision (ie, assessment may not be possible).		Table 1, Table 2, Section 7.1.2.3, Section 7.1.3.3
A PK/PD predose blood sample at Visit 2a and 2b is not required for subjects self-administering investigational product without supervision (ie, collection of sample may not be possible).		Table 4, Section 7.1.2.3, Section 7.1.3.3
Removed double-barrier methods as an acceptable form of female contraception.		Section 4.3.1
Provided details on the supply of commercial icatibant as rescue medication for the treatment of acute angioedema attacks. The product will be appropriately labeled for clinical trial use. Added recommended storage conditions for icatibant.		Section 5.2.1, Section 6.1
Subjects who self-administer investigational product (or when needed, icatibant as rescue medication) will be instructed on transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Added details on investigational product and ancillary supplies to be provided to subjects at investigational site. Written instructions on investigational product and self-administration procedures will be provided to subjects at the screening or first dosing visit		Section 6.5.1, Section 6.6

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3.1	Amendment Date 20 Jun 2016	Global/Country/Site Specific Germany
Description of Change		Section(s) Affected by Change
(Visit 1a).		
For subjects without documented C1 INH antigen level and/or C1 INH functional activity as part of eligibility criteria to confirm HAE diagnosis, a blood sample will be collected at screening and sent to a local or central laboratory (as appropriate). Repeat blood sampling is allowed if the test is non-confirmatory despite a suspected diagnosis of HAE.		Section 7.1.1, Section 7.2.3.1, Section 7.2.3.5
Clarified that injection site reactions resulting from the administration of icatibant (as rescue medication for acute angioedema attacks) will be reported as an AE with causality linked to icatibant.		Section 7.2.3.10
Added “and/or other study product (eg, icatibant)” to clarify how the relatedness of AEs is to be captured in the CRF.		Section 8.1.2
Updated product information for consistency with other patient instructions.		Appendix 1