CINRYZE/PROTOCOL 0624-301

(Compound Number VP 20624)

A PHASE 3, MULTICENTER, RANDOMIZED, SINGLE-BLIND, DOSE-RANGING, CROSSOVER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF CINRYZE® (C1 ESTERASE INHIBITOR [HUMAN]) FOR THE PREVENTION OF ANGIOEDEMA ATTACKS IN CHILDREN 6 TO 11 YEARS OF AGE WITH HEREDITARY ANGIOEDEMA

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Amendment 2: 11 December 2013
Amendment 3: 02 June 2014
Amendment 4: 26 January 2015

PROTOCOL REVIEW AND APPROVAL FORM

SUBMISSION OF PROTOCOL 0624-301 WITH AMENDMENTS 1, 2, 3, AND 4

PRODUCT NAME (CODE): CINRYZE (VP 20624)

Title: **A PHASE 3, MULTICENTER, RANDOMIZED, SINGLE-BLIND, DOSE-RANGING, CROSSOVER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF CINRYZE® [C1 ESTERASE INHIBITOR (HUMAN)] FOR THE PREVENTION OF ANGIOEDEMA ATTACKS IN CHILDREN 6 TO 11 YEARS OF AGE WITH HEREDITARY ANGIOEDEMA**

26 January 2015

DEPARTMENT	NAME	SIGNATURE	DATE
Clinical Operations	, MS		
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-versus-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-versus-time curve from time 0 to infinity
$AUC_{0-\tau}$	Area under the plasma concentration-versus-time curve from time 0 to selected time point
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
C1 INH	C1 esterase inhibitor or C1 inhibitor
C_{avg}	Average concentration at steady state
CBC	Complete blood count
CHO	Chinese hamster ovary
CL	Clearance
CL/F	Apparent plasma clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRU	Clinical Research Unit
CT	Computer axial tomography
CTA	Clinical Trial Agreement
DC	Discontinuation
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic study diary
EDTA	Ethylenediaminetetraacetic acid
ER	Emergency room
EU	European Union
F	Fahrenheit; Bioavailability
FDA	Food and Drug Administration
h, hr	Hour(s)
HAE	Hereditary angioedema
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonisation
ID	Intradermal
IEC	Independent Ethics Committee
INR	International normalized ratio
IRA	Independent Reviewing Authority (e.g., Institutional Review Board or Independent Ethics Committee)

Abbreviation	Definition
ISR	Incurred sample reproducibility
ISS	Incurred sample stability
ITT-E	Intent-to-Treat Efficacy (population)
ITT-S	Intent-to-Treat Safety (population)
IUD	Intrauterine device
IV	Intravenous
IXRS	Interactive voice and web response system
K_{el}	Elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mM	Millimolar
mOsmol	Milliosmole
n, N	Sample size
NA	Not applicable
NDA	New Drug Application
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
PEG	Polyethylene glycol
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetic(s)
PT	Prothrombin time
QoL	Quality of life
RBC	Red blood cells
R_{max}	Maximum pharmacodynamic response
RSI	Reference safety information
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
SPC, SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
SWFI	Sterile water for injection
T/TE	Thrombotic/thromboembolic
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent AE
t_{max}	Time to maximum concentration or maximum pharmacodynamic response
TX	Treatment
U	Unit(s)
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
VAS	Visual analogue scale
V/Q	Ventilation/perfusion scan
VTE	Venous thromboembolism
V_z/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

NOTE: Table includes comprehensive list of abbreviations used in CINRYZE regulatory documents.

AMENDMENT 4: 26 JANUARY 2015

Amendment 4 to Protocol 0624-301 incorporates revisions related to study drug reconstitution and administration. An administrative look will occur following the completion of the first 6 subjects. Safety, efficacy and pharmacokinetics results will be reviewed, summarized and presented in a clinical study report. This study report will serve as the basis for a regulatory submission to satisfy the EU Pediatric Investigation Plan. In addition, text has been added to Section 3.0 (Investigational Plan), to allow the flexibility of adding countries or regions if necessary to complete enrollment. This amendment also incorporates Administrative Revision 1 (dated 25 September 2014) which updated the protocol title page with the contact information of the new medical monitor (PPD , MD) for this study.

1. Study Drug Administration:

European Investigators recommended revising the protocol language to allow more flexibility regarding study drug administration. Amendment 3 specifies that CINRYZE treatments will be prepared and administered by qualified site personnel or qualified home healthcare professionals. Physicians have shared their experience in the pediatric population and have indicated that pediatric patients aged 6-11 who they see in routine practice often self-administer (after training) or have a parent administer C1 Inhibitor (C1 INH) treatment (after training). These Investigators have indicated that pediatric patients who currently self-administer, or who are routinely administered treatment by a non-healthcare professional (e.g., parent), will not agree to enter a study requiring that study site personnel or home healthcare professionals administer the treatment for the study.

Therefore, Amendment 4 incorporates the following changes:

- Clarifies that home healthcare professionals may prepare study drug at the subject's home.

- Allows self-administration of study drug for subjects who self-administer C1 INH in routine practice and who want to continue to do so in this study. If a subject who does not routinely self-administer would like to begin this practice, this will be permitted and appropriate training will be provided by the study site personnel.

- Allows administration of study drug by trained non-healthcare professionals (e.g., parent, legal guardian) for subjects in whom this occurs in routine practice and where the preference is to continue to do so. If a non-healthcare professional (e.g., parent, legal guardian) who does not routinely administer C1 INH would like to begin this practice, it will be permitted and appropriate training will be provided by the site.

Regardless of self-administration or administration by a non-healthcare professional, all study drug will be administered under the supervision of qualified healthcare personnel (i.e., if study drug is self-administered, or administered by a non-healthcare professional, a qualified healthcare professional will always be present). Investigators will use their clinical judgment and knowledge of the home situation to determine whether self-administration or administration by a non-healthcare professional is in the best interest of the pediatric subject.

Added text is **bolded** and deleted text is ~~struck through~~, as applicable.

All protocol sections affected by the amendment are noted below, and the synopsis and schedules of procedures have been updated accordingly.

3.0 INVESTIGATIONAL PLAN

This multicenter, randomized, single-blind, dose-ranging, crossover study will be conducted in multiple countries including the US, EU, and Latin America. **Other countries/regions may be added if necessary to complete enrollment.**

Subjects and parents/caregivers will be blinded to treatment sequence and dose. Study site personnel, qualified home healthcare professionals, and the Sponsor will not be blinded to treatment assignment and the dose of study drug administered. Study drug will be prepared and administered intravenously by qualified personnel at the investigational site, or by qualified home healthcare professionals at the subject's home or other agreed upon location. **Alternatively, if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g., parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator. Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device, compression and applying a bandage to the injection site, and disposal of all infusion materials.**

For those subjects who are administered study drug **at a location other than the study site ~~by home healthcare professionals~~**, study personnel will contact the parent/caregiver by telephone twice during each treatment period (Week 3 after Dose 6 [Visits 6a and 6b] and Week 9 after Dose 18 [Visits 18a and 18b]).

5.3 Study Drug

See Section 8.0 for a complete description of study drug. Instructions for the reconstitution of CINRYZE are provided in a separate Pharmacy Manual. CINRYZE treatments will be prepared and administered by qualified study site personnel or qualified home healthcare professionals. **Home healthcare professionals may prepare and administer CINRYZE treatments at the subject's home. Alternatively, if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g., parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator). Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device, compression and applying a bandage to the injection site, and disposal of all infusion materials.**

7.0 STATISTICAL METHODOLOGY

An administrative look will occur following completion of the first 6 subjects. Safety, efficacy and pharmacokinetic results will be reviewed, summarized and presented in a clinical study report. This study report will serve as the basis for a regulatory submission to satisfy the EU Pediatric Investigation Plan. A final CSR will be completed after 12 subjects finish the study.

AMENDMENT 3: 02 JUNE 2014

Amendment 3 to Protocol 0624-301 incorporates 2 revisions:

1. European Investigators recommended that a modification be made to the angioedema attack criteria qualifying subjects for study inclusion. Physicians may opt to provide early intervention with acute treatment when the attack is considered mild to minimize the risk of subsequent complications with ongoing severity. Therefore to allow angioedema attacks that require acute treatment to qualify, inclusion criteria #3 and #6 have been modified.

2. Investigators requested clarification of the analytical tests performed on blood samples collected from subjects when they present to the investigator site with an angioedema attack.

Added text is bolded and deleted text is ~~struck through~~, as applicable.

All protocol sections affected by the amendment are noted below, and the synopsis and schedules of procedures have been updated accordingly.

Section 4.1, Inclusion Criteria

Inclusion Criteria

3. Have a history of ≥1.0 **angioedema attacks per month (average) that are** moderate[1] or severe[2] **or require acute treatment[3]** ~~angioedema attacks per month (average)~~ during the 3 consecutive months prior to screening.

Additional Inclusion Criteria (Qualifying for Randomization)

6. Have experienced ≥1.0 **angioedema attacks per month (average) that are** moderate[1] or severe[2] **or require acute treatment[3]** ~~angioedema attacks per month (average)~~ during the 12-week baseline observation period.

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1 Moderate: Angioedema attack sign/symptom(s) interferes with the subject's ability to attend school or participate in family life and social/recreational activities.

2 Severe: Angioedema attack sign/symptom(s) significantly limits the subject's ability to attend school or participate in family life and social/recreational activities.

3 'Treatment' refers specifically to standard of care therapies used to treat an angioedema attack (e.g., C1 INH, kallikrein inhibitor, bradykinin receptor antagonist). Products used for the treatment of attack symptoms (e.g., analgesics, anti-emetics) do not qualify for this study inclusion criterion.

Section 6.6, Pharmacokinetic, Pharmacodynamic, and C1 INH Antibody Analyses

NOTE: If a subject presents to the site with an angioedema attack, every effort should be made to obtain a PK blood sample prior to any treatment. In addition, if the subject is treated with commercial C1 INH, every effort should be made to obtain a 1-hour post-treatment sample. **These samples will be analyzed for C1 INH antigen and functional C1 INH activity.**

Other administrative revisions (e.g., updating Sponsor's contact information) and editorial revisions have been made throughout the protocol for consistency.

AMENDMENT 2: 11 DECEMBER 2013

Amendment 2 to Protocol 0624-301 encompasses three revisions. Added text is bolded and deleted text is struck through, as applicable.

- Exclusion Criterion #7 (Synopsis and Section 4.2), has been revised since some of the temperature conversions were incorrect:

  7. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F) tympanic >38.5°C (101.~~2~~**3**°F), axillary >38.~~1~~°C (100.~~64~~°F) or rectal/core >3~~9~~**8.5**°C (101.~~2~~**3**°F) within 24 hours prior to the first dose of study drug in Treatment Period 1.

- In Section 8.1, the storage conditions for CINRYZE have been corrected to be consistent with the US product label:

  The US sourced **vials of** CINRYZE ~~and SWFI~~ will be stored at ~~20°C–25°C (68°F–77°F)~~ **2°C–25°C (36°F–77°F)** ~~in the original carton~~ and protected from light. **Do not freeze.**

- Appendix I (Reconstitution of CINRYZE) and all references throughout the protocol to this Appendix have been removed. Subsequent appendices were renumbered. Instructions for the reconstitution of CINRYZE will be detailed in a separate Pharmacy Manual.

AMENDMENT 1: 09 OCTOBER 2013

Amendment 1 to Protocol 0624-301 encompasses nine substantive revisions:

- In Schedule 3 (Clinical Study Assessments – Treatment Period 2), footnote "h" has been added to clarify that if an angioedema attack is ongoing at Visit 24b, then recording of signs and symptoms and completing the EQ-5D-Y should continue daily in the eDiary until the attack resolves.

- In Schedule 5 (Blood Sample Collection for PK/PD and Post-treatment Immunogenicity Assessments), two blood sampling time points have been corrected; the Post-dose time point was incorrectly noted as Dose 1 rather than Dose 12.

  Treatment Period 1 – Visit 12a / Dose 12
  Post-dose time point should be 1 h post Dose **12** (± 15 min)

  Treatment Period 2 – Visit 12b / Dose 12
  Post-dose time point should be 1 h post Dose **12** (± 15 min)

- In the Synopsis, Section 6.9 (Electronic Study Diary), and Section 6.11.1 (Health-related Quality of Life), text has been revised to state that the EQ-5D-Y (QoL assessment) is to be completed by subjects and not by parents or caregivers, as was stated in the original protocol. The EQ-5D-Y is designed to be a self-reported questionnaire for children and adolescents.

- In the Synopsis and Section 6.10 (Angioedema Attacks), the definition of an angioedema attack has been revised to clarify that there must be a "full symptom-free calendar day" preceding the onset of symptoms for an attack to be considered a new attack. The original protocol stated that there was to be a "24-hr symptom-free interval", however only the date (not time) of symptom onset and resolution for an angioedema attack is to be recorded.

- In Sections 3.0 (Investigational Plan), 6.9 (Electronic Study Diary), and 6.11.1 (Health-related Quality of Life), information about integration of eDiary/QoL data into the eCRF has been deleted; details about handling of these data will be provided in a separate Data Management Plan.

- In Section 6.3.2 (Concomitant Medication), the requirement for study personnel to record the start and stop "time" of medications administered in the management of angioedema attacks has been deleted.

- In Section 6.9 (Electronic Study Diary), the details on all questions contained within the eDiary have been deleted. Instead there is a general high level description of the information to be collected and the responsibility of the parent/caregiver and subject to complete this information in the eDiary. At the

screening visit, study personnel will instruct subjects and parents/caregivers how to complete the eDiary.

- In Section 6.10.1 (Recording of Angioedema Attacks), "Other (describe)" has been deleted as option for the location (site) of the swelling or pain associated with an angioedema attack.

- In Section 6.12 (Discontinuation From Treatment and/or Study), the sentence referring to the possibility of enrolling additional subjects to replace subjects who withdraw or discontinue has been removed. This referred to a scenario when the plan was to enroll a sufficient number of subjects (8) to ensure that 6 would complete the study. Per request from the FDA, the protocol now states that the target enrollment is 12 subjects and the Sponsor believes that it would be neither necessary nor realistic to address the issue of replacing subjects who drop out of the study.

Other editorial revisions have been made to the schedules of clinical assessments to clarify study procedures and also throughout the protocol for consistency with the nine revisions noted above. In addition, CINRYZE recently received marketing authorization in Israel (August 2013); this information has been added to Sections 1.1 and 1.2.

PROTOCOL SYNOPSIS

Study Title: A phase 3, multicenter, randomized, single-blind, dose-ranging, crossover study to evaluate the safety and efficacy of intravenous administration of CINRYZE® (C1 esterase inhibitor [human]) for the prevention of angioedema attacks in children 6 to 11 years of age with hereditary angioedema (Protocol 0624-301).

Study Objectives:

Primary Objective

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

Secondary Objectives

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

Other Objective

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

Study Population:

Number of Subjects

Twelve subjects will be randomized in this study.

Inclusion Criteria

To be eligible for this protocol, a subject must:

1. Be a child (male or female), ≥6 to <12 years of age at the time of screening.
2. Have a confirmed diagnosis of Type I or Type II HAE and have a functional C1 inhibitor (C1 INH) level less than 50% of normal.

3. Have a history of ≥1.0 angioedema attacks per month (average) that are moderate[1] or severe[2] or require acute treatment[3] during the 3 consecutive months prior to screening.
4. Agree to adhere to the protocol-defined schedule of assessments and procedures.
5. 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).

Additional Inclusion Criteria (Qualifying for Randomization)

6. Have experienced ≥1.0 angioedema attacks per month (average) that are moderate[1] or severe[2] or require acute treatment[3] during the 12-week baseline observation period.

Exclusion Criteria

To be eligible for this protocol, a subject must not:

1. Have a history of hypercoagulability (abnormal blood clotting).
2. Have a diagnosis of acquired angioedema or known to have C1 INH antibodies.
3. Have a history of allergic reaction to C1 INH products, including CINRYZE (or any of the components of CINRYZE), or other blood products.
4. Be pregnant or breastfeeding.
5. Have received an investigational drug other than those required for prevention or treatment of angioedema attacks within 30 days prior to screening.
6. Have, as determined by the Investigator and the Sponsor's medical monitor, any surgical or medical condition that could interfere with the administration of study drug or interpretation of study results.

Additional Exclusion Criteria (Disqualifying from Randomization)

7. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in Treatment Period 1.

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[1] Moderate: Angioedema attack sign/symptom(s) interferes with the subject's ability to attend school or participate in family life and social/recreational activities.

[2] Severe: Angioedema attack sign/symptom(s) significantly limits the subject's ability to attend school or participate in family life and social/recreational activities.

[3] 'Treatment' refers specifically to standard of care therapies used to treat an angioedema attack (e.g., C1 INH, kallikrein inhibitor, bradykinin receptor antagonist). Products used for the treatment of attack symptoms (e.g., analgesics, anti-emetics) do not qualify for this study inclusion criterion.

8. Have had signs or symptoms of an angioedema attack within 2 days prior to the first dose of study drug in Treatment Period 1.

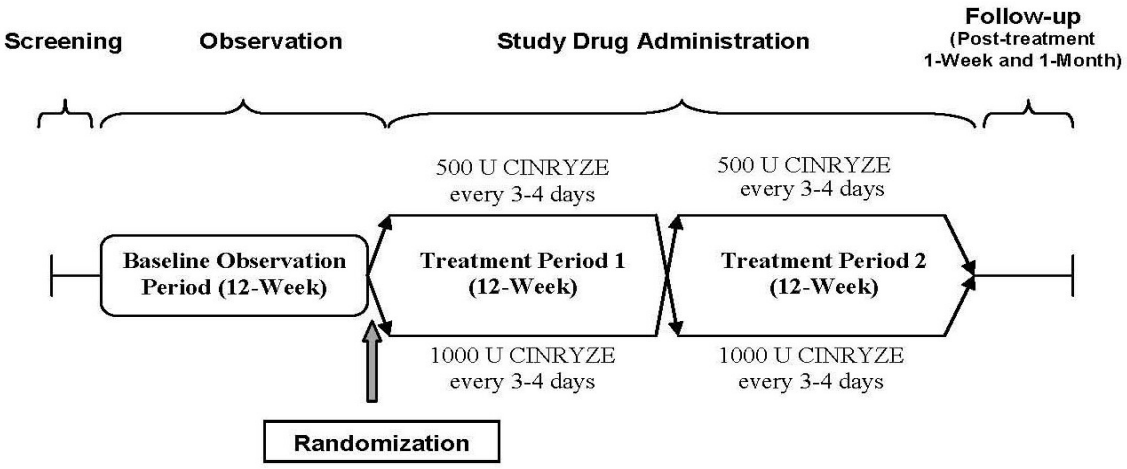
Duration of Study: Individual participation from screening through the completion of 1-month safety follow-up visit will be approximately 10 months (1-day screening visit, 12-week baseline observation period, two 12-week treatment periods [consecutive without any washout between treatment periods], and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

Drug Product: CINRYZE is supplied as a lyophilized powder of 500 Units (U) C1 INH per vial. Each vial of CINRYZE will be reconstituted for IV infusion with 5 mL of sterile water. Each infusion will require reconstitution of one (1) or two (2) 500 U vials depending on the treatment scheduled (Treatment A [500 U] or Treatment B [1000 U]). The solution must be used within 3 hours of reconstitution.

Study Drug Administration: CINRYZE (500 U or 1000 U) will be administered by IV injection twice weekly (every 3 or 4 days) for 12 weeks in two crossover treatment periods. Study drug will be administered intravenously by qualified healthcare personnel at the investigational site or at a location outside of the investigative site (e.g., home). Alternatively, if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g., parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator). Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device, compression and applying a bandage to the injection site, and disposal of all infusion materials.

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

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



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

Throughout the study, an electronic study diary (eDiary) will be used to collect specific information regarding the subject's symptoms of HAE. The eDiary will consist of two sections:

(a) Section to record daily if any elective procedures have been performed, signs and symptoms of angioedema attacks, triggers for angioedema attacks, medications used for the management of angioedema attacks, and interruptions in activities of daily living due to an angioedema attack. Section (a) is to be completed by the parent/caregiver, and when possible, the same parent/caregiver should be responsible for completing this section of the eDiary throughout the study.

(b) Section to record the impact of HAE on quality of life (EQ-5D-Y). Section (b) is to be completed by the subject at specified time points throughout the study **and on each day the subject experiences signs or symptoms of an angioedema attack**.

Study personnel will contact the parent/caregiver by telephone bi-weekly (Weeks 2, 4, 6, 8, 10, and 12) during the baseline observation period to discuss study compliance (completion of the eDiary daily) and to evaluate the subject's angioedema attack frequency (Schedule 1).

During the baseline observation period, subjects are allowed to remain on any prophylactic HAE therapy they were receiving prior to study enrollment, if clinically indicated. However, it is recommended that consideration by the Investigator be given to discontinuing subjects from any prophylactic antifibrinolytic or androgen therapy during the first 6 weeks of the observation period. If these medications cannot be discontinued, stable doses should be used during Treatment Periods 1 and 2. At least 3 days prior to first dose of study drug, subjects receiving commercial C1 INH for prevention of attacks must discontinue this therapy.

In the event that during the 12 weeks of baseline observation subjects do not meet the attack criteria qualifying for randomization (≥1.0 angioedema attacks per month [average] that are moderate or severe or require acute treatment), despite having met this same criteria historically for study enrollment, additional weeks of observation will be considered at the discretion of the Investigator and Sponsor to allow qualification for randomization and entry into the treatment periods of the study. In this case, subjects will maintain the same schedule of assessments by beginning at Week 1 again for the additional weeks of observation (Schedule 1).

After the completion of the baseline observation period, subjects who remain eligible per study criteria will be randomized to one of two treatment sequences, with each sequence consisting of two treatment periods. In Treatment Period 1, subjects will receive CINRYZE at a dose of either 500 U or 1000 U IV twice weekly (every 3 or 4 days), depending upon their randomized assignment. After completion of the first treatment period, subjects will immediately crossover to the alternate CINRYZE dose and begin Treatment Period 2.

This is a single-blind study. Subjects and parents/caregivers will be blinded to the treatment administered. Study site personnel, home healthcare professionals, and the Sponsor will not be blinded to dose and treatment sequence. Study drug will be administered intravenously by qualified personnel at the investigational site, or by qualified home healthcare professionals at the subject's home or other agreed upon location. Alternatively if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g. parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator). Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device, compression and applying a bandage to the injection site, and disposal of all infusion materials.

The Investigator or designee will monitor and document study compliance, tolerability of each CINRYZE dose, and adverse events. The following doses of study drug in each treatment period must be administered at the investigational site: Dose 1 (Visits 1a and 1b, where a=treatment period 1 and b=treatment period 2), Dose 12 (Visits 12a and 12b) and Dose 24 (Visits 24a and 24b). At these visits, subjects will also have other scheduled procedures performed (Schedules 2 and 3). For those subjects who are administered study drug at a location other than the study site, study personnel will contact the parent/caregiver by telephone twice during each treatment period (Week 3 after Dose 6 [Visits 6a and 6b] and Week 9 after Dose 18 [Visits 18a and 18b]). If study drug is administered at the site (Doses 6 and 18), no telephone contact is necessary.

To the extent possible, subjects will postpone elective procedures (e.g., dental work) while participating in the study. In the event a procedure cannot be postponed, parents/caregivers will notify the Investigator and the information will be recorded in the subject's eCRF.

A post-treatment visit will be performed at the investigative site 1 week (±2 days) after the last dose of study drug for follow-up safety assessments. In addition, subjects will have a blood sample for C1 INH antibody testing collected 30 (±2) days after the last dose of study drug. If a subject discontinues prematurely from treatment and/or the study, the Investigator will perform the early discontinuation visit safety procedures as soon as possible (Schedule 4). For those subjects who discontinue prematurely from treatment, every effort should be made to complete protocol evaluations for the 1-month post-treatment follow-up visit.

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

- **Schedule 1:** Clinical study assessments – Screening and Baseline Observation Period (Weeks 1 to 12).
- **Schedule 2:** Clinical study assessments –Treatment Period 1 (Visits 1a to 24a).
- **Schedule 3:** Clinical study assessments – Treatment Period 2 (Visits 1b to 24b).
- **Schedule 4:** Clinical study assessments – Early Discontinuation, 1-week Post-treatment, and 1-month Post-treatment Follow-up Visits.
- **Schedule 5:** Blood sample collection – PK/PD and post-treatment immunogenicity assessments.

Definition of an Angioedema Attack

An angioedema attack will be defined as any subject-reported (or parent/caregiver-reported) indication of swelling or pain at any location following a report of no swelling or pain on the previous day (i.e., 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 one site to another will be considered a single attack,
- Attacks that begin to regress and then worsen before complete resolution will be considered one attack, and
- 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 one attack.

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

Management of Angioedema Attacks

If a subject experiences an angioedema attack that in the opinion of the healthcare provider requires medical intervention, the choice of acute treatment will be left to the Investigator's

discretion. Where appropriate, CINRYZE can be provided for acute treatment of angioedema attacks.

If a subject has an angioedema attack at any time during any study treatment period, study drug administration and study procedures will continue for that subject adhering to the study schedule, regardless of whether C1 INH therapy or other products were administered to treat the attack.

NOTE: If a subject presents to the site with an angioedema attack, every effort should be made to obtain a PK blood sample prior to any treatment. In addition, if the subject is treated with commercial C1 INH, every effort should be made to obtain a 1-hour post-treatment sample. These samples will be analyzed for C1 INH antigen and functional C1 INH activity.

To the extent possible during the study, subjects should avoid any stimuli (e.g., foods, activities, environments) known to trigger their angioedema attacks. Otherwise, subjects may maintain their normal diets, medications, and activities of daily living.

Safety Monitoring

Safety will be monitored through the recording of adverse events (AEs) and any changes in medical history, physical examinations, vital signs, and clinical safety laboratory testing (hematology, chemistry, and coagulation). Testing of blood samples for clinical laboratory parameters will be performed at a Central Laboratory.

Investigators will report all serious adverse events (SAEs) occurring up to 30 days after the last dose of study drug to Shire ViroPharma and their respective IRA according to local reporting requirements. In addition, SAEs with an onset more than 30 days after the last dose of study drug should be reported if considered by the Investigator to be related to study drug.

Stopping Rules

If an anaphylactic reaction or a thrombotic or thromboembolic event occurs in any subject, pre-specified stopping rules for individual subjects and for the study as a whole are detailed in Section 5.5 of the protocol.

Monitoring for C1 INH Antibodies

Blood samples will be obtained from subjects prior to the first dose of study drug in each treatment period, 1 week post-treatment (or if prematurely discontinued), and at the 1-month post-treatment follow-up visit to monitor for C1 INH antibodies (see Schedules 2, 3, 4, and 5).

Pharmacokinetics and Pharmacodynamics

Blood samples for PK (functional and antigenic C1 INH) and PD (complement C4) assessments will be collected at pre-specified time points in both treatment periods (see Schedule 5).

Quality of Life Measurements

EQ-5D-Y[1] (Youth version of EQ-5D) is a descriptive system of youth health-related quality of life states consisting of five dimensions each of which can have one of three responses. The responses record the level of severity within a particular EQ-5D dimension. EQ-5D-Y is not intended for use in children 6 years of age; however in this study all subjects (6 to 11 years of age and where translated language version is available) will be assessed. The EQ-5D-Y will be completed by the subject at the time points specified in Schedules 1, 2, 3, and 4, as well as on each day that a subject experiences signs or symptoms of an angioedema attack.

Statistical Considerations:

Sample Size: Twelve subjects will be randomized in this study. Subjects will be randomized to one of two treatment sequences so that upon completion of the study, each subject will have received both dose levels of CINRYZE (500 U and 1000 U). Based on the EU Pediatric Investigation Plan, an administrative look for regulatory purpose may be completed after 6 patients have finished the study. A final CSR will be completed after 12 subjects finish the study.

Primary efficacy endpoint: The primary efficacy endpoint is the number of angioedema attacks normalized to a 12-week treatment period. This endpoint will be measured for each subject in each treatment period.

Secondary efficacy endpoints:

The following will be measured for each subject in each treatment period:

- 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.
- Time (measured in days from the first dose of study drug in a treatment period) to the first angioedema attack reported in that treatment period.
- Change from pre- to post-dose in C1 INH functional activity, C1 INH antigen, and C4 levels.
- Number of angioedema attacks requiring acute treatment during each treatment period.

Analysis of efficacy endpoints will employ descriptive statistics and will include all subjects randomized and treated with study drug.

If warranted by the data, the comparison of CINRYZE doses will employ a paired t-test to perform a two-sided test of superiority (1000 U vs. 500 U) conducted at α=0.10.

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

Safety Endpoints:

The following will be assessed during the study:

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

PK/PD Endpoints:

- Concentrations of C1 INH antigen, functional C1 INH activity, and complement C4 for individual subjects will be determined using validated analytical methods. Results will be summarized using descriptive statistics for values at each time point and for change from baseline at each post-injection time.

Other Endpoints:

- Results of the EQ-5D-Y health status questionnaire will be presented in accordance with the EQ-5D-3L User Guide (version 4.0[1]), and adapted as appropriate for the youth version.

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

SCHEDULE 1: CLINICAL STUDY ASSESSMENTS – SCREENING AND BASELINE OBSERVATION PERIOD

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

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

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

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

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

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

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

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

SCHEDULE 2: CLINICAL STUDY ASSESSMENTS – TREATMENT PERIOD 1

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

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

a: Study drug administration and scheduled procedures will occur twice weekly (every 3 or 4 days) during the 12-week treatment period (Treatment Period 1, Visits 1a-24a).
b: Specified study procedures and blood samples should be performed/collected prior to study drug administration, on the same day.
c: Randomization will occur on Dosing Day 1 (Visit 1a) prior to the first dose of study drug in Treatment Period 1.
d: Medical history will be updated prior to randomization at Visit 1a. Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.
e: Vital signs will be measured using standard methods at each study site. On dosing days, vital signs should be obtained prior (within 60 minutes) to the injection of study drug and between 10 to 30 minutes after completion of the injection of study drug. Additional vital signs measurements may be performed if clinically indicated.
f: Body temperature should be measured prior to randomization at Visit 1a.
g: HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).
h: Pregnancy testing (urine) will be performed on females who have reached menarche.
i: Study drug will be administered by/under supervision of qualified personnel to all subjects at the investigational site for Dosing Visits 1a, 12a, and 24a.
j: For those subjects who are administered study drug at a location other than the study site, study personnel will contact the parent/caregiver by telephone on Weeks 3 and 9 (after Dosing Visits 6a and 18a, respectively) to discuss and document study compliance, tolerability of CINRYZE dose, and adverse events. All telephone contacts will be documented in the source notes at the clinical site.
k: **In addition, subjects should complete the EQ-5D-Y on each day that they experience signs or symptoms of an angioedema attack.**

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

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

SCHEDULE 3: CLINICAL STUDY ASSESSMENTS – TREATMENT PERIOD 2

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

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

a: Study drug administration and scheduled procedures will occur twice weekly (every 3 or 4 days) during the 12-week treatment period (Treatment Period 2, Visits 1b-24b).
b: Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.
c: Vital signs will be measured using standard methods at each study site. On dosing days, vital signs should be obtained prior (within 60 minutes) to the injection of study drug and between 10 to 30 minutes after completion of the injection of study drug. Additional vital signs measurements may be performed if clinically indicated.
d: Specified study procedures and blood samples should be performed/collected prior to study drug administration, on the same day.
e: Study drug will be administered by/under supervision of qualified personnel to all subjects at the investigational site for Dosing Visits 1b, 12b, and 24b.
f: For those subjects who are administered study drug at a location other than the study site, study personnel will contact the parent/caregiver by telephone on Weeks 3 and 9 (after Dosing Visits 6b and 18b, respectively) to discuss and document study compliance, tolerability of CINRYZE dose, and adverse events. All telephone contacts will be documented in the source notes at the clinical site.
g: **In addition, subjects should complete the EQ-5D-Y on each day that they experience signs or symptoms of an angioedema attack**.
h: If an angioedema attack is ongoing at Visit 24b, then recording of signs and symptoms and completing the EQ-5D-Y should continue daily until the attack resolves.

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

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

SCHEDULE 4: CLINICAL STUDY ASSESSMENTS – EARLY DISCONTINUATION, 1-WEEK POST-TREATMENT, AND 1-MONTH POST-TREATMENT FOLLOW-UP VISITS

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

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

a: Early discontinuation visit will be performed as soon as possible in the event a subject prematurely discontinues from treatment and/or the study. For those subjects who discontinue prematurely from treatment, every effort should be made to complete protocol evaluations for the 1-month post-treatment follow-up visit.
b: 1-Week post-treatment visit will be performed at the investigational site 1 week (±2 days) after the last dose of study drug.
c: 1-Month post-treatment follow-up visit will be performed 30 (±2) days after the last dose of study drug.
d: Physical examinations will be targeted based on reporting of adverse events and performed in accordance with standards at the site.
e: Vital signs will be measured using standard methods at each investigational site.
f: Pregnancy testing (urine) will be performed on females who have reached menarche.
g: HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

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

SCHEDULE 5: BLOOD SAMPLE COLLECTION FOR PK/PD AND POST-TREATMENT IMMUNOGENICITY ASSESSMENTS

TREATMENT PERIOD 1

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

TREATMENT PERIOD 2

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

NOTE: If a subject presents to the investigational site with an angioedema attack, every effort should be made to obtain a PK blood sample prior to any treatment. In addition, if the subject is treated with commercial C1 INH, every effort should be made to obtain a 1-hour post-treatment sample. These samples will be analyzed for C1 INH antigen and functional C1 INH activity.

POST-TREATMENT

Visit	Blood Sampling Time Points Immunogenicity (C1 INH antibody)
1-week post-treatment	1 week (± 2 days) after the last dose of study drug
1-month post-treatment	30 (± 2) days after the last dose of study drug

1.0 INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disease resulting from mutations of the C1 inhibitor (C1 INH) gene and deficient plasma C1 INH protein. Nearly all affected individuals experience symptoms of the disease; however, the symptoms vary in both their frequency and severity (Gompels et al., 2005; Zuraw, 2003). 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. A low level of C4 in combination with a low level of either C1 INH antigen (Type I HAE) or functional C1 INH (Type II HAE) are confirmatory for the diagnosis of HAE (Frank et al., 1976). In rare instances, C4 levels may be normal in HAE patients between attacks, but are almost always decreased during episodes of HAE swelling (Frank et al., 1976). In this circumstance, a low serum C4 level during an episode of idiopathic swelling can be used to confirm the diagnosis of HAE (Frank et al., 1976; Waytes et al., 1996).

Attacks of HAE are usually self-limiting, but can be quite painful, disfiguring, disabling, and sometimes fatal. Edema can involve the skin and visceral organs, but most frequently manifests in the extremities or bowel; the swelling generally lasts 2 to 5 days (Nzeako et al., 2001; Zuraw, 2008). Abdominal attacks have been reported to occur in >93% of patients and account for nearly 50% of all angioedema attacks (Zuraw, 2008). Not infrequently, an abdominal HAE attack can imitate a surgical emergency. Life-threatening laryngeal edema may also occur and this accounts for the majority of the 30% to 40% mortality rate reported for this disease (Agostoni and Cicardi, 1992; Bork et al., 2000).

Intravenous administration of C1 INH, the plasma protein that is deficient in patients with HAE, has been used in Europe for more than 30 years for the treatment of acute attacks of HAE (Wall and Frank, 1990; Gadek et al., 1980). C1 INH concentrates are prepared from pooled human plasma. The efficacy of purified C1 INH concentrates in the treatment of acute angioedema in HAE has previously been described (Agostoni et al., 1980; Bergamaschini et al., 1983; Logan and Greaves, 1984; Späth et al., 1984).

The median age at the onset of initial symptoms is reported to between 8 and 12 years; however HAE can occur in the first year of life (Farkas et al., 2007; Farkas et al., 2002). A large-scale study conducted by Bork et al. (2006) showed that the yearly number of attacks is approximately double in patients when the disease appeared before age 5 compared with those in whom HAE appeared after the age of 15. Early diagnosis and early treatment are important as they allow efficient prevention and appropriate treatment of life-threatening complications.

The HAE development program for IV CINRYZE included data in the pediatric population that is among the largest for any C1 INH therapy based on published literature. However, further investigation is warranted to evaluate safety, tolerability, and treatment effect in children 6 to 11 years of age who require long-term C1 INH replacement therapy due to the morbidity imposed by frequent angioedema attacks.

1.1 CINRYZE® (C1 esterase inhibitor [human])

CINRYZE® (C1 esterase inhibitor [human]) consists of a protein fraction prepared 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.

CINRYZE was approved by the United States (US) Food and Drug Administration (FDA) for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE in October 2008. CINRYZE was approved throughout the European Union (EU), via the Centralized Procedure, in June 2011 for treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE, and routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. CINRYZE has also received marketing authorization in Australia (2012), Canada (2012), India (2013), Switzerland (2013), and Israel (2013).

1.1.1 Nonclinical Experience with Intravenous Administration

Acute and repeated-dose toxicity studies were performed in rats with IV administration of CINRYZE at dose levels of 20, 100, and 400 units (U)/kg/day. The highest dose evaluated in animals without observable adverse effects (400 U/kg) represents a safety margin of approximately 10 to 28 times the recommended human dose for adults and pediatrics (1000 U in adults, adolescents, and children 6 years of age and above). In the repeated-dose study, the signs of toxicity were limited to minor increases in inflammatory changes in the lungs and germinal center hypertrophy in the spleens of animals dosed at 400 U/kg/day for 14 days, as compared to control animals. The amount of germinal center hypertrophy in the spleens of rats treated at 400 U/kg/day was within the normal background histopathological range in both incidence and severity, but did correlate with a small increase in splenic weights, which may have been a reflection of the inflammatory increase in the lungs. Since CINRYZE is derived from human plasma, an immunological effect in rats is to be expected.

Results of an *ex vivo* thrombogenicity study utilizing healthy human volunteer whole blood and platelet poor plasma showed no evidence of a hypercoagulable effect of CINRYZE at concentrations of 0.14-7.0 U/mL (approximately 7 times physiologic concentration). These findings were consistent with a toxicology study of CINRYZE in rats, where no signs of thrombogenicity were observed at doses up to 400 U/kg/day for 14 days.

No effects of C1 INH on embryo-fetal development were observed at dose levels up to 400 U/kg. No animal studies have been completed to evaluate the effects of CINRYZE on carcinogenesis, mutagenesis, or impairment of fertility.

1.1.2 Clinical Experience with Intravenous Administration

The HAE development program for IV CINRYZE in the US included 2 multicenter studies of CINRYZE for prevention of angioedema attacks (1 double-blind, placebo-controlled study; 1 open-label study) and 2 multicenter studies of CINRYZE for treatment of angioedema attacks (1 double-blind, placebo-controlled study; 1 open-label study). In the double-blind prevention study (LEVP 2005-1/B), CINRYZE was shown to reduce the incidence of HAE attacks in 22 subjects analyzed (mean normalized 12-week HAE attack rate: 6.3 for CINRYZE vs. 12.7 for

placebo[1]; p<0.0001). In the double-blind treatment study (LEVP 2005-1/A), subjects receiving CINRYZE achieved beginning of unequivocal relief of the defining HAE symptom at a rate 2 times greater than subjects receiving placebo (p=0.017 for the Efficacy Dataset of 68 subjects [35 CINRYZE, 33 placebo]).

More than 14,500 IV infusions of CINRYZE were administered to 262 unique subjects in 8 completed clinical studies in the HAE development program of IV CINRYZE. The vast majority of infusions were CINRYZE doses of 1000 U. In the clinical studies, local reactions (e.g., pain, bruising, or rash at the injection/catheter site, venous burning or phlebitis) occurred in association with approximately 0.2% of infusions. No subjects were discontinued from CINRYZE due to an adverse event (AE) in any CINRYZE study completed to date evaluating the IV formulation. No serious adverse events (SAEs) were considered by the Investigator to be possibly, probably, or definitely related to treatment with CINRYZE.

Thrombotic and thromboembolic (T/TE) events have been reported following administration of IV CINRYZE 1000 U every 3 or 4 days as well as with higher than the recommended dose. Five subjects in the completed studies of the HAE development program for IV CINRYZE experienced SAEs that were thrombotic or thromboembolic in nature. The majority (4/5, 80%) of these events occurred in subjects with thrombogenic risk factors and none of these events were considered by the Investigator to be related to CINRYZE.

In a post-approval open-label study (0624-400) there were no systemic thrombotic events in subjects (n=20) who received IV CINRYZE up to 2500 U every 3 or 4 days for up to 12 months. One subject developed a blood clot in an intravenous central catheter, which was treated locally without systemic complication. Nevertheless, patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely.

Evaluation of the clinical PK and pharmacodynamics (PD) following IV administration of CINRYZE in subjects with HAE was primarily based on the results of Protocol LEVP 2006-5. After IV administration of CINRYZE 1000 U, functional C1 INH

[1] Mean observed 12-week HAE attack rate: 6.1 for CINRYZE vs. 12.7 for placebo per CINRYZE US Package Insert (2012).

concentrations increased from a mean baseline value of 0.31 U/mL to a maximum concentration (C_{max}) of 0.68 U/mL. Two consecutive 1000 U doses administered 60 minutes apart produced a mean C_{max} of 0.85 U/mL. Median time to maximum concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal elimination half-life ($t_{1/2}$) of functional C1 INH was approximately 60 hours using noncompartmental methods. Mean clearance (CL) values for functional C1 INH were 0.85 and 1.17 mL/min for the single and double doses, respectively. Mean C_{max} values for C1 INH antigen following IV administration of CINRYZE were 1.48 and 1.70 U/mL for the single and double doses, respectively. Median t_{max} was approximately 1.5 hours. The mean $t_{1/2}$ of antigenic C1 INH was approximately 45 to 47 hours and mean CL was 0.70 mL/min.

1.1.3 Pediatric Experience with Intravenous Administration

In the 2 multicenter studies of CINRYZE for prevention of angioedema attacks and 2 multicenter studies of CINRYZE for treatment of angioedema attacks, 46 unique pediatric subjects (aged 2-17 years) received a total of 2,237 infusions of IV CINRYZE (see Table 1; Lumry et al., 2013). There were 19 unique subjects 6-11 years old who received a total of 1,056 infusions of CINRYZE. The vast majority of infusions used CINRYZE doses of 1000 U. While the pediatric subsets in various studies had few subjects, analyses of efficacy by age showed that the clinical benefit of CINRYZE (as either HAE treatment or prevention) was generally comparable between children and adults.

Table 1. Number of Pediatric Subjects Exposed to CINRYZE and Total Infusions by Age Group, Indication, and Study – ITT-S Population

Indication Study [a]	2-5 years Number of Subjects (number of infusions)	6-11 years Number of Subjects (number of infusions)	12-17 years Number of Subjects (number of infusions)
Treatment			
LEVP 2005-1/A	0	6 (19)	6 (11)
LEVP 2006-1	1 (2)	10 (116)	13 (75)
Prevention			
LEVP 2005-1/B	0	1 (93)	3 (126)
LEVP 2006-4	2 (47)	9 (828)	12 (920)
Total [b]	**3 (49)**	**26 (1,056)**	**34 (1,132)**

a: Subjects may have been exposed to CINRYZE in one or more studies.
b: A subject may be counted more than once in the total if the subject participated in more than one study; therefore, this number represents the total number of subject exposures within each age subset.

CINRYZE had a favorable safety profile, with no clinically meaningful adverse trends observed among pediatric subjects. An overall summary from the 4 studies of treatment-emergent AEs in pediatric subjects that were considered by the Investigator to be related to study drug is provided in Table 2.

Table 2. Incidence of Treatment-Emergent Adverse Events Related to Study Drug Among Pediatric Subjects Exposed to CINRYZE by Age Group, Indication, and Study – ITT-S Population

Indication Study [a]	2-5 years	6-11 years	12-17 years
	n/N (%)		
Treatment			
LEVP 2005-1/A	---	0/6 (0%)	0/6 (0%)
LEVP 2006-1	0/1 (0%)	0/10 (0%)	0/13 (0%)
Prevention			
LEVP 2005-1/B	---	1/1 (100%)	0/3 (0%)
LEVP 2006-4	0/2 (0%)	2/9 (22%)	2/12 (17%)
Total, n/N [b]	**0/3 (0%)**	**3/26 (12%)**	**2/34 (6%)**

n/N=number of subjects with ≥1 treatment-related AE/number of subjects in a given age group by study
a: Subjects may have been exposed to CINRYZE in one or more studies.
b: n/N=number of subjects with ≥1 treatment-related AE across studies (a given subject may be counted more than once in the total if the subject participated and had a treatment-related AE in more than one study)/total number of subject exposures within each age subset.

There were 5 pediatric subjects with AEs considered to be related to study drug and the events are described below:

- Study LEVP 2005-1/B: One child PPD years of age), experienced moderate pyrexia determined by the Investigator to be possibly related to study drug; the event resolved after a duration of 1 day.
- Study LEVP 2006-4: Four children reported ≥1 treatment-related AE, as detailed below:
  - 6-11 years of age: 2/9 (22%) subjects reported 4 related treatment-emergent AEs (dizziness, headache, mouth ulceration, and nausea)
  - 12-17 years of age: 2/12 (17%) subjects reported 3 related treatment-emergent AEs (infusion site erythema, metrorrhagia, and photosensitivity reaction)

Of note, several of these events are included among the *related* treatment-emergent AEs only because the Investigator considered them to be of "unknown" relationship to CINRYZE (dizziness, mouth ulceration, metrorrhagia, and photosensitivity reaction). The only events considered by the Investigator to be possibly, probably, or definitely related to CINRYZE were headache, nausea, and infusion site erythema, all of which were mild in severity and resolved after a duration of 1 to 2 days. There were no systemic thrombotic or thromboembolic events reported in pediatric subjects.

Prevention Studies

Study LEVP 2005-1/B

In the pivotal study of CINRYZE for the prevention of HAE attacks (Protocol LEVP 2005-1/B), 4 pediatric subjects were enrolled (range: PPD years; median: 15 years), each of whom had previously participated in Study LEVP 2005-1/A. Subjects were randomized in a 1:1 ratio to one of two prevention therapy sequences: 12 weeks of CINRYZE 1000 U every 3-4 days followed by 12 weeks of placebo, or 12 weeks of placebo followed by 12 weeks of CINRYZE 1000 U every 3-4 days. All 4 subjects completed both periods of therapy with CINRYZE or placebo. Since subjects in this study were allowed to receive open-label CINRYZE for the treatment of acute attacks, it is more appropriate for the placebo arm of this study to be considered an "on-demand" comparator.

A summary of the efficacy results from this study is provided in Table 3. CINRYZE therapy was as efficacious in the pediatric population compared with the overall population, with an approximate 2-fold reduction in the number of HAE attacks compared to placebo/on-demand therapy (mean number of attacks per period: 7.0 vs. 13.0).

Table 3. Summary of Efficacy Results for Pediatric Subjects (N=4) – Study LEVP 2005-1/B

Mean Observed No. of Attacks During Therapy		Mean Severity [a] of Attacks During Therapy		Mean Duration of Attacks During Therapy (Days)		Mean No. of OL CINRYZE Infusions During Therapy		Mean Total Days of Swelling During Therapy	
CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo
7.0	13.0	1.6	1.6	2.3	2.6	6.8	15.0	9.0	20.8

OL=open-label
a: 1=mild; 2=moderate; 3=severe

Treatment-emergent AEs reported in children in this study are summarized below:

- 6-11 years of age: 1 subject reported 13 AEs (excoriation, headache, HAE, influenza, joint injury, limb injury, lymphadenopathy, nasal congestion, nasopharyngitis, poor venous access, pyrexia, varicella, and vomiting). Only 1 event (pyrexia) was considered by the Investigator to be related to study drug; this event resolved after a duration of 1 day.
- 12-17 years of age: 3 subjects reported 9 AEs (cough, viral gastroenteritis, headache, nasopharyngitis, pharyngolaryngeal pain, rash, upper respiratory tract infection, urinary tract infection, and vomiting). None of these events were considered related to study drug.

Study LEVP 2006-4

In the open-label study of CINRYZE for the prevention of HAE attacks (Protocol LEVP 2006-4), 23 pediatric subjects were enrolled (age range: 3 to 17 years). All 23 subjects received at least 1 dose of CINRYZE for prevention therapy. A summary of the efficacy results by pediatric age group is provided in Table 4. With the exception of 2 subjects PPD PPD and PPD), all prophylactic doses of CINRYZE were administered to pediatric subjects per protocol (1000 U every 3-7 days).

Prior to enrollment, the 23 children in this study reported a median monthly HAE attack rate of 3.0 (range: 0.5-28.0). During the study while receiving CINRYZE prevention therapy, pediatric subjects experienced a median monthly attack rate of 0.39 (range: 0-3.36), the

majority (87%, 20/23) experienced ≤1 HAE attack per month, and 22% (5/23) of children reported no attacks. Thus, CINRYZE provided substantial clinical benefit in reducing the frequency of angioedema attacks in children and was comparable to that observed in adults.

Table 4. Summary of Efficacy Results for Pediatric Subjects (N=23) – Frequency of Angioedema Attacks Age Group in Study LEVP 2006-4

	CINRYZE		
Age group	**2-5 years**	**6-11 years**	**12-17 years**
N by age group	2	9	12
Monthly attack rate per subject [a]			
Mean (SD)	0.69 (0.977)	0.35 (0.453)	0.71 (0.897)
Median	0.69	0.16	0.47
Range	0-1.38	0-1.33	0-3.36
Distribution of monthly attack rate per subject, N (%) [a]			
0 attacks	1 (50.0%)	3 (33.3%)	1 (8.3%)
> 0 to ≤ 1 attack	0	5 (55.6%)	10 (83.3%)
> 1 to ≤ 2 attacks	1 (50.0%)	1 (11.1%)	0
> 2 to ≤ 3 attacks	0	0	0
> 3 to ≤ 4 attacks	0	0	1 (8.3%)
> 4 attacks	0	0	0

a: Monthly attack rate for each subject = 30.4 x (total # of attacks) / (last day of study drug – first day of study drug + 1).

In Study LEVP 2006-4, the proportion of pediatric subjects (N=23) reporting a TEAE during the study was 74% and similar to the proportion reported in adults (79%). The most common TEAE in the study (and the most common TEAE in children) was upper respiratory tract infection (reported in 26% of children and 22% of adults). Many of the TEAEs reported in children 6-17 years of age were associated with common childhood infections such as pharyngitis, tonsillitis, sinusitis, and other upper respiratory tract infections.

Treatment-emergent AEs reported in children in this study are summarized below:

- 2-5 years of age: 1/2 (50%) subjects reported treatment-emergent AEs of HAE (severe abdominal HAE attack) and upper respiratory tract infection, both of which were considered to be not related to CINRYZE.
- 6-11 years of age: 8/9 (89%) subjects reported 50 treatment-emergent AEs, 46 of which were considered to be not related to CINRYZE. Two subjects reported 4 treatment-related AEs (dizziness, headache, mouth ulceration, and nausea).

- 12-17 years of age: 8/12 (67%) subjects reported 60 treatment-emergent AEs, 57 of which were considered to be not related to CINRYZE. Two subjects reported 3 treatment-related AEs (infusion site erythema, metrorrhagia, and photosensitivity reaction).

Efficacy Data for Pediatric Subjects Aged 6 to 11 Years

There was one subject (PPD; PPD female) enrolled in Study LEVP 2005-1/B in the 6 to 11 years of age subset. This subject also participated in Study LEVP 2006-4 (prevention) and Study LEVP 2005-1/A (treatment). The randomized treatment assignment for this subject was Placebo/CINRYZE and all administrations of CINRYZE were 1000 U doses. As shown in Table 5, this subject experienced a greater than 2-fold reduction in the number of HAE attacks with CINRYZE compared to placebo/on-demand therapy (8.0 vs. 20.0). Furthermore, the severity of attacks was less (1.5 vs 1.7), the duration of attacks was shorter (2.5 vs. 3.1 days), and the total days of swelling was considerably lower (12.0 vs 42) with CINRYZE prevention therapy compared to placebo/on-demand therapy. Fewer open-label CINRYZE infusions for treatment of acute HAE attacks were administered to this subject while on CINRYZE compared with placebo/on-demand therapy (7.0 vs. 28.0).

Table 5. Detailed Efficacy Results for Pediatric Subject PPD – Study LEVP 2005-1/B

Observed No. of Attacks During Therapy		Mean Severity [a] of Attacks During Therapy		Mean Duration of Attacks During Therapy (Days)		No. of OL CINRYZE Infusions During Therapy		Total Days of Swelling During Therapy	
CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo	CINRYZE	Placebo
8	20	1.5	1.7	2.5	3.1	7	28	12	42

a: 1=mild; 2=moderate; 3=severe

Table 6 describes the demographic, exposure, and efficacy data from Study LEVP 2006-4 for the 9 pediatric subjects 6 to 11 years of age. Prior to enrollment in the study, these 9 subjects reported a median monthly HAE attack rate of 3 (range: 2-4). During the study, these subjects experienced a median monthly attack rate of 0.16 (range: 0-1.33); the majority of subjects (8/9, 89%) experienced ≤1 HAE attack per month, and 33% (3/9) reported no attacks. In terms of safety, 8/9 (89%) subjects reported 50 treatment-emergent AEs, 46 of which were considered to be not related to CINRYZE. As described previously, two subjects reported 4 treatment-related AEs (dizziness, headache, mouth ulceration, and nausea).

Table 6. Demographics, Extent of Exposure, and Attack Frequency for Pediatric Subjects 6-11 Years of Age (Study LEVP 2006-4)

Subject ID	Age/Gender	Prevention Dose	Days on Study	Attacks per Month	
				Baseline	On Study
PPD	PPDF	1000 U	582	4	0.16
PPD	PPDF	1000 U	246	2	0.00
PPD	PPDM	1000 U	301	2	0.30
PPD	PPDF	1000 U	697	4	0.39
PPD	PPDM	1000 U	344	4	1.33
PPD	PPDF	1000 U (750 days) 2000 U (90 days) 1000 U (83 days)	923	4	0.82
PPD	PPDF	1000 U	136	2	0.00
PPD	PPDM	1000 U	267	3	0.11
PPD	PPDF	1000 U	64	3	0.00

1.2 Study Rationale

Current international consensus recommendations for HAE therapy do not provide sufficient granularity across all age groups and cannot be unconditionally adopted for pediatric patients in various countries, due to medical and legal issues (Wahn et al., 2012). Further studies in pediatric subjects with HAE therapies currently approved for adults only, will provide pediatricians with therapeutic options for treating their patients. Regardless, experts indicate that plasma-derived C1 INH concentrate is the first choice and best treatment option for long-term prevention in pediatric patients and attenuated androgens and tranexamic acid are not recommended (Wahn et al., 2012).

CINRYZE IV (administration of 1000 U every 3 or 4 days) was approved by the US FDA for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE in October 2008. CINRYZE was also approved throughout the EU, via the Centralized Procedure, in June 2011 for treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE, and routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with

repeated acute treatment. CINRYZE has also received marketing approval in Australia (March 2012), India (February 2013), Switzerland (May 2013), and Israel (August 2013) for all three indications (treatment, routine prevention, and pre-procedure prevention) in adults and adolescents (as well as children 6 years and above in India) with HAE. CINRYZE was approved in Canada (October 2012) for routine prevention against angioedema attacks in adults and adolescents with HAE.

The HAE development program for IV CINRYZE included data in the pediatric population that is among the largest for any C1 INH therapy based on published literature. However, further investigation is warranted to evaluate safety, tolerability, and treatment effect in children 6 to 11 years of age who require long term C1 INH replacement therapy due to the morbidity imposed by frequent angioedema attacks. As of 07-Jun-2013, in the US a total of 110 patients less than 18 years of age with HAE are actively receiving commercial CINRYZE. Of 110 patients, 26 children are 6 to 11 years of age and 84 children are 12 to 17 years of age (data on file).

While CINRYZE has proven to be safe and effective in adults and adolescents, questions remain about the ideal pediatric dosing regimens, particularly for young and/or light-weight children. Additional information with regards to the pharmacokinetics and dosing of CINRYZE in children (≥2 to <12 years of age) is currently being assessed in a study for the treatment of acute angioedema attacks (Protocol 0624-203). Dosing in study 0624-203 is determined by subject weight category; 10 kg to 25 kg inclusive (500 U and 1000 U) and >25 kg (1000 U and 1500 U).

The aim of this study is to assess the safety and tolerability, relative efficacy, and PK/PD of two different doses (500 U and 1000 U) of CINRYZE administered by IV injection to further the knowledge of the management of HAE in children 6 to 11 years of age. Consistent with the recent consensus on therapeutic strategies for children and adolescents with HAE (Wahn et al., 2012), the current study will account for differences in body weight by administering 2 fixed doses of CINRYZE (500 U and 1000 U), and CINRYZE dosage will be related to plasma volume, body surface area, and body mass index. The optimal dose for this age group

may be less than the IV dose of 1000 U every 3-4 days approved for adult and adolescent patients and the proposed study allows a within subject comparison of the effectiveness and tolerability of two dosing regimens. In addition, the study will provide supportive data on potential immunogenicity and quality of life health status in this pediatric population, as well as prospective observational data on angioedema attack frequency in the "ultra-orphan" 6 to 11 years of age subgroup.

Detailed considerations regarding CINRYZE doses selected for this study are presented in Section 5.1.

2.0 STUDY OBJECTIVES

The objectives of the study are as follows:

Primary Objective

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

Secondary Objectives

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

Other Objective

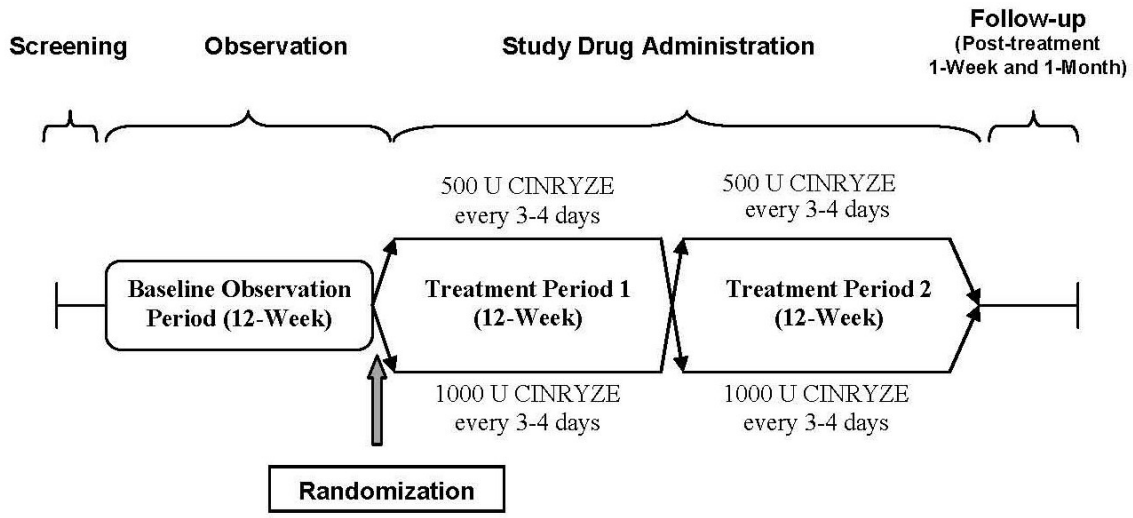
- To assess the impact of treatment on health status (quality of life) in children 6 to 11 years of age with HAE.

3.0 INVESTIGATIONAL PLAN

This multicenter, randomized, single-blind, dose-ranging, crossover study will be conducted in multiple countries including the US, EU, and Latin America. Other countries/regions may be added if necessary to complete enrollment. All study sites, irrespective of geographic location, will conduct the study in accordance with this study protocol and Good Clinical Practice (GCP) standards, including review and approval by independent ethics committee

(IEC). Data from all sites will be pooled for purposes of analysis and will be reported in the final clinical study report.

Figure 1. Study Design



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

Throughout the study, an electronic study diary (eDiary) will be used to collect specific information regarding the subject's symptoms of HAE. The eDiary will consist of two sections:

(a) Section to record daily if any elective procedures have been performed, signs and symptoms of angioedema attacks, triggers for angioedema attacks, medications used for the management of angioedema attacks, and interruptions in activities of daily living due to an angioedema attack. Section (a) is to be completed by the parent/caregiver, and when possible, the same parent/caregiver should be responsible for completing this section of the eDiary throughout the study.

(b) Section to record the impact of HAE on quality of life (EQ-5D-Y). Section (b) is to be completed by the subject at specified time points throughout the study **and on each day the subject experiences signs or symptoms of an angioedema attack**.

Study personnel will contact the parent/caregiver by telephone bi-weekly (Weeks 2, 4, 6, 8, 10, and 12) during the baseline observation period to discuss study compliance (completion of the eDiary daily) and to evaluate the subject's angioedema attack frequency (Schedule 1).

During the baseline observation period, subjects are allowed to remain on any prophylactic HAE therapy they were receiving prior to study enrollment, if clinically indicated. However, it is recommended that consideration by the Investigator be given to discontinuing subjects from any prophylactic antifibrinolytic or androgen therapy during the first 6 weeks of the observation period. If these medications cannot be discontinued, stable doses should be used during Treatment Periods 1 and 2. At least 3 days prior to first dose of study drug, subjects receiving commercial C1 INH for prevention of attacks must discontinue this therapy.

In the event that during the 12 weeks of baseline observation subjects do not meet the attack criteria qualifying for randomization (≥1.0 angioedema attacks per month [average] that are moderate or severe or require acute treatment), despite having met this same criteria historically for study enrollment, additional weeks of observations will be considered at the discretion of the Investigator and Sponsor to allow qualification for randomization and entry into the treatment periods of the study. In this case, subjects will maintain the same schedule of assessments by beginning at Week 1 again for the additional weeks of observation (Schedule 1).

After the completion of the baseline observation period, subjects who remain eligible per study criteria will be randomized to 1 of 2 treatment sequences prior to the first dose of study drug in Treatment Period 1 (i.e., Dosing Day 1). Twelve subjects will be randomized in this study. There is no washout period between Treatment Period 1 and Treatment Period 2. Subjects are required to maintain their twice weekly (every 3 or 4 days) schedule between the last dose of study drug in Treatment Period 1 and the first dose in Treatment Period 2.

Subjects and parents/caregivers will be blinded to treatment sequence and dose. Study site personnel, qualified home healthcare professionals, and the Sponsor will not be blinded to treatment assignment and the dose of study drug administered. Study drug will be administered intravenously by qualified personnel at the investigational site, or by qualified home healthcare professionals at the subject's home or other agreed upon location. Alternatively if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g., parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator. Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device, compression and applying a bandage to the injection site, and disposal of all infusion materials.

The Investigator or designee will monitor and document study compliance, tolerability of each CINRYZE dose, and adverse events. The following doses of study drug in each treatment period must be administered at the investigational site: Dose 1 (Visits 1a and 1b), Dose 12 (Visits 12a and 12b) and Dose 24 (Visits 24a and 24b). At these visits, subjects will also have other scheduled procedures performed (Schedules 2 and 3). For those subjects who are administered study drug at a location other than the study site, study personnel will contact the parent/caregiver by telephone twice during each treatment period (Week 3 after Dose 6 [Visits 6a and 6b] and Week 9 after Dose 18 [Visits 18a and 18b]). If study drug is administered at the site (Doses 6 and 18), no telephone contact is necessary.

To the extent possible, subjects will postpone elective procedures (e.g., dental work) while participating in the study. In the event a procedure cannot be postponed, parents/caregivers will notify the Investigator and the information will be recorded in the subject's eCRF (see Section 6.8).

Safety will be monitored through the recording of AEs and changes in medical history, physical examinations, vital signs, and clinical safety laboratory testing. Stopping rules following an anaphylactic reaction or a thrombotic or thromboembolic event are provided in Section 5.5. Details on the management of acute angioedema attacks are provided in Section 6.10. Study personnel will report any angioedema attacks that occur after the first dose of study drug as AEs (see Section 9.0).

A post-treatment visit will be performed at the investigative site 1 week (±2 days) after the last dose of study drug in Treatment Period 2 for follow-up safety assessments. In addition, subjects will have a blood sample for C1 INH antibody testing collected 30 (±2) days after the last dose of study drug. If a subject discontinues prematurely from treatment and/or the study, the Investigator will perform the Early Discontinuation Visit safety procedures as soon as possible. For those subjects who discontinue prematurely from treatment, every effort should be made to complete all applicable protocol evaluations for the 1-month post-treatment follow-up visit (see Schedule 4).

Investigators will report all SAEs occurring up to 30 days after the last dose of study drug to Shire ViroPharma and their respective Independent Reviewing Authority (IRA) according to local reporting requirements. In addition, SAEs with an onset more than 30 days after the last dose of study drug should be reported if considered by the Investigator to be related to study drug. All suspected unexpected serious adverse reactions (SUSARs) will be reported by the Sponsor to the relevant competent authorities in accordance with the European Directive 2001/20/EC, as applicable.

Subjects will remain outpatient throughout the study. Individual participation from screening through the completion of follow-up will be approximately 10 months. Subjects will adhere to the protocol-defined schedule of clinical assessments and procedures as outlined below:

- **Schedule 1** – Clinical study assessments during Screening and Baseline Observation Period (Weeks 1 to 12).
- **Schedule 2** – Clinical study assessments during Treatment Period 1 (Visits 1a to 24a).

- **Schedule 3** – Clinical study assessments during Treatment Period 2 (Visits 1b to 24b).
- **Schedule 4** – Clinical study assessments at Early Discontinuation, 1-week Post-treatment, and 1-month Post-treatment Follow-up Visits.
- **Schedule 5** – Blood sample collection for PK/PD and post-treatment immunogenicity assessments.

4.0 STUDY POPULATION

Inclusion and exclusion criteria for enrolling subjects in this study are presented in Sections 4.1 and 4.2 below. If there is any question about subject eligibility, the Investigator should consult with the Sponsor before enrolling the subject.

4.1 Inclusion Criteria

To be eligible for this protocol, a subject must:

1. Be a child (male or female), ≥6 to <12 years of age at the time of screening.
2. Have a confirmed diagnosis of Type I or Type II HAE and have a functional C1 inhibitor (C1 INH) level less than 50% of normal.
3. Have a history of ≥1.0 angioedema attacks per month (average) that are moderate[1] or severe[2] or require acute treatment[3] during the 3 consecutive months prior to screening.
4. Agree to adhere to the protocol-defined schedule of assessments and procedures.
5. 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).

Additional Inclusion Criteria (Qualifying for Randomization)

6. Have experienced ≥1.0 angioedema attacks per month (average) that are moderate[1] or severe[2] or require acute treatment[3] during the 12-week baseline observation period.

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[1] Moderate: Angioedema attack sign/symptom(s) interferes with the subject's ability to attend school or participate in family life and social/recreational activities.

[2] Severe: Angioedema attack sign/symptom(s) significantly limits the subject's ability to attend school or participate in family life and social/recreational activities.

[3] 'Treatment' refers specifically to standard of care therapies used to treat an angioedema attack (e.g., C1 INH, kallikrein inhibitor, bradykinin receptor antagonist). Products used for the treatment of attack symptoms (e.g., analgesics, anti-emetics) do not qualify for this study inclusion criterion.

4.2 Exclusion Criteria

To be eligible for this protocol, a subject must not:

1. Have a history of hypercoagulability (abnormal blood clotting).
2. Have a diagnosis of acquired angioedema or known to have C1 INH antibodies.
3. Have a history of allergic reaction to C1 INH products, including CINRYZE (or any of the components of CINRYZE), or other blood products.
4. Be pregnant or breastfeeding.
5. Have received an investigational drug other than those required for prevention or treatment of angioedema attacks within 30 days prior to screening.
6. Have, as determined by the Investigator and/or the Sponsor's medical monitor, any surgical or medical condition that could interfere with the administration of study drug or interpretation of study results.

Additional Exclusion Criteria (Disqualifying from Randomization)

7. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in Treatment Period 1.
8. Have had signs or symptoms of an angioedema attack within 2 days prior to the first dose of study drug in Treatment Period 1.

5.0 STUDY DRUG ADMINISTRATION

5.1 Dose Selection

As discussed in Sections 1.1.2 and 1.1.3, the vast majority of IV CINRYZE infusions administered in clinical studies were doses of 1000 U for both adults and children, although the two youngest subjects (ages PPD and PPD years old) received 500 U per IV dose. In the US, the approved dose of CINRYZE for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE is 1000 U IV every 3 or 4 days.

The effectiveness of this dose is supported by data from Studies LEVP 2005-1/B and LEVP 2006-4, where all pediatric subjects had a clinically significant reduction in the number of angioedema attacks while receiving 1000 U of IV CINRYZE every 3-7 days (see Table 5 and Table 6). This dosing regimen had a favorable safety profile in children when administered for routine prevention of angioedema attacks.

Although the data support that higher doses of CINRYZE are not necessary for subjects in the 6 to 11 year age group, the efficacy of a lower dose (500 U every 3-4 days) has not been evaluated in this "ultra-orphan" subgroup. The proposed study will provide additional data on a dosage range of CINRYZE for the prevention of angioedema attacks in children 6 to 11 years of age.

5.2 Randomization

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

5.3 Study Drug

See Section 8.0 for a complete description of study drug. Instructions for the reconstitution of CINRYZE are provided in a separate Pharmacy Manual. CINRYZE treatments will be prepared and administered by qualified study site personnel or qualified home healthcare professionals. Home healthcare personnel may prepare and administer CINRYZE treatments at the subject's home. Alternatively if allowed per local regulations, subjects who have been trained to self-administer C1 INH or who have a non-healthcare provider (e.g., parent) who has been trained to administer C1 INH will be permitted to do so based upon the request of the subject (and with approval of the parent(s)/legal guardian and the Investigator). Note: self-administration will always occur under the supervision of a qualified healthcare professional at the study site or the subject's home (or other agreed upon location). Supervision by a qualified healthcare professional will include real time direct visual observation of the following: selection of the injection site, preparation of the injection site, insertion of the infusion device into the vein, study drug infusion, removal of infusion device,

compression and applying a bandage to the injection site, and disposal of all infusion materials.

For **Treatment A** (500 U CINRYZE dose), an additional vial of 5 mL sterile water for injection (SWFI) will be added to the 5 mL vial of reconstituted CINRYZE to make a total volume of 10 mL. For **Treatment B** (1000 U CINRYZE dose), two 5 mL vials of reconstituted CINRYZE will make a total volume of 10 mL. CINRYZE will be administered intravenously as a single 10-mL injection and at a rate of approximately 1 mL (50-100 U) per minute, as tolerated.

The following doses of study drug in each treatment period must be administered at the investigational site: Dose 1 (Visits 1a and 1b), Dose 12 (Visits 12a and 12b) and Dose 24 (Visits 24a and 24b). At these visits, subjects will also have other scheduled procedures performed (Schedules 2 and 3). For each dose administered, date and time at start of infusion and the date and time at completion of infusion will be recorded in the eCRF. Any departure from the expected dosing regimen will be recorded in the eCRF.

5.4 Blinding

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

To maintain the treatment blind (for subjects and parents/caregivers), each dose of study drug will consist of a single IV injection (total volume of 10 mL; see Section 5.3).

5.5 Stopping Rules

5.5.1 Anaphylactic Reaction

If an anaphylactic reaction occurs in any subject, study drug will be discontinued. The subject will follow the schedule of assessments for early discontinuation and complete the protocol evaluations for the 1-month post-treatment follow-up visit (see Schedule 4). Other enrolled subjects will continue with study drug administration and procedures.

5.5.2 Thrombotic or Thromboembolic Event

If a T/TE event occurs in any subject, no further enrollment will occur pending a complete review of all available data. Other enrolled subjects will continue with study drug administration and 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 study drug or other C1 inhibitors, which may have been administered for an angioedema attack.

If a T/TE event occurs in any subject, study drug administration for that subject will be interrupted; however, other study procedures will continue, as clinically appropriate. Investigators will comply with protocol-defined algorithms to assist in the diagnosis and management of all suspected T/TE events (see Appendix II). Following a complete medical review by the Sponsor, in conjunction with the Investigator, dosing with study drug may be resumed to complete a total of 24 doses in the treatment period that was interrupted. Study procedures including PK/PD testing will resume relative to dosing. If study drug cannot be restarted within 30 days of temporary interruption, the subject will be discontinued from treatment and will follow the schedule of assessments for early discontinuation (see Schedule 4).

6.0 STUDY PROCEDURES

Subjects meeting the eligibility criteria listed in Section 4.0 may be enrolled in the study after the nature and purpose of the protocol have been explained and written permission to participate has been voluntarily granted by the parent/legal guardian and assent has been provided by the subject (to the extent that is compatible with the subject's understanding) (see Section 14.0). Schedules 1, 2, 3, and 4 provide details of study procedures for clinical study assessments and Schedule 5 provides timing of blood sampling for PK/PD and post-treatment immunogenicity testing.

6.1 Medical History and Physical Examination

A medical history will be taken at the screening visit, and updated prior to randomization on Day 1 of Treatment Period 1 to ensure that the subject remains eligible for study participation.

All medical history findings that have been present/active within 1 year prior to enrollment will be recorded in the eCRF regardless of clinical relevance or presence at study start. Medical history findings that have not been present within 1 year prior to enrollment will be recorded if deemed clinically relevant by the Investigator to the conduct of the study. The medical history is to include any history of allergic reactions to drugs.

The Investigator or designee will perform physical examinations at the time points specified in Schedules 2, 3, and 4. General physical examinations will be performed in accordance with standard practices at the study site. Clinically significant physical examination abnormalities observed prior to dosing with study drug also will be recorded in the medical history section of the eCRF. Any new or worsening clinically significant abnormality observed any time after the start of study drug administration should be recorded as an AE (see Section 9.0).

Body weight and height will be measured at the time points specified in Schedules 2 and 3. Measurements should be performed without shoes and underclothes only and measured by the same individual at each assessment time point (if possible).

6.1.1 HAE History

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

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

6.2 Vital Signs

Blood pressure and heart rate will be measured at the time points specified in Schedules 2, 3 and 4. Body temperature will be measured prior to randomization at Visit 1a. During the study, additional vital signs measurements will be performed if clinically indicated. Vital signs performed on dosing days should be obtained prior (within 60 minutes) to the start of the injection and between 10 to 30 minutes after completion of the injection of study drug. Every effort should be made to measure and record vital signs prior to any blood sample collection.

6.3 Prior and Concomitant Medications

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

6.3.1 Prior Medications

A HAE medication history will be taken during the screening visit, and updated prior to study drug administration on Day 1 of Treatment Period 1 to ensure that the subject remains eligible for study participation. Parents or caregivers should record in the eDiary any medications taken by the subject for the management of angioedema attacks during the baseline observation period.

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

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

6.3.2 Concomitant Medications

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

6.3.3 Prohibited Medications

Use of C1 INH therapy (other than study drug) for prophylaxis against angioedema attacks is prohibited during the study after completion of the baseline observation period. At least 3 days prior to randomization, subjects receiving commercial C1 INH for prevention of attacks must discontinue this therapy. It is recommended that consideration by the Investigator be given to discontinuing subjects from any prophylactic antifibrinolytic or androgen therapy during the first 6 weeks of the observation period, if clinically indicated. If these medications cannot be discontinued, stable doses should be used during Treatment Periods 1 and 2.

Details on the management of acute angioedema attacks are discussed in Section 6.10.

6.4 Nonpharmacologic Treatments and Procedures

Nonpharmacologic treatments and procedures (e.g., surgical, diagnostic, or dental) that occur during the baseline observation period through 1-week post-treatment will be recorded in the eCRF.

6.5 Clinical Laboratory Parameters

Subjects will have blood samples collected for routine clinical laboratory testing at the time points specified in Schedules 1, 2, 3 and 4. Testing will be performed at a Central Laboratory,

except for the urine pregnancy test and for any other parameter that the Investigator will need to assess urgently for the acute care of any subject. The following clinical laboratory parameters will be analyzed:

- **Hematology:**
  - ***Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued):*** CBC consisting of WBC and differential counts and percentages, RBC count, hemoglobin, hematocrit, and platelet count.
- **Clinical Chemistry:**
  - ***Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued):*** Blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, carbon dioxide (CO_2), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK), total bilirubin, calcium, phosphorus, total protein, and albumin.
- **Coagulation:**
  - ***Dosing Visits 1a (pre-dose), 12a, 1b (pre-dose), 12b, 24b, and 1-week post-treatment (or if prematurely discontinued):*** Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).
- **Virology:**
  - ***Dosing Visit 1a (pre-dose) and 1-week post-treatment (or if prematurely discontinued):*** Human immunodeficiency virus (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

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

Additional clinical laboratory testing may be performed if clinically indicated, at the discretion of the Investigator, and may be sent to central laboratory or performed locally, and all results will be recorded.

6.6 Pharmacokinetic, Pharmacodynamic, and C1 INH Antibody Analyses

Blood samples for the determination of plasma concentrations of C1 INH antigen, functional C1 INH, and C4 complement will be collected from subjects during each treatment period as

shown in Schedule 5. In addition, plasma samples collected prior to the dose of CINRYZE on Visit 1a (Dose 1 of Treatment Period 1), and Visit 1b (Dose 1 of Treatment Period 2), will be analyzed for C1 INH antibodies (see Schedules 2 and 3). Additional blood samples for C1 INH antibody testing will be collected 1 week post-treatment (or if prematurely discontinued) and 30 days after the last dose of study drug (see Schedules 4 and 5).

NOTE: If a subject presents to the site with an angioedema attack, every effort should be made to obtain a PK blood sample prior to any treatment. In addition, if the subject is treated with commercial C1 INH, every effort should be made to obtain a 1-hour post-treatment sample. These samples will be analyzed for C1 INH antigen and functional C1 INH activity.

The actual date and time of each sample collection will be recorded. Plasma samples for the determination of antigenic C1 INH, functional C1 INH, complement C4 concentrations, and C1 INH antibodies will be analyzed using validated methodology. All samples, except for incurred samples, will be processed according to the procedure outlined in Appendix I.

Selected samples may be analyzed to investigate incurred sample reproducibility (ISR) of the bioanalytical methods and/or incurred sample stability (ISS). These analyses are only to investigate the reproducibility of the bioanalytical methods used to determine concentrations of antigenic C1 INH and functional C1 INH activity in study samples to investigate the stability of incurred samples. All ISR and ISS results collected will be reported in a separate table in the bioanalytical report. All samples will be disposed of at the conclusion of the study. Details of disposal will be documented and maintained with the study file at the analytical laboratory.

6.7 Total Blood Volume Collected

Subjects will have approximately 172 mL of blood collected for clinical safety laboratory testing (hematology, chemistry, and coagulation), PK/PD, and immunogenicity (C1 INH antibodies) assessments during the study.

6.8 Restrictions

Subjects should maintain their normal diets, medications, and activities of daily living. During the study, subjects will be asked to avoid known triggers of angioedema attacks to the best of their ability. To the extent possible, subjects will postpone elective procedures (e.g., dental work) while participating in the study. In the event a procedure cannot be postponed, the parent/caregiver will notify the Investigator and the information will be recorded in the eCRF (see Section 6.4).

6.9 Electronic Study Diary (eDiary)

Throughout the trial, an eDiary will be used to collect specific information regarding the subject's symptoms of HAE. The eDiary will consist of two sections:

(a) Section to record daily if any elective procedures have been performed, signs and symptoms of angioedema attacks, triggers for angioedema attacks, medications used for the management of angioedema attacks, and interruptions in activities of daily living due to an angioedema attack. Section (a) is to be completed by the parent/caregiver, and when possible, the same parent/caregiver should be responsible for completing this section of the eDiary throughout the study.

(b) Section to record the impact of HAE on quality of life (EQ-5D-Y, see Section 6.11.1). Section (b) is to be completed by the subject at specified time points throughout the study **and on each day the subject experiences signs or symptoms of an angioedema attack**.

At the screening visit, study personnel will instruct subjects and parents/caregivers how to complete the eDiary. The diary will be completed on each day during the baseline observation period and Treatment Periods 1 and 2.

Study personnel will review each subject's eDiary for completeness and accuracy at each visit. The eDiary is intended to be used by study personnel in conjunction with direct subject interviews, inpatient records (if applicable), and any other study-specific records as source documentation.

Details about the use of the eDiary are provided in a separate study manual.

6.10 Angioedema Attacks

An angioedema attack will be defined as any subject-reported (or parent/caregiver-reported) indication of swelling or pain at any location following a report of no swelling or pain on the previous day (i.e., 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 one site to another will be considered a single attack,
- Attacks that begin to regress and then worsen before complete resolution will be considered one attack, and
- 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 one attack.

NOTE: An angioedema attack does NOT include swelling due to trauma and symmetrical non-painful swelling of the lower extremities.

6.10.1 Recording of Angioedema Attacks

During the observation period and both treatment periods, parents/caregivers will use the eDiary each day to record any symptoms or occurrences of an angioedema attack experienced by the subject. The Investigator will complete a separate angioedema attack eCRF for each attack based upon their review of the data in the eDiary and include:

- Characterization of whether swelling or pain is (indicate all that apply):
  - Mucosal (pharyngeal, laryngeal, gastrointestinal, genitourinary)
  - Non-mucosal (truncal, external, 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)
  - Facial
  - Extremity or peripheral (e.g., buttocks, external head/neck, trunk)

- Severity (intensity) of the sign/symptom at each location listed:
  - None
  - Mild: the angioedema attack sign/symptom(s) is noticeable but is easily tolerated by the subject and does not interfere with routine activities.
  - Moderate: angioedema attack sign/symptom(s) interferes with the subject's ability to attend 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 school or participate in family life and social/recreational activities.
- Angioedema attack trigger(s)
- Answer the question, "Was treatment administered for the attack?" If yes, record treatment administered.

In addition to recording the above information, study personnel will report any angioedema attack that occurs after the first dose of study drug as an AE (see Section 9.0).

6.10.2 Management of Acute Angioedema Attacks

If a subject experiences an acute angioedema attack at any time during study that in the opinion of the healthcare care provider requires medical intervention, the choice of acute treatment will be left to the Investigator's discretion. Where appropriate, CINRYZE can be provided for acute treatment of angioedema attacks. Acute treatment(s) for angioedema attacks should be recorded in the eCRF (see Sections 6.3.2 and 6.4).

6.10.3 Angioedema Attacks During Treatment Periods

If a subject has an angioedema attack at any time during the study treatment periods, study drug administration and study procedures will continue for that subject adhering to the study schedule, regardless of whether C1 INH therapy or other products were administered to treat the attack.

6.11 Quality of Life Measurements

6.11.1 Health-related Quality of Life (EQ-5D-Y)

EQ-5D-Y[1] (Youth version of EQ-5D) is a descriptive system of youth health-related quality of life states consisting of five dimensions, each of which can have one of three responses. The responses record the level of severity within a particular EQ-5D dimension. EQ-5D-Y is not intended for use in children 6 years of age (Noyes and Edwards, 2011); however in this study all subjects (6 to 11 years of age and where translated language version is available) will be assessed. The EQ-5D-Y will be completed by the subject at the time points specified in Schedules 1, 2, 3 and 4, as well as on each day that a subject experiences signs or symptoms of an angioedema attack (see Section 6.9).

Details about the use and administration of the EQ-5D-Y questionnaire are provided in a separate study manual.

6.12 Discontinuation From Treatment and/or Study

When a subject is discontinued from treatment and/or study, Early Discontinuation Visit procedures will be performed (see Schedule 4). For those subjects who discontinue prematurely from treatment, every effort should be made to complete protocol evaluations for the 1-month post-treatment follow-up visit.

For those subjects who enter the observation period but discontinue prior to randomization or who discontinue after randomization but prior to receiving study drug, the following information will be recorded in the eCRF:

- Demographic information
- Inclusion/exclusion information
- HAE history and HAE medications for the 9 months prior to the observation period and also for the duration of the observation period
- Angioedema attack data (all attributes of the attacks such as location, severity, pain assessment, possible trigger, treatment received, missed school)

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

- EQ-5D-Y data
- Reason for not receiving study drug (e.g., not randomized as subject failed to meet qualifying attack criteria or Investigator concern regarding subject's or parent/caregiver's compliance with study procedures)

No additional study procedures or follow-up will be performed on subjects who discontinue prior to receiving a dose of study drug.

6.12.1 Discontinuation From Treatment

A subject may be discontinued prematurely from study drug treatment for the following reasons:

- Withdrawal by subject (i.e., assent withdrawn) [specify reason in the eCRF]
- Withdrawal by parent/guardian [specify reason in the eCRF]
- Adverse event (which in the opinion of the Investigator, due to the nature and severity, requires discontinuation from treatment)
- Lost to follow-up
- Physician decision (i.e., Investigator decision based on protocol violation, assessment that it is not in the subject's best interest to continue, or other reason) [specify reason in the eCRF]
- Sponsor decision [specify reason in the eCRF]

Subjects who discontinue study drug due to an AE will be followed until the event is either resolved or assessed as stable by the Investigator.

6.12.2 Discontinuation From Study

A subject may be discontinued prematurely from the study for the following reasons:

- Withdrawal by subject (i.e., assent withdrawn) [specify reason in the eCRF]
- Withdrawal by parent/guardian [specify reason in the eCRF]
- Lost to follow-up
- Death
- Physician decision (i.e., Investigator decision based on protocol violation, assessment that it is not in the subject's best interest to continue, or other reason) [specify reason in the eCRF]
- Sponsor decision [specify reason in the eCRF]

7.0 STATISTICAL METHODOLOGY

Based on the EU Pediatric Investigation Plan, an administrative look for regulatory purpose may be completed after 6 patients have finished the study. This will facilitate timely reporting of study results to the European Medicines Agency's Paediatric Committee after 6 children have completed the study as agreed in the Pediatric Investigation Plan. A final CSR will be completed after 12 subjects finish the study.

7.1 Sample Size

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

7.2 Populations

Data will be collected and summarized for all subjects randomized and treated with study drug.

7.3 Efficacy Analysis

All efficacy endpoints will be determined for each subject in each treatment period:

- Number of angioedema attacks, normalized to a 12-week treatment period
- 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.
- Time (measured in days from the first dose of study drug in a treatment period) to the first angioedema attack reported in that treatment period.
- Change from pre- to post-dose in C1 INH functional activity, C1 INH antigen, and C4 levels.
- Number of angioedema attacks requiring acute treatment during each treatment period.

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

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

a: Maximum Severity across all anatomic locations on the corresponding study day.
b: Maximum Severity across all anatomic locations and days with symptoms for the corresponding attack.

In this hypothetical example, a patient recorded 9 days of symptoms in an 11-day study period. Because individual attacks require at least one symptom-free calendar day between episodes, this diary fragment identifies three angioedema attacks. The maximum severity of each attack is determined on the last day of symptoms and is derived as Mild, Moderate, or Severe. Coding these categories as Mild=1, Moderate=2, and Severe=3 and summing over the three unique attacks, yields a Cumulative Attack Severity of 8. Finally, summing the

reported severity scores over the 9 days with symptoms yields a Cumulative Daily Severity of 19. With respect to these defined endpoints, this hypothetical eleven-day symptom diary would be quantitatively described by:

Endpoint	Value
Number of Attacks	3
Cumulative Attack Severity	8
Cumulative Daily Severity	19

Analysis of efficacy endpoints will employ descriptive statistics and will include all subjects randomized and treated with study drug. If warranted by the data, the comparison of CINRYZE doses will employ a paired t-test to perform a two-sided test of superiority (1000 U vs. 500 U) conducted at α=0.10.

7.4 Safety Analysis

The following will be assessed during the study:

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

7.5 Other Endpoints

Results of the EQ-5D-Y health status questionnaire will be presented in accordance with the EQ-5D-3L User Guide (version 4.0[1]), and adapted as appropriate for the youth version.

7.6 Pharmacokinetic and Pharmacodynamic Analyses

Concentrations of C1 INH antigen, functional C1 INH activity, and complement C4 for individual subjects will be determined. Results will be summarized using descriptive

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

statistics (number, mean, standard deviation, median, minimum, and maximum) for values at each time point and for change from baseline at each post-injection time.

PK/PD analyses will be performed based on correlation of plasma concentrations of C1 INH antigen, functional C1 INH, and C4 complement in conjunction with various safety parameters (e.g., 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.

8.0 DRUG SUPPLIES

CINRYZE and supplies required for CINRYZE reconstitution will be provided by the Sponsor.

8.1 How Supplied

CINRYZE is supplied as a lyophilized powder of 500 U (C1 INH)/vial. The vial of CINRYZE also contains the following inactive ingredients: trisodium citrate, sodium chloride, L-Valine, L-Alanine, L-Threonine, and sucrose.

CINRYZE product and sterile water for injection(s) (SWFI) approved for commercial distribution in the US will be used at all sites. The US sourced vials of CINRYZE will be stored at 2°C–25°C (36°F–77°F) and protected from light. Do not freeze.

8.1.1 Reconstitution of CINRYZE for Intravenous Infusion

Each vial of CINRYZE will be reconstituted with 5 mL of SWFI. The following supplies will be required for reconstitution using aseptic technique: United States Pharmacopeia (USP) SWFI, disinfecting strips, Mix2Vial® transfer device, and silicone-free disposable syringes.

Each infusion will require reconstitution of one (1) or two (2) 500 U vials depending on treatment scheduled (Treatment A [500 U] or Treatment B [1000 U]; see separate Pharmacy Manual). The solution must be used within 3 hours of reconstitution.

8.2 Drug Accountability

The Principal Investigator must maintain records of study drug product received, including dates of receipt, expiry and dispensing, in addition to lot numbers. Study personnel will enter each lot number of CINRYZE administered to a subject in the subject's eCRF. In addition, records must be kept on when and how many study drug vials were dispensed for each individual subject in the trial. Reasons for departure from the expected dosing regimen must also be recorded in both source documents and the eCRF. Sponsor representatives will review drug accountability on an ongoing basis throughout the study. An overall summary of all drug supplies received and used must be recorded on the appropriate forms and signed by the Principal Investigator and clinical monitor at the conclusion of the study. Written records will be maintained documenting a final accounting of study drug received at the investigational site and study drug vials dispensed to subjects. All unopened/unused/used study drug vials will be returned by the clinical research associate (CRA) to the central distributor or destroyed by the Investigator per local regulations or standard operating procedures.

8.3 Drug Labels

Drug will be labeled in accordance with applicable regulatory requirements.

9.0 ADVERSE EVENTS

An AE is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a subject participating in a clinical study with study drug, regardless of causal relationship. An AE includes any condition that (1) was not present prior to study therapy but appeared following initiation of study therapy or (2) was present prior to study therapy, but worsened in severity and/or frequency following initiation of study therapy. **NOTE:** In this study, angioedema attacks after the first dose of study drug will be reported as AEs.

Adverse events will be monitored from the first dose of study drug in Treatment Period 1 through 1-week post-treatment. The Investigator will follow a subject with any AE until the event is either resolved or assessed as stable and, where appropriate, additional written reports

will be provided. The Investigator will evaluate and report the onset date, outcome, end date, duration (if <24 hours), severity (intensity), relationship to study drug, actions taken, and determination of seriousness for each AE. In addition, the Investigator will report if the AE onset occurred during study drug administration or within 24 hours following completion of study drug administration.

9.1 Severity (Intensity) Assessment

The severity (intensity) of AEs will be assessed according to the following definitions:

- Mild: The AE is noticeable to the subject but is easily tolerated and does not interfere with routine activity. The AE may or may not require medication therapy or other therapy.
- Moderate: The AE interferes with routine activity but usually responds to medication therapy or other therapy.
- Severe: The AE significantly limits the subject's ability to perform routine activities and may not respond to medication therapy or other therapy.

If the intensity of an AE changes over time, the maximum intensity experienced should be recorded.

9.2 Relationship to Study Drug

The Investigator will determine the relationship between an AE and the study drug using his or her clinical judgment and the following definitions.

Associated With the Use of Study Drug

There is a reasonable possibility that the event may have been caused by the study drug, as follows:

- **Definitely Related:** The event follows a reasonable temporal sequence relative to the administration of the study drug, and there is no other cause to explain the event (or the event reappears after repeat exposure [positive re-challenge]).
- **Probably Related:** The event follows a reasonable temporal sequence relative to the administration of the study drug, and the event is more likely to be explained by the study drug than by another cause.

- **Possibly Related:** The event follows a reasonable temporal sequence relative to the administration of the study drug, but could have been due to another cause such as the subject's clinical state or other drugs/therapies.

Not Associated With the Use of Study Drug

There is not a reasonable possibility that the event may have been caused by the study drug, as follows:

- **Unlikely to be Related:** The temporal sequence of the event relative to the administration of the study drug makes a causal connection improbable, or the event could plausibly be explained by another cause such as the subject's clinical state or other drugs/therapies.
- **Not Related:** Sufficient information exists to indicate that the event is unrelated to the study drug. For example, the event does not follow a reasonable temporal sequence relative to the administration of the study drug, a causal relationship is considered biologically implausible, or the event is readily explained by another cause such as the subject's clinical state or other drugs/therapies.

9.3 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death.
- A life-threatening event (refers to any AE that places the subject at immediate risk of death from the event as it occurred; a life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death).
- Inpatient hospitalization or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). Emergency room (ER) visits are not considered serious until any of the other serious outcomes are met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Other medically important events that, based upon appropriate medical judgment, jeopardize the subject or may require intervention to prevent any of the above serious outcomes (e.g., a subject is treated in the ER but is not admitted to the hospital).

Serious adverse events must be reported to Shire ViroPharma Drug Safety. Contact information, including telephone and fax numbers, will be provided in the study procedures manual. The Investigator, study coordinator, other designated study personnel, or CRA will report SAEs within 24 hours of becoming aware of the event. Investigators will report all SAEs occurring up to 30 days after the last dose of study drug to Shire ViroPharma and their respective IRA according to local reporting requirements. If there is any doubt whether an AE qualifies as an SAE based on the definitions above, the Investigator should contact the Sponsor. In addition, SAEs with an onset more than 30 days after the last dose of study drug should be reported if considered by the Investigator to be related to study drug (i.e., possibly, probably, or definitely associated with the use of study drug; see Section 9.2).

If an AE is assessed as serious, all SAE information must be recorded using the SAE form (paper or electronic) provided by the Sponsor. Additional follow-up information (e.g., test results, physician narrative, discharge summary, autopsy findings) will be provided to supplement the SAE report, with additional follow-up SAE reports submitted as needed. A copy of all initial and follow-up SAE reports, including supplemental documents, will be maintained by the Sponsor.

All suspected unexpected serious adverse reactions (SUSARs) will be reported by the Sponsor to the relevant competent authorities in accordance with the European Directive 2001/20/EC, US FDA regulation 21CFR312.32, and additional relevant regulatory authorities in accordance with country-specific regulations, as applicable.

9.3.1 Reference Safety Information

For study sites in countries where CINRYZE has received marketing approval for HAE, the approved country product label will serve as the Reference Safety Information (RSI). For study sites in countries where CINRYZE has not received marketing approval, the company core data sheet will serve as the RSI.

9.4 Other Reportable Events

Certain events that occur in the absence of an AE should be reported to Shire ViroPharma Drug Safety as other reportable events using the Other Reportable Information form (paper or electronic) provided by the Sponsor. These include the following:

- Pregnancy exposure (subject becomes pregnant while taking study drug). Should a female subject (or the female partner of a male subject) become pregnant during the study, the subject will inform the Investigator. The subject will be asked to follow up with the study site to report the eventual outcome of the pregnancy. This information will be tracked by Shire ViroPharma Drug Safety.
- Lactation exposure (subject was taking study drug while nursing an infant)
- Accidental exposure (someone other than the study subject was exposed to study drug)
- Overdose (subject received more than the prescribed dose of study drug within a given timeframe)
- Other medication errors that potentially place subjects at a greater risk of harm than was previously known or recognized (e.g., study drug was administered intramuscularly instead of intravenously)

9.5 Recording Adverse Events

All AEs must be recorded in the appropriate section of the eCRF. To improve the quality and consistency of AE data, Investigators should observe the following general guidelines:

- Standard medical terminology should be used rather than colloquial expressions or abbreviations.
- Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.
- If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.
- **Angioedema attacks:** Any angioedema attacks that occur after the first dose of study drug will be recorded as an AE or SAE, as appropriate.

10.0 STUDY MONITORING

The study will be carefully monitored by Shire VIROPHARMA authorized individuals, acting as Shire VIROPHARMA agents with respect to current Good Clinical Practice and standard operating procedures for compliance with applicable government regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

Frequent communication between the study site and the Sponsor is essential to ensure that the study is adequately monitored for safety. The Investigator will make all appropriate safety assessments (e.g., AEs, clinical laboratory tests, vital signs, results from physical examinations) on an ongoing basis. The Sponsor's medical monitor will review safety information from all study sites as it becomes available throughout the study.

11.0 DATA HANDLING

Site staff will enter data into a 21 CFR Part 11 compliant eCRF built and programmed by Shire VIROPHARMA personnel. Data will be reviewed via programmed edit checks triggered by site data entry and manual data validation performed by Shire VIROPHARMA's Clinical Data Management group according to current standard operating procedures (SOPs). Data discrepancies found during data review will be resolved through queries created within the eCRF database (automatic or manual) and answered by site staff. Coding of medical terms/conditions and medications will be performed by Shire VIROPHARMA's Medical Coding Group utilizing the versions of the MedDRA and WHO Drug dictionaries currently at use by Shire VIROPHARMA at the time of the study.

Only individuals with the appropriate user role and training will be granted access to the eCRF. All training must be documented and tracked via Shire VIROPHARMA's SOP and electronic database training policy. Database security is maintained by the use of a unique username and password combination for each approved user, along with user verification checks at set intervals. All database user administration is performed by Shire VIROPHARMA's eCRF Support Group. Database hosting services will be performed by the eCRF software vendor. For Study 0624-301, eCRF software and hosting services will be

provided by Medidata Solutions, New York. Validation certificates for software vendors are on file at Shire VIROPHARMA.

At database lock, all user roles will be changed to 'read only' and no further updates to the database will be allowed. Database close-out documentation will be created by Shire VIROPHARMA's eCRF Support Group and compact discs containing subject data entered into the database will be sent to each site's primary Investigator.

12.0 ETHICAL CONDUCT OF THE STUDY

Sponsor will require investigators to conduct the study in accordance with the ethical principles stated in the Declaration of Helsinki and in compliance with the International Conference on Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice and applicable regulatory requirements.

13.0 SUBJECT CONFIDENTIALITY

Investigator and his/her staff will be required to manage patient data collected for the study in accordance with applicable laws and regulations on personal data protection.

Monitors, auditors and other authorized representatives of Shire VIROPHARMA, the IRA approving the study, as well as any applicable regulatory authorities, will be granted access to the study patients' original medical records for permitted study purposes, in accordance with applicable laws and regulations. In any presentation of study results at meetings or in publications, subject identity will remain confidential.

14.0 INFORMED CONSENT

The ICH has issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent. Legal age for consent to treatments or procedures involved in clinical investigations is defined under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

A properly executed, written **permission** statement (i.e., informed consent) shall be obtained from each parent/legal guardian and **assent** shall be obtained from the child (to the extent that is compatible with the subject's understanding) prior to the subject entering the trial, or prior to performing any unusual or non-routine procedure that involves a risk to the subject. The permission statement must meet all of the required elements of informed consent. A separate assent form should be prepared which explains in very general terms the purpose of the study, what will be expected of or done to the child, and what risks or discomforts may be experienced. A copy of the written permission statement document and assent form to be used will be reviewed and approved by the Sponsor. The document(s) will then be submitted to the IRA for review and approval prior to the start of the study. The Investigator shall provide a copy of the signed and dated permission statement and assent form to the parent/legal guardian and a copy shall be maintained in the subject's medical record. The Investigator, or his/her designee, must document in the case history that informed consent/assent was obtained prior to study participation. If assent was not obtained, this should be recorded in the consent form signed by the parents/legal representative and the Investigator, with the reason(s).

All procedures and documentation required for obtaining parental/legal guardian permission and assent should be in compliance with ICH guidelines, FDA regulations, and local IRA requirements, as well as state and local law.

15.0 INDEPENDENT REVIEWING AUTHORITY APPROVAL

The IRA is the review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. An IRA that is adequately constituted to provide assurance of that protection will be utilized by each investigative site participating in the study.

The IRA will be provided with all appropriate material, including a copy of the informed consent/assent for review. The trial will not be initiated at an investigational site until written approval of the research plan and the informed consent/assent document is obtained from the appropriate IRA and copies of these documents are received by Shire ViroPharma.

Appropriate reports on the progress of this study will be made to the IRA in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

16.0 PUBLICATION POLICY

Investigator's right to publish study results is addressed in the clinical trial agreement between Investigator and Sponsor.

17.0 INVESTIGATOR'S STATEMENT (PROTOCOL 0624-301)

A Phase 3, Multicenter, Randomized, Single-blind, Dose-ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE® (C1 esterase inhibitor [human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of age With Hereditary Angioedema.

In conducting this clinical trial, I agree to be responsible for:

1. Ensuring that the clinical investigation is conducted according to the signed Form FDA 1572 Statement of Investigator (applies to all studies conducted under a US IND).
2. Protecting the rights, safety, and welfare of subjects under my care.
3. Controlling the drugs and biological products under investigation.

I also agree to conduct the trial as outlined in the protocol and in accordance with Shire VIROPHARMA guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

4. Permission to allow Shire VIROPHARMA (or its designee) and FDA, or other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, which ensures subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Shire VIROPHARMA as soon as possible thereafter (no later than 1 week).
5. Submission of the proposed clinical investigation, including the protocol and informed consent/assent form, to a duly constituted Independent Reviewing Authority (IRA) for approval, and acquisition of written approval for each, prior to the use of the study drug.
6. Obtaining written informed consent/assent only after ensuring that the subject, or his/her legal representative, is competent to make the decision, understands what is contained in the informed consent/assent document, and is consenting voluntarily. Written informed consent/assent will be obtained prior to administration of study drug or any non-routine procedures that involve risk; the document contains all the essential elements of consent and has been previously approved by the Sponsor and IRA. Reference of such will be provided in source documentation.
7. Submission of any proposed protocol amendment to the IRA. If the protocol amendment change(s) increase risk to the study population, or adversely affect the validity of the clinical investigation or the subject's rights, full IRA written approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, prior IRA approval may be obtained by expedited review.
8. Adherence to the study protocol. For potential inclusion/exclusion criteria protocol deviations, submission for approval to Shire VIROPHARMA prior to enrollment of study

subjects. Documentation and explanation of individual post-enrollment protocol deviations will be recorded on the appropriate eCRF page or provided in letters to Shire VIROPHARMA.

9. Notification to Shire VIROPHARMA of all serious adverse events, regardless of relationship to study drug, as specified in the protocol. Notification to the IRA of serious adverse events as specified in the protocol and per additional guidelines as provided by the IRA.
10. Notification to IRA of all unanticipated problems within timeframes provided by the IRA. Unanticipated problems may include any incident, experience, or outcome that meets **all** of the following criteria: (1) unexpected (in terms of nature, severity); (2) related or possibly related to participation in the study; (3) and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
11. Provision of adequate trial oversight by personally conducting or supervising the investigation, including, but not limited to: allotting sufficient time to properly conduct and complete the trial within the agreed upon time period; having available an adequate number of qualified staff and adequate facilities for the expected duration of the trial and to conduct the trial properly and safely; and ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and are capable of performing their trial related duties and functions. Qualifications of individuals assigned responsibility for the administration of the investigational product will be compliant with state and local law or national regulations, as applicable.
12. Submission of timely progress reports to the IRA and Shire VIROPHARMA at appropriate intervals not to exceed 1 year and submission of a final report to the IRA within 3 months after the completion, termination, or discontinuation of the clinical investigation.
13. Maintenance of accurate source records from which case reports are based as well as drug accountability records that show the receipt and disposition (on an overall and per subject basis) of all study drug(s) shipped to the Investigator by Shire VIROPHARMA.

In addition, I agree to provide all the information requested in the eCRF presented to me by Shire VIROPHARMA by carefully following the completion guidelines provided as part of the eCRF.

If I opt to terminate, the foregoing shall equally apply.

_____
Investigator's Name (Please Print)

_____ _____
Investigator's Signature Date

18.0 LIST OF REFERENCES

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APPENDIX I: PROCESSING OF SAMPLES FOR ANALYSES OF C1 INH ANTIGEN, C1 INH FUNCTION, C4 COMPLEMENT, AND C1 INH ANTIBODIES IN HUMAN PLASMA

Plasma samples will be analyzed for C1 INH antigen, functional C1 INH, C4 complement, and antibodies to C1 INH according to time points in Schedules 2, 3, 4 and 5. Details of the methods and results will be provided in the clinical study report. Samples for these analyses will be collected as follows:

1. A total of 4 mL of venous blood will be collected via venipuncture or through an indwelling venous catheter into **pre-chilled** K_3EDTA-tubes at **each** sampling time point.
    - If an indwelling catheter with a heparin lock is used to collect the sample, first flush the line, collect 1 mL of blood and properly discard, the next 4 mL of blood should be collected in tube containing K_3EDTA.

2. The K_3EDTA tubes should be kept cold and centrifuged as soon as possible after collection. Place the tubes on wet ice until the samples can be centrifuged. Centrifuge the samples at 1800 to 2000 times gravity (at 4ºC if possible) for 15 ± 2 minutes. Immediately transfer the resulting plasma as follows:
    - Transfer the plasma equally between the 2 pre-chilled plastic transfer tubes. Carefully remove the plasma from the cells, avoiding contamination of plasma with white cells or platelets, since these may contribute enzymes that will falsely elevate measurements. Tubes should be appropriately labeled using labels supplied by the Sponsor.
    - The **plasma must be stored frozen at −70ºC** or colder ideally within 30 minutes of collection. If necessary, samples can be stored on slushy ice for up to but not exceeding 4 hours. Samples should **never** be stored at -20ºC. In addition, thawing and re-freezing can also lead to ex vivo cleavage of complement components and spurious production of activation products. Therefore, samples cannot be allowed to thaw until analysis. Samples are to be assayed on the first thaw.
    - All deviations to the collection procedures should be recorded and be included in the documentation with the sample shipment to the analytical laboratory.
    - All shipping instructions will be provided in a separate laboratory manual.

CAUTION! Samples for complement testing are sensitive to cold inactivation. Samples must be stored at −70°C or colder.

One set of plasma samples for each subject will be shipped frozen on dry ice to the analytical laboratory using shipping containers supplied by the Sponsor. The other set of samples will be stored frozen at −70°C or below and shipped to the laboratory following the schedule/instructions provided in the laboratory manual.

All samples will be analyzed within the established stability for the samples and will be properly disposed of after they have exceeded their established stability.

APPENDIX II: RECOMMENDED PROCEDURES FOR SUSPECTED VENOUS THROMBOEMBOLISM OR OTHER THROMBOTIC OR THROMBOEMBOLIC EVENTS