PROTOCOL: 0624-209

TITLE:	A Phase 3, Open-label, Single-period Study to Evaluate the Safety and Treatment Effect of Intravenous Administration of CINRYZE® (C1 Inhibitor [Human]) for the Prevention of Angioedema Attacks and Treatment of Breakthrough Attacks in Japanese Subjects with Hereditary Angioedema (HAE)
DRUG:	C1 Inhibitor [Human]
IND:	Non-IND
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire ViroPharma, Inc. 300 Shire Way, Lexington, MA 02421 USA
INVESTIGATORS:	Multicenter
SPONSOR MEDICAL MONITOR	PPD, MD, PhD Office phone: PPD Mobile phone: PPD Email: PPD
LOCAL MEDICAL MONITOR	PPD, MD, PhD PAREXEL International 1-21-2, Shinkawa, Chuo-Ku Tokyo, Japan, 104-0033 Office phone: PPD Mobile phone: PPD Email: PPD
PROTOCOL HISTORY:	Original Date: 20 January 2014 Amendment 1: 02 June 2014 Amendment 2: 05 August 2014 Amendment 3: 17 September 2014 Amendment 4: 16 February 2016 Amendment 5: 30 August 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: PPD	**Date:** PPD
Peng Lu, MD, PhD	

Investigator's Acknowledgement

I have read this protocol for Shire ViroPharma Study 0624-209.

Title: A Phase 3, Open-label, Single-period Study to Evaluate the Safety and Treatment Effect of Intravenous Administration of CINRYZE® (C1 Inhibitor [Human]) for the Prevention of Angioedema Attacks and Treatment of Breakthrough Attacks in Japanese Subjects with Hereditary Angioedema (HAE)

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

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

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

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

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

Investigator Name and Address: (please hand print or type)	{***The investigator completes the bottom section of the protocol signature page***}

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Amendment 5 to Protocol 0624-209 includes the following changes:

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **30 Aug 2016**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The Sponsor's Medical Monitor has changed to PPD, MD, PhD.		Title Page, Signature Page
Clarified that caregivers (such as a parent or guardian) are allowed to administer the investigational product to any subject who may need assistance after the caregiver completes the detailed self-administration training outlined in the protocol.		Synopsis, Sections 3, 5.3.1, 6.12.1, 6.14, and 8.1.1
Modified exclusion criteria to decrease the time from 7 days to 3 days for use of C1 INH therapy or blood products prior to the first dose of investigational product.		Synopsis, Schedule 1, Sections 3 and 4.2
Modified exclusion criteria to require that females have no change in hormonal contraceptive regimen or hormonal replacement therapy within 2 months (not 3 months as previously stated) before the first dose of investigational product, to be consistent with the inclusion criteria regarding female contraception.		Synopsis, Schedule 1, and Section 4.2
Clarified that subjects (or caregivers) also have the option to self-administer one or more doses of CINRYZE at the study site, once they have completed the required training and are deemed independent.		Synopsis, Schedule 2, Sections 3 and 5.3.1
Clarified procedures related to any breakthrough attack reported during the study and the required assessments if the subject is treated with CINRYZE for the breakthrough attack.		Synopsis, Sections 3, 6.11, 6.12.1, and 6.12.2
Clarified that subjects less than 5 years of age are not required to complete the pain assessment using a visual analogue scale (VAS).		Synopsis, Sections 6.1 and 6.12.2
Modified the definitions for symptom severity (intensity) of breakthrough attacks so that the definitions reflect the impact on subject's daily living rather than the need for medications or therapies.		Synopsis, Section 6.12.2
Clarified that the 1-month post-treatment visit is to occur at 30 (±2) days post-treatment.		Synopsis, Schedule 3, Sections 3 and 6.8
Clarified the efficacy analyses for treatment of breakthrough attacks to allow bridging to prior Phase 3 clinical studies assessing the efficacy of CINRYZE for treatment of acute attacks.		Synopsis and Section 7.6.2
Clarified text and inclusion criteria regarding HAE diagnosis which allows the collection of a blood sample at screening to confirm the deficiency in the levels of C1 INH and/or C1 INH activity for subjects who have no historical confirmation of HAE.		Schedule 1 (footnote b) Synopsis, Sections 4.1 and 6.1
Revised the schedule of assessments for measurement of body weight and blood sample collection for coagulation parameters; Visit 12 assessments have been deleted and Visits 8 and 16 have been added.		Schedule 1
Clarified PK/PD blood sample collections for subjects who prematurely discontinue from the study.		Schedule 3 and Schedule 4

Clarified collection of PK blood samples for subjects who present to the site with a breakthrough angioedema attack and receive treatment with CINRYZE.	Schedule 4 and Section 6.8
Clarified that vital sign assessments include the measurement of pulse rather than heart rate. In addition, the window around collection of pre- and post-dose vital signs has been extended to allow flexibility for site personnel.	Schedule 1, Schedule 3, and Section 6.3
Extended the duration for recording of concomitant medications to include from the start of dosing (Dosing Visit 1) through the 1-Month Post-treatment Follow-up Visit.	Schedule 3 and Section 6.5.2
Added 3 post-marketing studies with IV CINRYZE to clinical experience section of the introduction, along with a cross-reference to CINRYZE Investigator's Brochure.	Section 1.1.2
Deleted text allowing sites to use the PQ interval if the PR interval was not reported on the 12-lead ECG. The PR interval is more clinically relevant than the PQ interval.	Section 6.4
Revised the total volume of blood collected during the study for subjects who weigh 25 kg or more.	Section 6.9
Removed the requirement to record in the CRF the total amount of investigational product received for subjects who discontinue study medication.	Section 6.15
Added definition for considering a subject is lost to follow-up.	Section 6.15.1
Provided a definition of treatment-emergent adverse events (TEAEs) and clarified that the safety endpoint will include TEAEs.	Synopsis and Section 7.4
Added a summary table of all previous protocol amendments.	Appendix 1

Other administrative and clarifying revisions have been made throughout the protocol for consistency with these modifications.

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the Investigator must fax or email the Shire Clinical Trial Serious Adverse Event Form within 24 hours to PAREXEL International Pharmacovigilance, acting on behalf of Shire Pharmacovigilance, using the details below.

Fax: PPD

Email: PPD

For protocol- or safety-related issues, the Investigator must contact the PAREXEL Medical Monitor:

PPD, MD, PhD
PPD, Medical Services, PAREXEL International

Office phone: PPD (Monday–Friday, 09:00–17:00 JST)

Fax: PPD

Mobile phone: PPD (24-hour coverage)

Email: PPD

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 9.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	**Email Address**
North and South America	PPD
European Union and Rest of World	PPD

Telephone numbers (provided for reference if needed):

Shire, Wayne, PA (USA)
PPD or PPD

Shire, Basingstoke, Hampshire (UK)
PPD

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
AE-QoL	Angioedema quality of life
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\tau}$	Area under the plasma concentration-versus-time curve from time 0 to selected time point
BP	Blood pressure
BUN	Blood urea nitrogen
C1 INH	C1 esterase inhibitor or C1 inhibitor
C_{avg}	Average concentration at steady state
CBC	Complete blood count
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
EACA	Epsilon-aminocaproic acid
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good clinical practice
HAE	Hereditary angioedema
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonisation
ICSR	Individual case safety report
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Incurred sample reproducibility
ISS	Incurred sample stability
ITT-S	Intent-to-Treat Safety (population)
IV	Intravenous
K_{el}	Elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
RBC	Red blood cells
SAE	Serious adverse event
SOP	Standard operating procedure
SWFI	Sterile Water for Injection
T/TE	Thrombotic/thromboembolic

Abbreviation	Definition
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to maximum concentration or maximum pharmacodynamic response
US	United States
USP	United States Pharmacopeia
VAS	Visual analogue scale
V_Z	Volume of distribution
WBC	White blood cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study Title: A Phase 3, open-label, single-period study to evaluate the safety and treatment effect of intravenous administration of CINRYZE® (C1 inhibitor [human]) for the prevention of angioedema attacks and treatment of breakthrough attacks in Japanese subjects with hereditary angioedema (HAE) (Protocol 0624-209).

Study Objectives:

The objectives of the study are to assess:

- The safety and tolerability of CINRYZE administered by intravenous (IV) infusion in Japanese subjects with HAE;
- The pharmacokinetics (PK) and pharmacodynamics (PD) of CINRYZE administered by IV infusion in this subject population; and
- The treatment effect of CINRYZE administered by IV infusion for the prevention of angioedema attacks and treatment of breakthrough attacks in this subject population.

NOTE: A breakthrough attack is defined as an angioedema attack that occurs during long-term prevention therapy with CINRYZE.

Study Population:

Number of Subjects

A sufficient number of subjects will be enrolled to ensure that a minimum of 6 subjects complete the study. When 6 subjects have completed the 12-week treatment period, no further subjects will be enrolled; however, all subjects already enrolled in the study will be followed to study completion. If subjects withdraw or discontinue after enrollment, additional subjects may be enrolled to ensure at least 6 subjects complete the study.

Inclusion Criteria

To be eligible for this protocol, a subject must:

1. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. Be ≥2 years of age.
3. Meet the following minimum body weight criteria:
    - Subjects 2 to 5 years of age must weigh at least 12.5 kg; and
    - Subjects 6 years of age and above must weigh at least 25 kg.
4. Have a confirmed diagnosis of Type I or Type II HAE. **NOTE:** Diagnosis may be based on historical data including family history, clinical symptoms (characteristic attacks), and documentation of low level of C1 INH protein and/or C1 INH activity.
5. Have a history of at least one angioedema attack per month (on average) during the 3 consecutive months immediately before enrollment.

6. Agree to adhere to the protocol-defined schedule of assessments and procedures.
7. Agree to avoid his/her known angioedema attack triggers during the study to the best of his/her ability.
8. If a female of reproductive age, be postmenopausal (≥12 months following cessation of menstruation), surgically sterile, or following an acceptable method of birth control (and agree to continue its use through 1 month after the last dose of study drug):
   - Non-hormonal methods (eg, abstinence, barrier control) for at least 1 complete menstrual cycle before the Screening Visit.
   - Stable doses of estrogen and/or progestin containing products for at least 2 months before the Screening Visit.
9. If a male of reproductive age, be surgically sterile or agree to follow an acceptable method of birth control (eg, abstinence, barrier control) from the Screening Visit through 2 months after the last dose of study drug.
10. If an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

    OR

    If a child or minor (<20 years of age), have a parent/legal guardian who is informed of the nature of the study provide written informed consent (ie, permission) for the child to participate in the study before any study-specific procedures are performed. Assent will be obtained from children ≥14 years of age.

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 be 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. Have received C1 INH therapy or any blood products within 3 days before the first dose of study drug.
5. Have had signs or symptoms of an angioedema attack within 2 days before the first dose of study drug.
6. Have any change (start, stop, or change in dose) in androgen therapy (eg, danazol, oxandrolone, stanozolol, testosterone), tranexamic acid, epsilon-aminocaproic acid (EACA), or other antifibrinolytics within 14 days before the first dose of study drug.
7. If female, have started taking or changed the dose of any hormonal contraceptive regimen or hormone replacement therapy (eg, estrogen/progestin containing products) within 2 months before the first dose of study drug.
8. Be pregnant or breastfeeding.

9. Have received an investigational drug other than those required for prevention or treatment of angioedema attacks within 30 days before the first dose of study drug.
10. 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.

Duration of Study: Individual participation from Screening through completion of the 1-Month Post-treatment Follow-up Visit will last approximately 5 months.

Drug Product: CINRYZE is supplied as a lyophilized powder in single use vials containing 500 U of C1 INH per vial. Each vial of CINRYZE will be reconstituted with 5 mL of Sterile Water for Injection, USP. When reconstituted, CINRYZE contains C1 INH at a concentration of 100 U/mL in a citrate-buffered solution comprising sucrose, sodium chloride, L-valine, L-alanine, and L-threonine. Each 500 U dose will require reconstitution of 1 vial, and each 1000 U dose will require reconstitution of 2 vials. The solution must be used within 3 hours after reconstitution.

Study Drug Administration: Doses of CINRYZE for the prevention of angioedema attacks will be administered at the investigational site or at the subject's home (including the option for independent self-administration). Two different doses of CINRYZE will be administered depending on subject age, as described below:

Subjects 2 to 5 years of age – 500 U of CINRYZE will be administered by IV infusion twice weekly (every 3 or 4 days) for 12 weeks.

Subjects 6 years of age and older – 1000 U of CINRYZE will be administered by IV infusion twice weekly (every 3 or 4 days) for 12 weeks.

Study Design: This single-period, open-label study will be conducted at multiple investigational sites in Japan. All study sites will conduct the study in accordance with the protocol, International Conference on Harmonisation, and Good Clinical Practice standards. Data from all sites will be pooled for purposes of analysis and will be reported in the final clinical study report.

This is an outpatient study; however, subjects may require an overnight stay at the site for those days on which serial PK/PD blood samples are collected. Subjects would be discharged the following day after collection of the 24-hour PK/PD blood sample.

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

Subjects who are at least 12 years of age and/or considered suitable candidates (ie, those with a physical and mental capability of learning, adequate venous access, and willing to self-administer) will undergo detailed training at the study site on the skills needed for self-administration of investigational product (see Schedule 2). Alternatively, a subject's caregiver

(such as a parent or guardian) can receive this training and will be allowed to administer the investigational product to a subject who requires assistance. The administration of the first 2 doses of investigational product should be done by the Investigator or qualified delegate at the study site, while subjects (or caregivers) who elect to self-administer will receive training materials and be instructed on the process of handling and reconstituting CINRYZE, proper venous access, and correct administration by IV infusion. Initiation of subject (or caregiver) self-administration with supervision by the Investigator or qualified delegate can begin on Dosing Visit 3 and continue as long as needed, but it is expected that subjects (or caregivers) may require supervised training through to Dosing Visit 8. After completing the required training, and provided the subject (or caregiver) is deemed independent according to the criteria described in Section 5.3.1, a subject (or caregiver) may elect to self-administer one or more doses of CINRYZE at home or at the study site. The Investigator's acknowledgement that a subject (or caregiver) is certified for independent self-administration will be entered in the CRF.

During the study, subjects will be asked to avoid known triggers of angioedema attacks to the best of their ability (eg, foods, activities, medical procedures, environments). To the extent possible, subjects should postpone elective procedures (eg, dental work) while participating in the study. If a procedure cannot be postponed, the subject (or caregiver) will notify the Investigator and the information will be recorded in the CRF.

It is recommended that treatment of breakthrough attacks (ie, angioedema attacks that occur during long-term prevention therapy with CINRYZE) occurs at the investigational site whenever possible so that clinical assessments can be completed as specified. It is preferred that subjects receive CINRYZE within 4 hours but not more than 8 hours after the onset of breakthrough attack symptoms if treatment can occur at the investigational site.

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

Post-treatment follow-up visits will be performed 1 week (±1 day) and 1 month (30 ±2 days) after the last dose of study drug. If a subject prematurely discontinues investigational product, regardless of the reason, the Early Discontinuation Visit procedures listed in Schedule 3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-Week and 1-Month Post-treatment Follow-up visits.

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

- Schedule 1: Clinical Study Assessments – Screening and Treatment Period;
- Schedule 2: Investigational Product and Self-administration Training;
- Schedule 3: Clinical Study Assessments – Early Discontinuation Visit and 1-Week and 1-Month Post-treatment Follow-up Visits;
- Schedule 4: Blood Sample Collection Time Points for PK/PD Assessments.

Study Diary

Throughout the study, subjects (or caregivers) will use a study diary each day to document specific information about any angioedema attack symptoms that occur (eg, including the location, severity, pain score, and duration of symptoms) and details on self-administration of investigational product. At the first dosing visit (Dosing Visit 1), study personnel will instruct each subject (or caregiver) how to complete the study diary.

Study personnel will review the diary for completeness and accuracy at each scheduled dosing visit. The Investigator or designee will use subject-reported diary data as reference information, in addition to any other available medical records, to record and evaluate events related to breakthrough angioedema attacks in the CRF.

Definition of an Angioedema Attack

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

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

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

In this study, angioedema attacks will not be reported as adverse events unless the attack meets the definition of a serious adverse event.

Treatment of Breakthrough Angioedema Attacks

A breakthrough attack is defined as an angioedema attack that occurs during long-term prevention therapy with CINRYZE. If a subject receives CINRYZE for treatment of a breakthrough angioedema attack, they should continue their protocol-defined treatment schedule without alteration regardless of when the supplemental dose is administered.

If a breakthrough angioedema attack occurs during the 12-week treatment period through 1-week post-treatment, a supplemental dose of CINRYZE may be administered by IV infusion for treatment of the attack either by the Investigator (or qualified delegate) or subject (or caregiver) if trained and deemed independent to self-administer (1000 U for subjects ≥6 years of age or 500 U for subjects 2-5 years of age). If the subject does not adequately respond to the initial dose within 1 hour, a second dose of CINRYZE may be administered (1000 U for subjects ≥6 years of age or 500 U for subjects 2-5 years of age). It is recommended that treatment of breakthrough

attacks occurs at the investigational site whenever possible so that clinical assessments can be completed as specified. It is preferred that subjects receive CINRYZE within 4 hours, but not more than 8 hours after the onset of breakthrough attack symptoms, if treatment can occur at the investigational site.

Subjects at least 12 years of age or their caregivers) who have completed the required self-administration training and deemed independent (per criteria specified in Section 5.3.1) may elect to self-administer CINRYZE for a breakthrough attack. Note: Subjects (or caregivers) who are participating in self-administration training and not yet qualified as independent cannot self-administer CINRYZE for a breakthrough attack; rather they must seek treatment at the investigational site. If a subject (or caregiver) who self-administers CINRYZE for treatment of a breakthrough attack does not respond adequately after instructed treatment (ie, 2 doses separated by 1 hour), they should notify the Investigator and seek medical attention or report to study site to seek further treatment and relief of symptoms.

In addition to administration of CINRYZE, subjects are allowed to receive symptomatic treatment for breakthrough angioedema attacks (eg, IV fluids). The administration of narcotics and antiemetics is discouraged during the 4-hour post-infusion assessment period to allow for evaluation of the response to CINRYZE. Other treatments for angioedema attacks (eg, another C1 INH product such as Berinert P, tranexamic acid, fresh frozen plasma) are not permitted at the investigational site unless a subject does not adequately respond following treatment with CINRYZE (ie, 2 doses separated by 1 hour).

Assessment of Breakthrough Angioedema Attacks

If a breakthrough attack occurs, subjects (or caregivers) should assess and record the following information in the study diary:

- Presence of pain or swelling at each anatomic location (ie, upper airway [laryngeal], gastrointestinal/abdominal, facial, genitourinary, and extremity/peripheral) by indicating the overall severity (ie, mild, moderate, or severe [as defined below])
- Overall amount of pain associated with the breakthrough attack using a visual analogue scale (VAS; only for subjects at least 5 years of age)
- Any triggers associated with the attack
- Any health care visit for the attack (investigational site, clinic or hospital/emergency department)
- Any medications received to manage attack symptoms
- Duration of symptoms (ie, time symptoms start to improve and time symptoms completely resolve)

In addition to the subject's self-assessment, the Investigator should assess and record the overall severity of the attack if the subject seeks treatment for symptoms at the site.

Treatment with CINRYZE

The Investigator (or qualified delegate) or subject (trained and deemed independent) may administer a supplemental dose of CINRYZE to treat the breakthrough attack. Subjects self-administering CINRYZE will record clinical assessments associated with breakthrough attacks in the study diary.

Following the administration of CINRYZE, subjects (or caregivers) will record their symptoms (the presence of pain or swelling at each anatomic location) and assess the overall severity of the breakthrough attack every 15 minutes for up to 4 hours post-infusion using the following scale:

- No symptoms.
- Mild: The attack symptoms are noticeable but are easily tolerated by the subject and do not interfere with the subject's daily activities.
- Moderate: The attack symptoms interfere with the subject's ability to attend work/school or participate in family life and social/recreational activities.
- Severe: The attack symptoms significantly limit the subject's ability to attend work/school or participate in family life and social/recreational activities.

Subjects (or caregivers) also will rate the overall amount of pain associated with the breakthrough attack using a VAS (for subjects at least 5 years of age) on the same schedule as overall attack severity.

In addition to the subject's self-assessment, the Investigator should assess and record the overall severity every 15 minutes for up to 4 hours post-infusion if the subject seeks treatment at the site.

NOTE: If a subject has adequately responded to treatment with CINRYZE, the subject may omit further assessments up to 4 hours post-infusion (and if applicable, be discharged from the investigational site) provided that overall attack severity has been assessed for at least 1 hour.

Subject diary data will be used by study personnel to record the onset date and time of the breakthrough attack, as well as the date and time of onset of symptom improvement and Complete Resolution (defined in Efficacy Endpoints) in the CRF.

Safety Monitoring

Safety will be assessed by monitoring adverse events and changes in physical examinations, vital signs, and clinical safety laboratory testing. In addition, subjects will be monitored for the development of antibodies to C1 INH. If clinically indicated, study personnel may perform examinations to actively monitor subjects for possible venous thromboembolism or other thrombotic or thromboembolic (T/TE) events. Investigators will comply with recommended procedures for the management of all suspected T/TE events.

Stopping Rules

If an anaphylactic reaction or a thrombotic or thromboembolic event occurs in any subject, stopping rules for the individual subject and for the overall study will be employed (see Section 5.5).

Sample Collection for PK, PD, and C1 INH Antibody Analyses

Subjects will have blood samples collected for the determination of plasma concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), complement C4, and C1q. In addition, blood samples will be collected at Visits 1 (baseline), 8, 16, and 24 and 1 month (30 ±2 days) after the last dose of study drug for C1 INH antibody analyses.

Quality of Life

The Angioedema Quality of Life (AE-QoL) is a questionnaire on the quality of life of patients suffering from recurrent angioedema. It consists of 17 specific questions that are associated with work, physical activity, free time, social relations, and diet. Subjects will be asked by study personnel how often they were restricted by—as well as the difficulties and problems that could be associated with—recurrent swellings (angioedema) during the previous 4 weeks. The AE-QoL questionnaire will be completed at the time points specified in Schedule 1 and Schedule 3. This instrument will be administered as appropriate for each subject's age (ie, includes option of guidance from parent/guardian).

Self-administration Survey

A self-administration survey containing questions for subjects (or caregivers) and the Investigator's assessment of the overall experience with self-administration of IV CINRYZE will be completed on Visit 24 (see Schedule 1).

Statistical Considerations:

Statistical Methods: Data will be summarized using the same methods that were used in the overseas development program for IV CINRYZE. Experimental results will be summarized using descriptive statistics (n, mean, standard deviation or standard error, median, and range for continuous endpoints; number and percent of subjects in each category for categorical endpoints). To establish context, efficacy/pharmacology results from this study may be superimposed (eg, graphically) on experimental data from previous overseas studies, as appropriate.

Safety Analyses:

The following will be assessed:

- Adverse events (including treatment-emergent adverse events).
- Summary statistics and changes from baseline to post-baseline for laboratory testing, vital signs, and, if applicable, any ECG findings will be presented.

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

PK/PD Analyses: Concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), and complement C4 and C1q for individual subjects will be determined using fully validated bioanalytical methods. Results will be summarized using descriptive statistics at each time point with and without baseline correction. C1q concentrations will be assessed at baseline only (ie, pre-infusion, Dosing Visit 1).

Pharmacokinetic/pharmacodynamic parameters will be calculated using observed and/or baseline-corrected concentration-versus-time data using non-compartmental techniques. An exploratory PK/PD analyses may be performed based on correlation of plasma concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), and C4 complement and efficacy and safety responses.

Efficacy Analyses:

Prevention of Angioedema Attacks

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

- The number of angioedema attacks recorded during the treatment period, normalized for the number of days the subject participated in the period.
- The overall frequency of angioedema attacks occurring during the treatment period will be calculated and compared with historical baseline values.
- Summary of all attacks during the treatment period, including:
    - Anatomic location.
    - Severity (intensity).
    - Duration.
    - Number of rescue treatments (including antiemetics, narcotics, or C1 INH therapy, including administration of rescue CINRYZE).
- Effects of therapy on quality of life (results of AE-QoL questionnaire).

Treatment of Breakthrough Angioedema Attacks

The following efficacy endpoints for treatment of breakthrough angioedema attacks will be assessed by CINRYZE-treated attack number:

- The number of subjects who achieve Clinical Relief. Clinical Relief is defined as a sustained reduction from pre-infusion in the attack severity within 4 hours after initiation of treatment with CINRYZE.
- Time to onset of Clinical Relief.
- The number of subjects who achieve Complete Resolution. Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack.

- Time to Complete Resolution.

Other analyses may be performed to establish context of the efficacy results from this study with previous Phase 3 CINRYZE studies.

Schedule 1: Clinical Study Assessments – Screening and Treatment Period

Procedure	Screening [a]	TREATMENT PERIOD (BY STUDY WEEK)																							
		1		2		3		4		5		6		7		8		9		10		11		12	
		DOSING VISITS (1 to 24)																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Informed consent (or written permission and assent)	X																								
Medical/angioedema history and physical exam	X [b]																								
Physical exam update [c]		X							X								X								X
Prior/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	X	X
Height	X																								
Body weight	X								X								X								X
Vital signs (BP, pulse) [d, e]	X	X	X		X		X		X		X		X		X		X		X		X		X		X
12-lead ECG [d]	X																								
Hematology and clinical chemistry [c]	X	X							X								X								X
Urinalysis with microscopy [c]	X								X								X								X
Coagulation (PT, aPTT, INR) [c]	X								X								X								X
Virology screening [f]	X																								
Pregnancy testing [c, g]	X	X																								X
Study drug administration		See Schedule 2																							
Daily angioedema attack monitoring and study diary [h]		X———																							———X
Adverse events	X [i]	X———																							———X
Immunogenicity (C1 INH antibody) [c]		X							X								X								X
Quality of life questionnaire (AE-QoL) [c]		X							X								X								X
Self-administration survey																									X
PK/PD assessments		X———												See Schedule 4											———X

Schedule 1: Clinical Study Assessments – Screening and Treatment Period

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

AE-QoL=angioedema quality of life; aPTT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 inhibitor; ECG=electrocardiogram; INR=international normalized ratio; PD=pharmacodynamics; PK=pharmacokinetics; PT=prothrombin time

a: All subjects will have a screening evaluation within 21 days before the first dose (Dosing Visit 1). Subjects must not have received any C1 INH or blood products within 3 days before the first dose of study drug and must not have had signs or symptoms of an angioedema attack within 2 days before the first dose of study drug. If at the screening visit, a subject meets both of these criteria, the screening and Dosing Visit 1 assessments can occur on the same day (see Section 6). For subjects who weigh less than 25 kg, screening must occur at least 14 days before Dosing Visit 1.

b: If functional C1 INH testing is not performed as standard of care to diagnose HAE, a blood sample will be collected at screening to confirm the deficiency in the levels of C1 INH and/or C1 INH activity.

c: On dosing days, specified procedures and blood and urine sample collections should be performed prior to study drug administration.

d: Vital signs and ECGs will be measured using standard methods at each study site. Additional vital signs measurements and ECGs may be performed during the study if clinically indicated. Vital sign measurements will not be collected at Visits 10, 12, 14, 18, 20, and 22 from subjects who independently self-administer investigational product at home.

e: On dosing days, vital signs should be obtained ≤30 min before the start of the infusion, ≤15 min after completion of the infusion, and between 30 min and 1 h after completion of the infusion.

f: HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).

g: All females of childbearing potential (in accordance with standards at the site).

h: Subjects (or caregivers) will also record information on the self-administration of investigational product in the study diary.

i: Adverse events will be collected from the time informed consent is signed.

See Schedule 3 for clinical study assessments at the Early Discontinuation Visit (if applicable) and the 1-Week and 1-Month Post-treatment Follow-up Visits.

Schedule 2: Investigational Product and Self-administration Training

	TREATMENT PERIOD (BY STUDY WEEK)																							
	1		2		3		4		5		6		7		8		9		10		11		12	
	DOSING VISITS (1 to 24)																							
Procedure	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Investigational product administration [a]																								
Study site visits	X[b]	X[b]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c,d]								X[f]								X[f]
Optional at home visits									X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	
Follow-up contact										X[g]		X[g]		X[g]				X[g]		X[g]		X[g]		
Training at the study site associated with self-administration																								
Investigator or qualified delegate instruct subjects	X[b]	X[b]																						
Subject self-administration with supervision [f]			X[c]	X[c]	X[c]	X[c]	X[c]	X[c,d]								X[f]								X[f]

a: Subjects will receive study drug twice weekly (every 3 or 4 days) during the 12-week treatment period (Dosing Visits 1-24). Study drug will be administered to all subjects at the investigational site for Dosing Visits 1 through 8, 16, and 24. Other doses of study drug may be administered at the investigational site or at the subject's home. Subjects (at least 12 years of age or their caregivers) considered suitable candidates (ie, those with a physical and mental capability of learning, adequate venous access, and willing to be trained) will be allowed to self-administer one or more doses of study drug after receiving detailed training by the Investigator or qualified delegate (see Section 5.3.1) and having demonstrated the necessary skills. Doses of CINRYZE that are self-administered will be entered as such in the CRF.

b: Investigator or qualified delegate will administer the first 2 doses of investigational product while instructing the subject on the process.

c: Subjects may initiate the practice of self-administration with direct supervision by the Investigator or qualified delegate.

d: Self-administration supervised by the Investigator or qualified delegate at the study site may continue after Dosing Visit 8 until the subject (or caregiver) feels confident with the technical and medical aspects and is deemed independent for self-administration. Details regarding self-administration will be documented and entered in CRF.

e: When deemed independent (ie, subjects [or caregivers]are able to correctly reconstitute study drug, access a vein for infusion, and successfully administer the drug on at least 2 consecutive training visits), a subject may elect to self-administer doses of investigational product at home or at the study site. The Investigator's acknowledgement that a subject is certified for independent self-administration will be entered in the CRF.

f: Subjects (or caregivers) will be allowed to self-administer at the study site. The Investigator or qualified delegate will be available for follow-up training if any of the necessary skills on self-administration have not been retained and to address any issues from the subject's perspective.

g: Study personnel will contact the subject (or caregivers) by telephone to check on study compliance/competency with self-administration, document any AEs, and update any concomitant medications. Telephone contact will be documented in the source notes at the study site.

See Schedule 3 for clinical study assessments at the Early Discontinuation Visit (if applicable) and the 1-Week and 1-Month Post-treatment Follow-up Visits.

Schedule 3: Clinical Study Assessments – Early Discontinuation Visit and 1-week and 1-month Post-treatment Follow-up Visits

Procedure	Early Discontinuation Visit [a] [If Applicable]	1-Week (±1 day) Post-treatment Visit [All Subjects]	1-Month (30 ±2 days) Post-treatment Visit [All Subjects]
Physical exam update	X		
Concomitant/post-treatment medications	X	X	X
Body weight	X		
Vital signs (BP, pulse) [b]	X		
Hematology and clinical chemistry	X		
Urinalysis with microscopy	X		
Coagulation (PT, aPTT, INR)	X		
Pregnancy testing [c]	X		
Daily angioedema attack monitoring and study diary	X [d]	X	
Adverse events/SAEs [e]	X	X	X
Immunogenicity (C1 INH antibody)	X		X
Quality of life questionnaire (AE-QoL)	X		
PK/PD assessments	X [f]		

AE-QoL=angioedema quality of life; aPTT=activated partial thromboplastin time; BP=blood pressure; C1 INH=C1 inhibitor; INR=international normalized ratio; PD=pharmacodynamics; PK=pharmacokinetics; PT=prothrombin time; SAE=serious adverse event

a: If a subject prematurely discontinues investigational product, regardless of the reason, the Early Discontinuation Visit procedures listed in Schedule 3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-Week and 1-Month Post-treatment Follow-up visits.

b: Vital signs will be measured using standard methods at each study site.

c: All females of childbearing potential (in accordance with standards at the site).

d: Subjects who prematurely discontinue should complete the study diary on the day of discontinuation.

e: Adverse events will be collected through 7 days after the last dose of investigational product. Investigators will report all serious adverse events (SAEs) that occur up to 30 days after the last dose of study drug to PAREXEL International Pharmacovigilance. In addition, SAEs considered by the Investigator to be related to study drug that occur >30 days after the last dose will be reported.

f: If a subject prematurely discontinues on a blood sample collection day for PK/PD assessments (see Schedule 4), every effort should be made to collect the PK/PD sample(s) according to schedule. If a subject discontinues on a day when PK/PD assessments are not scheduled, a single PK/PD blood sample should be collected with sampling time recorded in the CRF.

Schedule 4: Blood Sample Collection Time Points for PK/PD Assessments

C1 INH Antigen (Protein Volume), Functional C1 INH Activity (Potency), and Complement C4	TREATMENT PERIOD (BY STUDY WEEK)				Early Discontinuation Visit [If Applicable]
	Week 1	Week 2	Week 3	Week 12	
Sample Time	Dosing Visit 1	Dosing Visit 3	Dosing Visit 5	Dosing Visit 24	
Prior to infusion of study drug	X [a]	X	X	X	X [g]
0.5 hour after start of infusion	X [b]			X [b]	
1 hour after start of infusion	X [c]			X [c]	
2 hours after start of infusion	X [c]			X [c]	
6 hours after start of infusion	X [c]			X [c]	
24 hours after start of infusion	X [d]			X [d]	
48 hours after start of infusion	X [d]			X [d]	
72 hours after start of infusion	X [d, e]			X [d]	
96 hours after start of infusion	X [d, f]			X [d]	

C1 INH=C1 inhibitor; PD=pharmacodynamics; PK=pharmacokinetics

a: C1q concentration will also be assessed from the baseline sample (pre-infusion at Dosing Visit 1).

b: Collect within ± 5 min of the specified time.

c: Collect within ± 15 min of the specified time.

d: Collect within ± 2 h of the specified time.

e: If Dose 2 is scheduled to be administered 3 days after Dose 1, the 72-hour sample should be collected pre-infusion and the 96-hour sample should be omitted.

f: If Dose 2 is scheduled to be administered 4 days after Dose 1, the 96-hour sample should be collected pre-infusion.

g: If a subject prematurely discontinues on a day when PK/PD assessments are scheduled every effort should be made to collect the PK/PD sample(s) as indicated. If a subject discontinues on a day when PK/PD assessments are not scheduled, a single PK/PD blood sample should be collected with sampling time recorded in the CRF.

NOTE: If a subject presents to the site with a breakthrough angioedema attack, every effort should be made to obtain a PK blood sample before treatment. In addition, if the subject receives CINRYZE for treatment of the attack, every effort should be made to obtain a 1-hour post-treatment sample; if a second dose of CINRYZE is administered, an additional 1-hour post-treatment sample should be obtained if possible. These samples will be collected as an unscheduled visit and analyzed for C1 INH antigen (protein volume) and functional C1 INH activity (potency).

1 INTRODUCTION

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by an inherited or spontaneous gene mutation on chromosome 11 that results in a quantitative or functional deficiency of C1 inhibitor (C1 INH) protein (Bernstein 2011).[1] C1 inhibitor is a serine protease inhibitor (or "serpin") that regulates the activity of several components of the complement, contact (bradykinin-forming), and fibrinolytic systems (Kaplan 2010). Dysregulation of these cascades (particularly the contact system) due to C1 INH deficiency causes the uninhibited production of bradykinin, which promotes inflammation through increased vascular permeability and excessive accumulation of fluid in body tissues (Kaplan and Joseph 2010). Thus, patients with HAE are susceptible to recurrent episodes of debilitating swelling throughout the body. Replacement of C1 INH through intravenous (IV) administration of CINRYZE® (C1 inhibitor [human]) increases serum concentrations of C1 INH antigen (protein volume) and functional C1 INH activity (potency), temporarily restoring the natural regulation of the complement, contact (bradykinin-forming), and fibrinolytic systems. C1 inhibitor replacement therapy can prevent the occurrence of angioedema attacks associated with HAE or stop and control the mechanism that causes swelling if an attack does occur.

Most HAE patients have a positive family history of angioedema, but the disease also occurs spontaneously, with de novo mutations accounting for approximately 25% of cases (Bowen et al. 2010). Symptoms typically first appear during childhood or adolescence, worsen during puberty, and persist throughout a patient's lifetime (Lumry 2013). Angioedema attacks can affect the face, tongue, larynx, gastrointestinal tract, genitourinary system, and extremities (Zuraw 2008). Gastrointestinal involvement can mimic an acute surgical emergency, and misdiagnosis often results in unnecessary procedures to remove normal appendices and gallbladders (Weis 2009). Laryngeal swelling can occlude the airway and cause death by asphyxiation.

The frequency and severity of angioedema attacks vary widely, even among members of the same family, and are unrelated to the degree of C1 INH deficiency or dysfunction. Although it is often unclear what precipitates attacks, commonly cited triggers include trauma, physical and psychological stress, medical, surgical, or dental procedures, menstruation, infections, use of estrogen-containing oral contraceptives, and angiotensin-converting enzyme (ACE) inhibitors (Longhurst and Nzeako 2012).

The estimated prevalence of HAE is 1:50,000 people worldwide (range: 1:10,000 to 1:150,000) (Horiuchi et al. 2012; Bowen et al. 2008). However, the current medical literature reflects far fewer identified cases in Japan. In 2009, a nationwide prevalence survey of 1389 larger hospitals in Japan identified 52 patients with HAE (Iwamoto et al. 2011). Yamamoto et al. (2012) reviewed the medical literature from 1969 to 2010 and identified 132 unique Japanese patients

[1] The World Health Organization disease classification for C1 INH deficiency is D84.1, "Defects in the Complement System," under "Other Immunodeficiencies" in "Diseases of the Blood and Blood-forming Organs and Certain Disorders Involving the Immune Mechanism" (ICD-10, Version 2010). The Japan Nanbyo Research Foundation classifies C1 INH deficiency as a subcategory of Specified Rare and Intractable Disease (Tokutei Shikkan) No. 35, Primary Immunodeficiency Syndrome.

with HAE. Although the prevalence of patients with HAE appears to be lower in Japan, the distribution and pattern of C1 INH mutations and clinical features of the patients identified appear to be similar to Western populations (Yamamoto et al. 2012).

The burden of HAE on patients and family members is considerable with respect to its detrimental effects on physical health, career and work productivity (missed days), education (missed days), and mental health (feelings of panic and anxiety) (Aygören-Pürsün et al. 2012; Caballero et al. 2014; Lumry et al. 2010). Individual patients may be debilitated by their symptoms for up to 100 days per year, making employment or education difficult (Nzeako et al. 2001). Because of its unpredictability, HAE can be life-altering regardless of angioedema attack frequency. Patients live in constant fear of the next attack, and often arrange their lives around these events. Some patients who have had laryngeal attacks, or who have had family members die due to laryngeal attacks, never leave their local environment for fear of being distant from the safety of their home and the physicians who know and understand their illness (Levi et al. 2006).

The only product approved in Japan for the management of patients with HAE is Berinert P, a human C1 inactivator indicated to treat acute attacks of HAE. There is no approved therapy in Japan for long-term C1 INH protein replacement or prevention of angioedema attacks in patients with HAE. Given the questionable safety and efficacy of unapproved therapies currently being used to prevent angioedema attacks in Japan (ie, danazol, tranexamic acid), an unmet medical need exists for a subset of Japanese patients who experience frequent or life-threatening attacks and are not adequately managed with repeated acute treatments. CINRYZE is the only C1 INH protein replacement therapy in the world that is approved for both long-term (routine) prevention of angioedema attacks and treatment of acute attacks in patients with HAE. Routine replacement of C1 INH in patients who experience frequent attacks, severe attacks, and/or laryngeal attacks has been associated with improved patient outcomes, including a reduction in potential mortality, number of hospitalizations, and increased quality of life (eg, relief from anxiety, flexibility to travel, freedom to pursue educational and professional goals) (Craig et al. 2009; Kalfus et al. 2012; Gower et al. 2012). Consequently, international consensus guidelines have endorsed long-term replacement of C1 INH in the appropriate patient populations (Cicardi et al. 2012; Bowen 2011; Bowen et al. 2010).

1.1 CINRYZE (C1 Inhibitor [Human])

CINRYZE is a highly purified, viral-inactivated, nanofiltered concentrate of C1 INH produced from human plasma. The manufacturing process includes 3 virus inactivation/removal steps: polyethylene glycol precipitation, pasteurization, and nanofiltration. CINRYZE is a normal human plasma protein that is not subject to Cytochrome P450 metabolism, excretion, or pharmacokinetic drug-drug interactions exhibited by many low molecular weight compounds.

In October 2008, IV administration of CINRYZE was approved by the US FDA for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE. In June 2011, CINRYZE was approved by the EMA via the Centralized Procedure for treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE, and for 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. Shire ViroPharma Incorporated also received marketing authorizations for CINRYZE in Canada (2012), Australia (2012), India (2013), Switzerland (2013), and Israel (2013). The marketing authorisations in India and Israel were later withdrawn for commercial reasons.

1.1.1 Nonclinical Experience

The acute toxicity of C1 INH following IV administration of CINRYZE was studied in a combined dose-ranging acute toxicity (single dose) and 7-day repeat-dose toxicity study in Sprague-Dawley rats at dose levels of 20, 100, and 400 U/kg/day. In addition, a 14-day repeat-dose study was conducted in rats at the same dose levels. No signs of toxicity were observed in the single dose study. In the 14-day repeat-dose study, no signs of toxicity were observed at the two lower doses (20 and 100 U/kg/day). Repeat dosing in the rat resulted in an antibody response between Days 1 and 14, but an immunologic response is expected because CINRYZE is derived from human plasma.

In a poorly designed study in the Wessler stasis model using an earlier generation C1 INH product, a potential thrombogenic threshold was suggested at doses greater than 200 U/kg (14-fold greater than recommended clinical dose for a 70 kg adult). However, results of an *ex vivo* thrombogenicity study utilizing healthy human 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 the physiologic concentration). These findings are 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.

Reproductive studies in Sprague-Dawley rats at doses up to 400 U/kg showed no evidence of harm to the fetus due to CINRYZE treatment during the period of organogenesis; however, it is unknown if there was an antibody-mediated effect due to administration of a heterologous protein. No specific studies on fertility, early embryonic, and postnatal development or carcinogenicity studies were conducted because they cannot be reasonably performed using conventional animal models due to development of antibodies following administration of heterologous human proteins. No genotoxicity studies were performed because C1 INH is unlikely to interact directly with DNA or other chromosomal material.

1.1.2 Clinical Experience

The overseas development program for IV CINRYZE included 2 multicenter studies of CINRYZE for prevention of angioedema attacks (1 double-blind, placebo-controlled study and 1 open-label study) and 2 multicenter studies of CINRYZE for treatment of angioedema attacks (1 double-blind, placebo-controlled study and 1 open-label study). All 4 studies were conducted in the US (LEVP 2005-1/A, LEVP 2005-1/B, LEVP 2006-1, and LEVP 2006-4). In the double-blind, placebo-controlled prevention study (LEVP 2005-1/B), CINRYZE was shown to reduce the incidence of angioedema attacks in 22 subjects analyzed (mean normalized 12-week angioedema attack rate: 6.3 for CINRYZE vs. 12.8 for placebo; $p<0.0001$). In the double-blind, placebo-controlled treatment study (LEVP 2005-1/A), subjects receiving CINRYZE achieved beginning of unequivocal relief of the defining attack 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]).

receiving placebo (p=0.017 for the Efficacy Dataset of 68 subjects [35 C CINRYZE INRYZE, 33 placebo]).

More than 14,500 IV infusions of CINRYZE were administered to 262 unique subjects in 8 completed clinical studies in the overseas development program for IV CINRYZE. The vast majority of infusions were doses of 1000 U. In the placebo-controlled study with the longest administration period (LEVP 2005-1/B, prevention of angioedema attacks), 1000 U of IV CINRYZE was administered every 3 or 4 days for 12 weeks. In this study, the only CINRYZE - related treatment-emergent adverse events that occurred in more than 1 subject were viral upper respiratory tract infection and rash, each occurring in 3 subjects (12%). Across studies, there were only occasional reports of infusion site pain, bruising, rash, or related localized conditions. No subjects were discontinued from CINRYZE due to an adverse event in any of the studies.

Thrombotic events have been observed following IV administration of the approved dose of CINRYZE. In the open-label prevention study (LEVP 2006-4), in which subjects received 1000 U of CINRYZE every 3 to 7 days (median duration of exposure: 8 months), 5 serious thrombotic events occurred (myocardial infarction, deep vein thrombosis, pulmonary embolism, and 2 events of cerebrovascular accident). The majority of these events occurred in subjects with thrombogenic risk factors. Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely. In the overseas development program for IV CINRYZE, no serious adverse events were considered by the Investigator to be possibly, probably, or definitely related to treatment with CINRYZE.

The pharmacokinetics (PK) and pharmacodynamics (PD) of CINRYZE following IV administration in subjects with HAE are primarily based on the results of Study LEVP 2006-5. After IV administration of 1000 U, functional C1 INH activity (potency) 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 activity (potency) was approximately 60 hours using non-compartmental methods. Mean clearance (CL) values were 0.85 and 1.17 mL/min for the single and double doses, respectively. Mean C_{max} values for C1 INH antigen (protein volume) 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 C1 INH antigen (protein volume) was approximately 45 to 47 hours and mean CL was 0.70 mL/min.

Three post-marketing studies of IV CINRYZE in subjects with HAE were initiated after US marketing approval. The 3 studies evaluated doses of CINRYZE higher or lower than the approved 1000 U dose and the doses were considered to be appropriate for the target population.

Study 0624-400, now complete, was a post-marketing requirement mandated by the US FDA. This open-label study assessed the safety and efficacy of escalating doses of IV CINRYZE (1500 U, 2000 U, and 2500 U twice per week) as prophylactic therapy in subjects ≥6 years of age who were not adequately controlled (>1 angioedema attack/month, regardless of severity) while receiving 1000 U of CINRYZE every 3 or 4 days. Study 0624-203, now complete, was an open-

label, single-dose study evaluating 3 different doses (500, 1000, or 1500 U) of IV CINRYZE (based on subject body weight category) for treatment of acute angioedema attacks in children ≥2 to <12 years of age. Study 0624-301 is currently an ongoing, randomized, single-blind, crossover study evaluating 2 dosing regimens (500 U and 1000 U twice per week) of IV CINRYZE for the prevention of angioedema attacks in pediatric subjects 6 to 11 years of age.

For additional details regarding CINRYZE clinical studies please refer to the latest edition of the CINRYZE Investigator's Brochure.

1.2 Study Rationale

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

2 STUDY OBJECTIVES

The objectives of the study are to assess:

- The safety and tolerability of CINRYZE administered by IV infusion in Japanese subjects with HAE;
- The PK and PD of CINRYZE administered by IV infusion in this subject population; and
- The treatment effect of CINRYZE administered by IV infusion for the prevention of angioedema attacks and treatment of breakthrough attacks in this subject population.

NOTE: A breakthrough attack is defined as an angioedema attack that occurs during long-term prevention therapy with CINRYZE.

3 INVESTIGATIONAL PLAN

This single-period, open-label study will be conducted at multiple investigational sites in Japan. All study sites will conduct the study in accordance with the protocol, International Conference on Harmonisation (ICH), and Good Clinical Practice (GCP) standards. All sites will be trained by Sponsor/designee for self-administration (see Section 5.3.1). Data from all sites will be pooled for purposes of analysis and will be reported in the final clinical study report. Each subject will participate for approximately 5 months (Figure 1).

Potential subjects will be screened within 21 days before receiving their first dose of study drug. Subjects who are deemed eligible will be enrolled (see Section 4). If subjects withdraw or discontinue after enrollment, additional subjects may be enrolled to ensure at least 6 subjects complete the study (see Section 6.15).

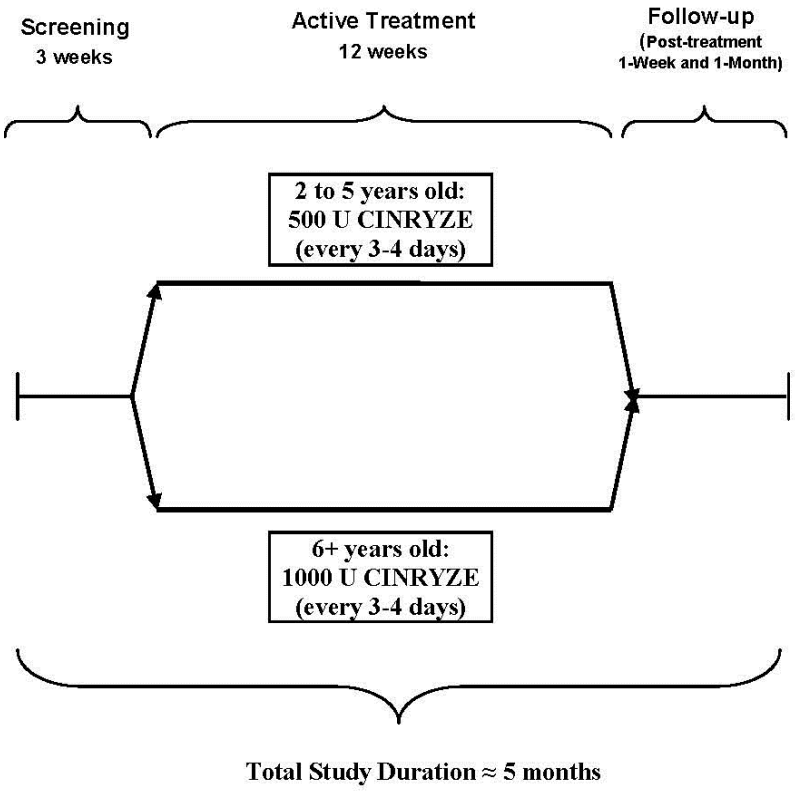
Subjects will be administered CINRYZE by IV infusion twice weekly (every 3 or 4 days) for 12 weeks. Subjects may not receive C1 INH therapy or any blood products within 3 days before the first dose of study drug or have signs or symptoms of an angioedema attack within 2 days before the first dose of study drug.

This is an outpatient study; however, subjects may require an overnight stay at the site for those days on which serial PK/PD blood samples are collected. Subjects would be discharged the following day after collection of the 24-hour PK/PD blood sample.

Study drug will be administered to all subjects at the investigational site for Dosing Visits 1 through 8, 16, and 24; during these visits, subjects may also have physical examinations and other procedures performed (see Schedule 1). Other doses of study drug may be administered at the investigational site or at the subject's home.

Subjects who are at least 12 years of age and considered suitable candidates (ie, those with a physical and mental capability of learning, adequate venous access, and willing to self-administer) will undergo detailed training at the study site on the skills needed for self-administration of investigational product (see Schedule 2). Alternatively, a subject's caregiver (such as a parent or guardian) can receive this training and will be allowed to administer the investigational product to a subject who requires assistance. The administration of the first 2 doses of investigational product should be done by the Investigator or qualified delegate at the study site, while subjects (or caregivers) who elect to self-administer will receive training materials and be instructed on the process of handling and reconstituting CINRYZE, proper venous access, and correct administration by IV infusion. Initiation of subject (or caregiver) self-administration with supervision by the Investigator or qualified delegate can begin on Dosing Visit 3 and continue as long as needed, but it is expected that subjects (or caregivers) may require supervised training through to Dosing Visit 8. After completing the required training, and provided the subject (or caregiver) is deemed independent according to the criteria described in Section 5.3.1, a subject (or caregiver) may elect to self-administer one or more doses of CINRYZE at home or at the study site. The Investigator's acknowledgement that a subject (or caregiver) is certified for independent self-administration will be entered in the CRF.

Figure 1: Study Design



It is recommended that treatment of breakthrough attacks (ie, angioedema attacks that occur during long-term prevention therapy with CINRYZE) occurs at the investigational site whenever possible so that clinical assessments can be completed as specified. It is preferred that subjects receive CINRYZE within 4 hours but not more than 8 hours after the onset of breakthrough attack symptoms if treatment can occur at the investigational site (see Section 6.12.1). Details on the assessment of breakthrough angioedema attacks treated with CINRYZE are provided in Section 6.12.2.

Throughout the trial, a study diary will be used by subjects (or caregivers) to record specific information about any angioedema attack symptoms and details on the self-administration of investigational product (see Section 6.11). Because of the potential to precipitate an angioedema attack, subjects will be requested to postpone elective medical procedures (eg, dental work) and avoid other known attack triggers while participating in the study (see Section 6.10).

Safety will be assessed by monitoring adverse events and changes in physical examinations, vital signs, and clinical safety laboratory testing. In addition, subjects will be monitored for the development of antibodies to C1 INH. If clinically indicated, study personnel may perform examinations to actively monitor subjects for possible venous thromboembolism or other thrombotic or thromboembolic (T/TE) events. Stopping rules are provided in Section 5.5.

In this study, angioedema attacks will not be reported as adverse events unless the attack meets the definition of a serious adverse event (see Section 9.1.4).

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

Post-treatment follow-up visits will be performed 1 week (±1 day) and 1 month (30 ±2 days) after the last dose of study drug. If a subject prematurely discontinues investigational product, regardless of the reason, the Early Discontinuation Visit procedures listed in Schedule 3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-Week and 1-Month Post-treatment Follow-up visits.

The schedules of study procedures are provided as follows:

- Schedule 1: Clinical Study Assessments – Screening and Treatment Period;
- Schedule 2: Investigational Product and Self-administration Training;
- Schedule 3: Clinical Study Assessments – Early Discontinuation Visit and 1-Week and 1-Month Post-treatment Follow-up Visits;
- Schedule 4: Blood Sample Collection Time Points for PK/PD Assessments.

4 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 of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. Be ≥2 years of age.
3. Meet the following minimum body weight criteria:
   - Subjects 2 to 5 years of age must weigh at least 12.5 kg; and
   - Subjects 6 years of age and above must weigh at least 25 kg.
4. Have a confirmed diagnosis of Type I or Type II HAE. **NOTE:** Diagnosis may be based on historical data including family history, clinical symptoms (characteristic attacks), and documentation of low level of C1 INH protein and/or C1 INH activity.
5. Have a history of at least one angioedema attack per month (on average) during the 3 consecutive months immediately before enrollment.
6. Agree to adhere to the protocol-defined schedule of assessments and procedures.
7. Agree to avoid his/her known angioedema attack triggers during the study to the best of his/her ability.
8. If a female of reproductive age, be postmenopausal (≥12 months following cessation of menstruation), surgically sterile, or following an acceptable method of birth control (and agree to continue its use through 1 month after the last dose of study drug):
   - Non-hormonal methods (eg, abstinence, barrier control) for at least 1 complete menstrual cycle before the Screening Visit.
   - Stable doses of estrogen and/or progestin containing products for at least 2 months before the Screening Visit.
9. If a male of reproductive age, be surgically sterile or agree to follow an acceptable method of birth control (eg, abstinence, barrier control) from the Screening Visit through 2 months after the last dose of study drug.
10. If an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

    OR

    If a child or minor (<20 years of age), have a parent/legal guardian who is informed of the nature of the study provide written informed consent (ie, permission) for the child to

participate in the study before any study-specific procedures are performed. Assent will be obtained from children ≥14 years of age.

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 be 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. Have received C1 INH therapy or any blood products within 3 days before the first dose of study drug.
5. Have had signs or symptoms of an angioedema attack within 2 days before the first dose of study drug.
6. Have any change (start, stop, or change in dose) in androgen therapy (eg, danazol, oxandrolone, stanozolol, testosterone), tranexamic acid, epsilon-aminocaproic acid (EACA), or other antifibrinolytics within 14 days before the first dose of study drug.
7. If female, have started taking or changed the dose of any hormonal contraceptive regimen or hormone replacement therapy (eg, estrogen/progestin containing products) within 2 months before the first dose of study drug.
8. Be pregnant or breastfeeding.
9. Have received an investigational drug other than those required for prevention or treatment of angioedema attacks within 30 days before the first dose of study drug.
10. 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.

5 STUDY DRUG ADMINISTRATION

5.1 Dose Selection

In countries where CINRYZE is approved for routine prevention of angioedema attacks in patients with HAE, the recommended dose for adolescents and adults is 1000 U administered intravenously every 3 or 4 days. Since the present study will enroll Japanese subjects as young as 2 years of age, two different doses of CINRYZE will be administered depending on subject age, as described below.

Subjects 2 to 5 years of age – 500 U of CINRYZE will be administered by IV infusion twice weekly (every 3 or 4 days) for 12 weeks.

For children younger than 6 years of age, the use of a 1000 U dose may be excessive and attain unnecessarily high C1 INH plasma concentrations. The scientific rationale supporting a lower dose of 500 U is the reduced plasma volume present in patients <6 years of age. Specifically, children between 2 and 5 years of age have an average plasma volume between 500-900 mL. The recommended dose of 500 U every 3 to 4 days is expected to increase plasma C1 INH concentrations between 55-100% from baseline. This dose was well tolerated when administered to 2 subjects between the ages of 2 and 5 in the overseas development program for IV CINRYZE, and is being evaluated in an ongoing pediatric study (0624-301) of CINRYZE in non-Asian children with C1 INH deficiency.

In a long-term, open-label clinical trial of CINRYZE for prevention of angioedema attacks (LEVP 2006-4), a PPD boy received 500 U of IV CINRYZE every 3 to 7 days for a total of 42 doses over a 288-day study period (PPD to PPD). This dose was well tolerated and efficacious. Over the course of his participation in the study, only two adverse events were reported (abdominal angioedema attack on Day 101 and upper respiratory tract infection on Day 103). [NOTE: There was a 9-day lag between his last dose of CINRYZE and the angioedema attack.] Neither event was considered by the Investigator to be related to CINRYZE, and both resolved. The subject completed the study.

Also supporting this dosing rationale are data from pediatric patients (who on average have a smaller plasma volume) demonstrating the safety and efficacy of a dosing regimen of 1000 U every 3 to 4 days in children as young as 6 years of age (Lumry et al. 2013).

Subjects 6 years of age and older – 1000 U of CINRYZE will be administered by IV infusion twice weekly (every 3 or 4 days) for 12 weeks.

The C1 INH activity of a 1000 U dose of CINRYZE represents the activity present in 1 litre of normal plasma (1 U/mL); consequently, in an average Western person with a 3 litre plasma volume this represents a 33% increase in the absolute concentration of functional C1 INH activity (potency). In a smaller subject with a plasma volume of 2 litres, this dose would increase the C1 INH concentration by 50% which is closer to the normal range but does not result in supra-physiologic concentrations. Hence, the dose rationale of a 1000 U dose every 3 to 4 days is appropriate for the Japanese population which may have a lower plasma volume.

Summary – Dosage recommendations of 500 U of CINRYZE for subjects 2 to 5 years of age and 1000 U of CINRYZE for subjects 6 years of age and older are justified by the safety, efficacy, and PK results from the overseas development program. The similar safety and efficacy profiles observed in adults, adolescents, and children indicate that CINRYZE offers safe and effective therapy for long-term replacement therapy (prevention of angioedema attacks) and treatment of both acute and breakthrough angioedema attacks. In addition, the similarity in functional C1 INH activity (potency) concentrations attained at 1 hour post-dose across age groups allays the potential concern that supra-physiologic levels of C1 INH might be attained in children as young as 2 years of age.

5.2 Randomization

Subjects will not be randomized in this study.

5.3 Study Drug

See Section 8 for a complete description of study drug. Instructions for the reconstitution of CINRYZE will be provided in a separate study manual. CINRYZE treatments will be prepared and administered at the investigational site or at the subject's home.

For a 500 U dose, 1 vial of CINRYZE is reconstituted with 5 mL of Sterile Water for Injection, USP for a total volume of 5 mL. For a 1000 U dose, 2 vials of CINRYZE are reconstituted for a total volume of 10 mL. CINRYZE will be administered intravenously at a rate of approximately 1 mL (100 U) per minute, as tolerated.

CINRYZE will be administered to all subjects at the investigational site for Dosing Visits 1 through 8, 16, and 24. Other doses of study drug may be administered at the investigational site or at the subject's home (including the option for independent self-administration). For each dose administered, the date and time of the start and end of the infusion and if self-administered (Y/N) will be recorded in the CRF.

5.3.1 Self-administration

The Sponsor has developed a set of training materials (eg, illustrated patient pamphlet, instructional video, dummy kit for injection) to assist the Investigators to teach and subjects to learn the skills needed for self-administering CINRYZE. The training materials were developed after careful review of Japanese and international guidelines for self-administration (MHLW 2005; Caballero et al. 2013; Cicardi et al. 2013).

The Investigator or qualified delegate responsible for teaching self-administration skills to the subjects will be required to undergo training (by Shire's designated physician) specifically on CINRYZE product labelling, including instruction on handling, reconstitution, administration, and disposal of used equipment (eg, sharps and infectious material). This will ensure that all subjects receive uniform training consistent with CINRYZE product information.

Subjects who are at least 12 years of age and considered suitable candidates (ie, those with a physical and mental capability of learning, adequate venous access, and willing to be trained)

will be allowed to self-administer after receiving detailed training as described below and demonstrating the necessary skills for independent self-treatment. Alternatively, a caregiver (such as a parent or guardian) can receive this training and will be allow to administer the investigational product to a subject who requires assistance. Multiple training sessions will be needed however the actual number will differ for each subject (or caregiver) based on attainment of the required skill set and the personal comfort level with the technical and medical aspects of self-administration. Hereditary angioedema patients in the US typically completed CINRYZE self-administration training within an average of 5 visits (Gregory et al. 2014). A subject (or caregiver) will be considered independent if they are able to correctly reconstitute study drug, access a vein for infusion, and successfully administer the drug on at least 2 consecutive training visits.

The administration of the first 2 doses of investigational product should be done by the Investigator or qualified delegate at the study site, while subjects (or caregivers) who elect to self-administer will receive training materials and be instructed as outlined below. Initiation of subject (or caregiver) self-administration with supervision by the Investigator or qualified delegate can begin on Dosing Visit 3 and continue as long as needed, but it is expected that subjects may require supervised training through Dosing Visit 8. After completing the required training, and provided the subject (or caregiver) is deemed independent, a subject (or caregiver) may elect to self-administer one or more doses of CINRYZE at home or at the study site. The Investigator's acknowledgement that a subject (or caregiver) is certified for independent self-administration will be entered in the CRF.

Training sessions will include the following:

- General information on CINRYZE, including storage and reconstitution of the lyophilized product according to manufacturer's instructions
- Techniques for safe and successful IV infusion (ie, proper venous access with infusion set and administration of study drug using aseptic techniques, safe disposal of used equipment [eg, needles and syringes])
- Manage and report any occurrence of adverse effects
- Trouble-shooting solutions (eg, if unable to perform an IV infusion)
- Appropriate action for treating laryngeal attacks or if there is inadequate relief of a breakthrough attack after treatment with CINRYZE (2 doses separated by 1 hour).

For compliance with study procedures, subjects (or caregivers) will also be instructed on recording in the study diary the date and time (both start and end) of each CINRYZE infusion, location of infusion site, and study drug lot number. In the case of self-administration of CINRYZE for a breakthrough attack (only if the subject or caregiver has completed training and is deemed independent), subjects (or caregivers) will also need to record the onset date and time of the attack, the overall amount of pain associated with the attack, assess symptom severity pre-infusion and every 15 minutes up to 4 hours after completing the CINRYZE infusion, onset time of symptom improvement and the time symptoms completely resolve (see Section 6.12.2 for details). Doses of CINRYZE that are self-administered will be entered as such in the CRF.

5.4 Blinding

This is an open-label study; therefore, blinding is not applicable.

5.5 Stopping Rules

5.5.1 Anaphylactic Reaction

If an anaphylactic reaction occurs in any subject, study drug will be discontinued for that subject. The subject will follow the schedule of assessments for the Early Discontinuation Visit and the 1-Week and 1-Month Post-treatment Follow-up Visits (see Schedule 3). Other enrolled subjects will continue with study drug administration and procedures.

5.5.2 Thrombotic or Thromboembolic Event

If a thrombotic or thromboembolic (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 it is determined that the event is not 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 deemed appropriate by the Investigator in conjunction with the Sponsor. Investigators will comply with protocol-defined algorithms to assist in the diagnosis and management of all suspected T/TE events (see Appendix 2). 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 if it is determined that the T/TE event is not related to study drug. 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 the Early Discontinuation Visit and the 1-Week and 1-Month Post-treatment Follow-up Visits (see Schedule 3).

6 STUDY PROCEDURES

Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily granted by the subject or permission for minors has been granted by a parent/legal guardian and assent has been provided by appropriate subjects (Section 14). For subjects who are screened (ie, those with signed written informed consent) but not enrolled, demographic information and reason for screen failure will be recorded in the CRF. Schedule 1, Schedule 2, and Schedule 3 provide details of study procedures and clinical assessments, and Schedule 4 provides timing of PK/PD blood sampling.

NOTE: It is possible for the Screening Visit and Dosing Visit 1 to occur on the same day. If this occurs—to prevent repetition of protocol procedures and avoid duplicate blood draws on the same day—following Screening procedures, only the following Dosing Visit 1 procedures will be performed:

- Concomitant medications
- Vital signs relative to study drug administration
- Study drug administration
- Daily angioedema attack monitoring and study diary
- Adverse event monitoring
- PK/PD and immunogenicity (C1 INH antibody) blood sampling
- Quality of life questionnaire

6.1 Medical History and Physical Examination

A medical history will be taken at the screening visit. All medical history findings that have been present/active within the 5 years before enrollment will be recorded in the CRF regardless of clinical relevance or presence at study start. Medical history findings that have not been present within the 5 years before enrollment will be recorded if deemed clinically relevant to the conduct of the study by the Investigator. The medical history should include any history of allergic reactions to drugs. In addition, the following information associated with the history of angioedema will be recorded in the CRF:

- HAE Type (I or II). If a subject does not have a confirmed diagnosis of HAE based on historical data, including C1 INH functional deficiency, the subject's diagnosis must be confirmed prior to treatment by C1 INH test results which demonstrate a quantitative and/or functional C1 INH deficiency; a blood sample may be collected at screening to determine a deficiency in the levels of C1 INH and/or C1 INH activity.
- Family history of HAE within first degree relatives (offspring, siblings, parents).
- If a central line has ever been used for administration of any medication, and if yes, is there currently a central line in place?
- Estimated onset date of last angioedema attack before enrollment (ie, prior to Day 1).

- Total number, typical locations, average overall duration (in days), and average overall severity of angioedema attacks experienced during the 3 consecutive months before the first dose.
- Visual Analogue Scale (VAS) - typical score for the subject's angioedema attack pain during the 3 consecutive months before the first dose. Note: Subjects younger than 5 years of age do not need to complete the VAS.

The Investigator or designee will perform physical examinations at the time points specified in Schedule 1 and Schedule 3. Physical examinations will be performed in accordance with standard practices at the study site. Physical examination abnormalities observed at the screening visit will be recorded as medical history. New abnormalities or worsened pre-existing abnormalities observed post-screening should be recorded as AEs, as determined by the Investigator (see Section 9).

Body weight and height will be measured at the time points specified in Schedule 1 and Schedule 3.

6.2 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events will be collected from the time informed consent is signed through 7 days after the last dose of investigational product. This includes events occurring during the screening phase of the study, regardless of whether or not the investigational product is administered. In addition, the investigator will report all SAEs that occur through 30 days after the last dose of investigational product to PAREXEL International Pharmacovigilance and the respective Independent Reviewing Authority according to local reporting requirements.

Please refer to Section 9, Adverse and Serious Adverse Events Assessment.

6.3 Vital Signs

Blood pressure (BP) and pulse will be measured at the time points specified in Schedule 1 and Schedule 3. Additional vital signs measurements may be performed during the study if clinically indicated. On dosing days, vital signs should be obtained ≤30 minutes before the start of the infusion, ≤15 minutes after completion of the infusion, and between 30 minutes and 1 hour after completion of the infusion. Vital sign measurements will not be collected at Visits 10, 12, 14, 18, 20, and 22 from subjects who independently self-administer investigational product at home. At applicable visits, every effort should be made to measure vital signs before the collection of blood samples.

6.4 12-Lead Electrocardiogram

Subjects will have a 12-lead ECG recorded as specified in Schedule 1. Additional ECGs may be performed during the study if clinically indicated. The following ECG data will be recorded in the CRF: HR, PR interval, QRS duration, QT interval, and QTc interval. The Investigator will

be responsible for providing the interpretation of all ECGs (clinically significant/not clinically significant).

6.5 Prior and Concomitant Medications

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

6.5.1 Prior Medications

A medication history will be taken at the screening visit and updated before the first dose on Day 1 to ensure that the subject remains eligible for study participation. Any therapy received for the management of HAE within 12 months before Day 1 should be recorded, including overall start and stop dates (if known) and the HAE indication (ie, long-term prevention, acute treatment, short-term prevention). All other medications taken within 1 week before Day 1 will be recorded in the CRF. In addition, any medications taken for an AE prior to Day 1 will be recorded.

6.5.2 Concomitant Medications

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

6.5.3 Prohibited Medications

Use of C1 INH therapy (other than study drug) for the prevention of angioedema attacks is prohibited during the study. Details on the management of breakthrough angioedema attacks are discussed in Section 6.12.

6.6 Nonpharmacologic Treatments and Procedures

Nonpharmacologic treatments received from the Screening Visit through the 1-Week Post-treatment Follow-up Visit will be recorded in the CRF. To the extent possible, procedures (eg, surgical, diagnostic, or dental) should be avoided during study participation (see Section 6.10); however, those occurring through the 1-Week Post-treatment Follow-up Visit will be recorded in the CRF.

6.7 Clinical Laboratory Parameters

Subjects will have blood samples collected for routine clinical laboratory testing at the time points specified in Schedule 1 and Schedule 3. Testing will be performed at a central laboratory. The following clinical laboratory parameters will be analyzed:

- Hematology: CBC consisting of WBC and differential counts and percentages, RBC count, hemoglobin, hematocrit, and platelet count.
- Coagulation: PT, aPTT, INR.
- Clinical Chemistry: BUN, creatinine, glucose, sodium, potassium, chloride, CO_2, AST, ALT, alkaline phosphatase (ALP), CPK, total bilirubin, calcium, phosphorus, total protein, and albumin.
- Virology: HIV (single assay antibody/Western Blot) and hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody).
- Urinalysis with microscopy: pH, specific gravity, dipstick (protein, glucose, ketones, hemoglobin), and microscopic evaluation (RBCs, WBCs, crystals, casts, bacteria).

For all females of childbearing potential, pregnancy testing (in accordance with standards at the site) will be performed at the time points specified in Schedule 1 and Schedule 3.

Additional clinical laboratory testing may be performed during the study if clinically indicated, and may be completed locally or sent to the central laboratory. Site staff will manually enter local laboratory results into the CRF.

6.8 Sample Collection for Pharmacokinetic, Pharmacodynamic, and C1 INH Antibody Analyses

Subjects will have blood samples collected for the determination of plasma concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), complement C4, and C1q at the time points specified in Schedule 4. In addition, blood samples will be collected at Visits 1 (baseline), 8, 16, and 24 and 1 month (30 ±2 days) after the last dose of study drug for C1 INH antibody analyses (see Schedule 1 and Schedule 3).

The actual date and time of each sample collection will be recorded. Plasma samples for the determination of C1 INH antigen (protein volume), functional C1 INH activity (potency), complement C4, and C1q concentrations and C1 INH antibodies will be analyzed using fully validated methodology. Details on the processing of blood samples for PK/PD and immunogenicity assessments will be provided in a separate study manual.

NOTE: If a subject presents to the site with a breakthrough angioedema attack, every effort should be made to obtain a PK blood sample before treatment. In addition, if the subject receives CINRYZE for treatment of the attack, every effort should be made to obtain a 1-hour post-treatment sample; if a second dose of CINRYZE is administered, an additional 1-hour post-treatment sample should be obtained if possible. These samples will be collected as an unscheduled visit and analyzed for C1 INH antigen (protein volume) and functional C1 INH activity (potency). Additional blood samples for PK/PD and C1 INH antibody assessments may be collected during the study if clinically indicated.

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

C1 INH antigen (protein volume) and functional C1 INH activity (potency) in study samples and/or to investigate the stability of the 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.

Selected samples may be retained to investigate immunogenicity to C1 INH.

6.9 Total Blood Volume Collected

During the study, subjects who weigh 25 kg or more will have approximately 220 mL of blood collected for clinical safety laboratory testing (hematology, chemistry, coagulation, and virology), PK/PD assessments, and immunogenicity (C1 INH antibody) testing (exclusive of unscheduled visits). Subjects who weigh less than 25 kg will have approximately 140 mL of blood collected (exclusive of unscheduled visits). In addition, for subjects who weigh less than 25 kg, the Screening Visit must occur at least 14 days before Dosing Visit 1.

6.10 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 (eg, foods, activities, medical procedures, environments). To the extent possible, subjects should postpone elective procedures (eg, dental work) while participating in the study. If a procedure cannot be postponed, the subject or parent/guardian will notify the Investigator and the information will be recorded in the CRF.

6.11 Study Diary

Beginning at Dosing Visit 1, subjects (or their caregivers such as a parent or guardian, based on the ability of a child) will use a study diary each day to document specific information about any angioedema attack symptoms that occur (eg, including the location, severity, pain score, and duration of symptoms) and details on the self-administration of investigational product. At the first dosing visit (Dosing Visit 1), study personnel will instruct each subject (or caregiver) how to complete the study diary.

Study personnel will review the diary for completeness and accuracy at each scheduled dosing visit. The Investigator or designee will use subject-reported diary data as reference information, in addition to any other available medical records, to record and evaluate events related to breakthrough angioedema attacks in the CRF.

6.12 Angioedema Attacks

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

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

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

In this study, angioedema attacks will not be reported as adverse events unless the attack meets the definition of a serious adverse event (see Section 9.1.4).

6.12.1 Treatment of Breakthrough Angioedema Attacks

A breakthrough attack is defined as an angioedema attack that occurs during long-term prevention therapy with CINRYZE. If a subject receives CINRYZE for treatment of a breakthrough angioedema attack, they should continue their protocol-defined treatment schedule without alteration regardless of when the supplemental dose is administered.

If a breakthrough angioedema attack occurs during the 12-week treatment period through 1-week post-treatment, a supplemental dose of CINRYZE may be administered by IV infusion for treatment of the attack either by the Investigator (or qualified delegate) or subject (or caregiver) if trained and deemed independent to self-administer (1000 U for subjects ≥6 years of age or 500 U for subjects 2-5 years of age). If the subject does not adequately respond to the initial dose within 1 hour, a second dose of CINRYZE may be administered (1000 U for subjects ≥6 years of age or 500 U for subjects 2-5 years of age).

It is recommended that treatment of breakthrough attacks occurs at the investigational site whenever possible so that clinical assessments can be completed as specified. It is preferred that subjects receive CINRYZE within 4 hours but not more than 8 hours after the onset of breakthrough attack symptoms if treatment can occur at the investigational site.

Subjects (at least 12 years of age or their caregivers) who have completed the required self-administration training and deemed independent (per criteria specified in Section 5.3.1) may elect to self-administer CINRYZE for a breakthrough attack. Note: Subjects (or caregivers) who are participating in self-administration training and not yet qualified as independent cannot self-administer CINRYZE for a breakthrough attack; rather they must seek treatment at the investigational site. If a subject (or caregiver) who self-administers CINRYZE for treatment of a breakthrough attack does not respond adequately after instructed treatment (ie, 2 doses separated by 1 hour), they should notify the Investigator and seek medical attention or report to study site to seek further treatment and relief of symptoms.

In addition to the administration of CINRYZE, subjects are allowed to receive symptomatic treatment for breakthrough angioedema attacks (eg, IV fluids). The administration of narcotics and antiemetics is discouraged during the 4-hour post-infusion assessment period to allow for evaluation of the response to CINRYZE. Other treatments for angioedema attacks (eg, another C1

INH product such as Berinert P, tranexamic acid, fresh frozen plasma) are not permitted at the investigational site unless a subject does not adequately respond following treatment with CINRYZE (ie, 2 doses separated by 1 hour).

6.12.2 Assessment of Breakthrough Angioedema Attacks

If a breakthrough attack occurs, subjects (or caregivers) should assess and record the following information in the study diary:

- Presence of pain or swelling at each anatomic location (ie, upper airway [laryngeal], gastrointestinal/abdominal, facial, genitourinary, and extremity/peripheral) by indicating the overall severity (ie, mild, moderate, or severe [as defined below])
- Overall amount of pain associated with the breakthrough attack using a VAS (only for subjects at least 5 years of age)
- Any triggers associated with the attack
- Any health care visit for the attack (investigational site, clinic or hospital/emergency department)
- Any medications received to manage attack symptoms
- Duration of symptoms (ie, time symptoms start to improve and time symptoms completely resolve)

In addition to the subject's self-assessment, the Investigator should assess and record the overall severity of the attack if the subject seeks treatment for symptoms at the site.

Treatment with CINRYZE

The Investigator (or qualified delegate) or subject (trained and deemed independent) may administer a supplemental dose of CINRYZE to treat the breakthrough attack. Subjects self-administering CINRYZE will record clinical assessments associated with breakthrough attacks in the study diary.

Following the administration of CINRYZE, subjects (or caregivers) will record their symptoms (the presence of pain or swelling at each anatomic location) and assess the overall severity of the breakthrough attack every 15 minutes for up to 4 hours post-infusion using the following scale:

- No symptoms.
- Mild: The attack symptoms are noticeable but are easily tolerated by the subject and do not interfere with the subject's daily activities.
- Moderate: The attack symptoms interfere with the subject's ability to attend work/school or participate in family life and social/recreational activities).
- Severe: The attack symptoms significantly limit the subject's ability to attend work/school or participate in family life and social/recreational activities.

Subjects (or caregivers) also will rate the overall amount of pain associated with the

breakthrough attack using a VAS (for subjects at least 5 years of age) on the same schedule as overall attack severity.

In addition to the subject's self-assessment, the Investigator should assess and record the overall severity every 15 minutes for up to 4 hours post-infusion if the subject seeks treatment at the site.

NOTE: If a subject has adequately responded to treatment with CINRYZE, the subject may omit further assessments up to 4 hours post-infusion (and if applicable, be discharged from the investigational site) provided that overall attack severity has been assessed for at least 1 hour.

Subject diary data will be used by study personnel to record the onset date and time of the breakthrough attack, as well as the date and time of onset of symptom improvement and Complete Resolution (defined in Section 7.6.2) in the CRF.

6.13 Quality of Life

6.13.1 Angioedema Quality of Life (AE-QoL) Questionnaire

The Angioedema Quality of Life (AE-QoL) is a questionnaire on the quality of life of patients suffering from recurrent angioedema. It consists of 17 specific questions that are associated with work, physical activity, free time, social relations, and diet. Subjects will be asked by study personnel how often they were restricted by—as well as the difficulties and problems that could be associated with—recurrent swellings (angioedema) during the previous 4 weeks. The AE-QoL questionnaire will be completed at the time points specified in Schedule 1 and Schedule 3. This instrument will be administered as appropriate for each subject's age (ie, includes option of guidance from parent/guardian).

6.14 Self-administration Survey

A self-administration survey containing questions for subjects (or caregivers) and the Investigator's assessment of the overall experience with self-administration of IV CINRYZE will be completed on Visit 24.

Subjects (or caregivers) who have self-administered treatment during the study, will be asked specific questions regarding training materials and oversight by the Investigator or qualified delegate, ease of reconstituting and self-administering CINRYZE, any challenges or obstacles encountered, and to rate their overall satisfaction with self-administered treatment. The Investigator or qualified delegate will provide their overall assessment of the training process and the success/challenges of teaching subject (or caregiver) self-administration skills. Study personnel will enter the survey responses in the CRF.

6.15 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The Investigator is encouraged to discuss the withdrawal of a subject from investigational product with the Medical Monitor when possible.

If investigational product is discontinued, regardless of the reason, the Early Discontinuation Visit procedures listed in Schedule 3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also complete the 1-Week and 1-Month Post-treatment Follow-up Visits. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and the date of stopping investigational product must be recorded in the CRF and source documents.

If subjects withdraw or discontinue after enrollment, additional subjects may be enrolled to ensure at least 6 subjects complete the study.

For those subjects who discontinue before receiving study drug, demographic information, inclusion/exclusion information, and the reason for not receiving study drug will be recorded in the CRF. No additional study procedures or follow-up will be performed on subjects who discontinue before receiving study drug.

6.15.1 Reasons for Discontinuation

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

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other [specify reason on the CRF].

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.

A subject will be considered lost to follow-up after 3 documented attempts are made, including at least one attempt via written communication.

7 STATISTICAL METHODOLOGY

7.1 Sample Size

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

7.2 Populations

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

7.3 Statistical Methods

Data will be summarized using the same methods that were used in the overseas development program for IV CINRYZE. Experimental results will be summarized using descriptive statistics according to data type (n, mean, standard deviation or standard error, median, and range for continuous endpoints; number and percent of subjects in each category for categorical endpoints). To establish context, efficacy/pharmacology results from this study may be superimposed (eg, graphically) on experimental data from previous overseas studies, as appropriate.

7.4 Safety Analyses

The following will be assessed:

- Adverse events (including treatment-emergent adverse events).
- Summary statistics and changes from baseline to post-baseline for laboratory testing, vital signs, and, if applicable, any ECG findings will be presented.
- Results of C1 INH antibody testing will be reported for individual subjects and summarized as appropriate.

NOTE: Treatment-emergent events include all adverse events that start during the treatment period (and up to 7 days after the last dose of investigational product) and were not seen at baseline, or were seen at baseline but worsened in frequency and/or severity during the treatment period (and up to 7 days after the last dose of investigational product).

7.5 Pharmacokinetic and Pharmacodynamic Analyses

Concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), and complement C4 and C1q for individual subjects will be determined. Results will be summarized using descriptive statistics at each time point with and without baseline correction. C1q concentrations will be assessed at baseline only (ie, pre-infusion, Dosing Visit 1).

Pharmacokinetic/pharmacodynamic parameters will be calculated using observed and baseline-corrected concentration-versus-time data using non-compartmental techniques. Pharmacokinetic/pharmacodynamic parameters to be determined include C_{max} and its time of occurrence (t_{max}), minimum observed concentration (C_{min}), average concentration at steady state (C_{avg}), area under the plasma concentration versus time curve from time 0 to selected time point ($AUC_{0-\tau}$), elimination rate constant (K_{el}), terminal elimination half-life ($t_{1/2}$), volume of distribution (V_Z), and plasma clearance (CL), as appropriate. Terminal elimination half-life will be estimated by log-linear regression and will use at least three time points. Other non-compartmental PK/PD parameter values also may be calculated. Non-compartmental PK/PD analyses will be performed using commercially available software (Phoenix® WinNonlin®, version 6.3 or higher; Pharsight, a Certara company).

If warranted, an exploratory PK/PD analyses will be performed based on correlation of plasma concentrations of C1 INH antigen (protein volume), functional C1 INH activity (potency), and C4 complement in conjunction with various safety parameters (eg, selected AEs, clinical laboratory results, antibodies generation; frequency, severity, or anatomic location of the HAE attack). Correlations that will be analyzed will be determined based on observed data.

Pharmacokinetic/pharmacodynamic parameters and PK/PD assessments will be summarized using descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) and categorical parameters will be summarized using frequency statistics (number and percentage of subjects).

7.6 Efficacy Analyses

7.6.1 Prevention of Angioedema Attacks

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

- The number of angioedema attacks recorded during the treatment period, normalized for the number of days the subject participated in the period.
- The overall frequency of angioedema attacks occurring during the treatment period will be calculated and compared with historical baseline values.
- Summary of all attacks during the treatment period, including:
    - Anatomic location.
    - Severity (intensity).
    - Duration.
    - Number of rescue treatments (including antiemetics, narcotics, or C1 INH therapy, including administration of rescue CINRYZE).
- Effects of therapy on quality of life (results of AE-QoL questionnaire).

7.6.2 Treatment of Breakthrough Angioedema Attacks

The following efficacy endpoints for treatment of breakthrough angioedema attacks will be assessed by CINRYZE-treated attack number:

- The number of subjects who achieve Clinical Relief. Clinical Relief is defined as a sustained reduction from pre-infusion in the attack severity within 4 hours after initiation of treatment with CINRYZE.
- Time to onset of Clinical Relief.
- The number of subjects who achieve Complete Resolution. Complete Resolution is defined as the cessation of all symptoms of the breakthrough angioedema attack.
- Time to Complete Resolution.

Other analyses may be performed to establish context of the efficacy results from this study with previous Phase 3 CINRYZE studies.

8 DRUG SUPPLIES

8.1 How Supplied

CINRYZE is supplied as a lyophilized powder in single use vials containing 500 U of C1 INH per vial. When reconstituted, CINRYZE contains C1 INH at a concentration of 100 U/mL in a citrate-buffered solution comprising sucrose, sodium chloride, L-valine, L-alanine, and L-threonine.

Vials must be stored at 2°C – 25°C (36°F – 77°F) and protected from light. Do not freeze.

8.1.1 For at Home Use

Subjects (or their caregivers) who elect to self-administer investigational product at home will be provided the following supplies at investigational site for transport to the home location:

- 4-week supply of investigational product, including sterile water for injection, and Mix2vial® transfer devices
- Ancillary supplies, including silicone-free syringes, needles, infusion sets, disinfecting strips, and disposal containers (eg, sharps and infectious materials)
- Transport container for investigational product
- Subject accountability log to record investigational product storage conditions, administration, and other details.

All used and unused vials of investigational product should be returned to the study site for inspection and drug accountability purposes.

8.2 Reconstitution of CINRYZE for Intravenous Infusion

Each vial of CINRYZE will be reconstituted with 5 mL of Sterile Water for Injection (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.

For subjects 6 years of age and older, each 1000 U infusion will require reconstitution of two 500 U vials of CINRYZE; for subjects 2 to 5 years of age, each 500 U infusion will require reconstitution of one 500 U vial of CINRYZE. The solution must be used within 3 hours after reconstitution.

Instructions for the reconstitution of CINRYZE will be provided in separate study manual.

8.3 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 CRF. In addition, records must be kept on <u>when</u> and <u>how many</u> study drug vials were dispensed and returned 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 CRF. 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 (SOPs).

8.4 Drug Labels

Clinical trial labels that are in accordance with applicable regulatory requirements will be applied. The label will comply with Japanese GCP.

9 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

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

9.1.1 Severity Categorization

The severity (intensity) of AEs will be assessed according to the definitions below. If the intensity of an AE changes over time, the maximum intensity experienced should be recorded.

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

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

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

Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

9.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

9.1.3 Outcome Categorization

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

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

9.1.4 Symptoms of the Disease Under Study

In this study, angioedema attacks will not be reported as adverse events unless the attack meets the definition of a serious adverse event (see Section 9.2.3).

9.1.5 Clinical Laboratory and Other Safety Endpoints

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment

or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

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

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

9.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 3.

Any report of pregnancy for any female study participant or the female partner of a male study participant must be reported within 24 hours to PAREXEL International Pharmacovigilance using the Shire Investigational and Marketed Products Pregnancy Report Form. The pregnant female study participant must be withdrawn from the study.

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

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

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

9.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to PAREXEL International Pharmacovigilance according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 9.2. **NOTE:** The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (**NOTE:** This includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol.)
- **Overdose** – No case of overdose has been reported. In the overseas development program (see Section 1.1.2), the largest dose of CINRYZE administered to an individual subject for treatment of a single angioedema attack was 4000 U (1000 U x 4 IV infusions) over a 4-hour time period. The largest amount of CINRYZE administered to an individual subject for prevention and treatment of angioedema attacks was 10,000 U (1000 U x 10 IV infusions) over a 7-day time period. These subjects experienced no adverse reactions.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the Sponsor only as defined below.

Medication errors should be collected/reported for all products under investigation.

Reportable medication errors include the administration and/or use of an expired investigational product and departures from prescribed procedures for the storage, reconstitution, and administration of study drug.

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

9.2 Serious Adverse Event Procedures

9.2.1 Reference Safety Information

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

9.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the Investigator to PAREXEL International Pharmacovigilance within 24 hours of the first awareness of the event. **NOTE:** The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 9.1.7) unless they result in an SAE.

The Investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents (**NOTE:** Source documents are not to be sent unless requested) and fax or email the form to PAREXEL International Pharmacovigilance.

9.2.3 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. **NOTE:** The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. **NOTE:** Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. **NOTE:** Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

9.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent up to 30 days after the last dose of study drug, and must be reported to PAREXEL International Pharmacovigilance within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the Investigator at any interval after the study has completed must be reported to PAREXEL International Pharmacovigilance within 24 hours of the first awareness of the event.

9.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

9.2.6 Fatal Outcome

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

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

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

The Sponsor and/or the clinical CRO is responsible for notifying the relevant regulatory authorities/Japanese central IRB/EC of related, unexpected SAEs.

In addition, the Sponsor and/or the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the VP 20624 program.

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

10 STUDY MONITORING

The study will be monitored by Sponsor authorized individuals, acting as Sponsor agents with respect to current ICH guidelines, GCP, and SOPs 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 (eg, AEs, clinical laboratory tests, vital signs, ECGs, 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 DATA HANDLING

11.1 Data Collection

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

11.2 Clinical Data Management

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

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

12 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 ICH Tripartite Guideline for GCP, the Ministerial Ordinance on Good Clinical Practice for Drugs, and applicable regulatory requirements.

13 SUBJECT CONFIDENTIALITY

Investigator and his/her staff will be required to manage subject 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 Incorporated, the IRBs/ECs approving the study, as well as any applicable regulatory authorities, will be granted access to the study subjects' 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, the subjects' identity will remain confidential.

14 INFORMED CONSENT

The ICH has issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for GCP 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.

14.1 Adults

A properly executed, written informed consent in compliance with the terms of these guidelines shall be obtained from each subject before entering the trial, or before performing any unusual or non-routine procedure that involves a risk to the subject. A copy of the informed consent documents to be used will be reviewed and approved by the Sponsor. The document(s) will then be submitted to the IRB/EC for review and approval before the start of the study. The Investigator shall provide a copy of the signed and dated informed consent to the subject 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 was obtained prior to study participation. All procedures and documentation required for obtaining informed consent should be in compliance with ICH guidelines, the Japanese Ministry of Health and Welfare regulations, and local IRB/EC requirements, as well as state and local law.

14.2 Children or Minors

A properly executed, written **permission** statement (ie, informed consent) shall be obtained from each parent/legal guardian and **assent** shall be obtained from each subject aged ≥14 years 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 IRB/EC for review and approval before 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, the Japanese Ministry of Health and Welfare regulations, and local IRB/EC requirements, as well as state and local law.

15 INDEPENDENT REVIEWING AUTHORITY APPROVAL

The IRB/EC 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 IRB/EC that is adequately constituted to provide assurance of that protection will be utilized by each investigative site participating in the study.

The IRB/EC will be provided with all appropriate material, including a copy of the informed consent (permission)/assent for review. The trial will not be initiated at an investigational site until written approval of the research plan and the informed consent (permission)/assent document is obtained from the appropriate IRB/EC and copies of these documents are received by Shire ViroPharma Incorporated. Appropriate reports on the progress of this study will be made to the IRB/EC in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

16 PUBLICATION POLICY

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

17 INVESTIGATOR'S STATEMENT (PROTOCOL 0624-209)

A Phase 3, Open-Label, Single-Period Study to Evaluate the Safety and Treatment Effect of Intravenous Administration of CINRYZE® (C1 Inhibitor [Human]) for the Prevention of Angioedema Attacks and Treatment of Breakthrough Attacks in Japanese Subjects with Hereditary Angioedema (HAE).

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

1. Protecting the rights, safety, and welfare of subjects under my care.
2. 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 Incorporated guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

3. Permission to allow Shire ViroPharma Incorporated (or its designee) and PMDA, 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 Incorporated as soon as possible thereafter (no later than 1 week).
4. Submission of the proposed clinical investigation, including the protocol and informed consent/assent form, to a duly constituted IRB/EC for approval, and acquisition of written approval for each, prior to the use of the study drug.
5. 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 IRB/EC. Reference of such will be provided in source documentation.
6. Submission of any proposed protocol amendment to the IRB/EC. 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 IRB/EC 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 IRB/EC approval may be obtained by expedited review.
7. Adherence to the study protocol. For potential inclusion/exclusion criteria protocol deviations, submission for approval to Shire ViroPharma Incorporated prior to enrollment of study subjects. Documentation and explanation of individual post-enrollment protocol deviations will be recorded on the appropriate CRF page or provided in letters to Shire ViroPharma Incorporated.

8. Notification to Shire ViroPharma Incorporated of all serious adverse events, regardless of relationship to study drug, as specified in the protocol. Notification to the IRB/EC of serious adverse events as specified in the protocol and per additional guidelines as provided by the IRB/EC.
9. Notification to IRB/EC of all unanticipated problems within timeframes provided by the IRB/EC. 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.
10. 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.
11. Submission of timely progress reports to the IRB/EC and Shire ViroPharma Incorporated at appropriate intervals not to exceed 1 year and submission of a final report to the IRB/EC within 3 months after the completion, termination, or discontinuation of the clinical investigation.
12. 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 Incorporated.

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

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

_____
Investigator's Name (Please Print)

_____ _____
Investigator's Signature Date

18 LIST OF REFERENCES

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	20 January 2014	Global
Amendment 1	02 June 2014	Global
Amendment 2	05 August 2014	Global
Amendment 3	17 September 2014	Global
Amendment 4	16 February 2016	Global

Amendment 4 to Protocol 0624-209 includes the following changes:

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **16 February 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The Sponsor Medical Monitor has changed to PPD , MD.		Title Page
Revised description of the study population in protocol title (replaced "C1 inhibitor deficiency" with "hereditary angioedema (HAE)").		Title Page, Protocol Signature Page, Synopsis, Section 17
Revised the protocol review and approval form and moved the protocol history to the appendix (summary of changes in protocol amendments 1, 2, and 3) to align with Shire's templates.		Protocol Signature Page, Appendix 1
Allow subjects (≥12 years of age) who are considered suitable candidates (ie, those with a physical and mental capability of learning, adequate venous access, and willing to be trained) to self-administer one or more doses of CINRYZE during the study after receiving the required training by the Investigator or qualified delegate and demonstrated the necessary skills to independently administer investigational product by IV infusion. A new schedule (Schedule 2) and section (5.3.1) has been added to the protocol to provide details on self-administration.		Synopsis, Schedule 2, Sections 3, 5.3, and 5.3.1
Details on self-administration of investigational product will be recorded in the study diary.		Synopsis, Schedule 1, Sections 3 and 6.11
Clarified the collection period for AE/SAEs.		Synopsis, Schedule 3, Sections 3 and 6.2
Clarified requirements for diagnosing subjects with Type I or II HAE for study inclusion.		Synopsis, Sections 4.1 and 6.1
Removed an efficacy endpoint for prevention of angioedema attacks since this time to event endpoint was not considered a clinically meaningful assessment of prophylactic therapy.		Synopsis, Section 7.6.1
Vital sign measurements will not be collected at Visits 10, 12, 14, 18, 20, and 22 from subjects who independently self-administer investigational product at home.		Schedule 1, Section 6.3
Addition of a self-administration survey for both subject and Investigator assessment of the training process and overall experience with patient self-administration.		Synopsis, Schedule 1, Section 6.14

Subjects (≥12 years of age) may also elect to self-administer CINRYZE at home for a breakthrough attack provided they have completed the required training and deemed independent by the Investigator. Subjects who are participating in self-administration training and not yet qualified as independent cannot self-administer CINRYZE for a breakthrough attack; rather they should seek treatment at the investigational site.	Synopsis, Section 6.12.1
Clarified procedures for the assessment of breakthrough attacks now that subjects are allowed to self-administer CINRYZE and will be responsible for capturing all assessments in the study diary.	Synopsis, Section 6.12.2
Added the benefits of self-administration to the study rationale.	Section 1.2
Provided details on investigational product and ancillary supplies needed by subjects who elect to independently self-administer CINRYZE at home.	Section 8.1.1
Updated the list of references to reflect changes made throughout the document.	Section 18

Other administrative and clarifying revisions have been made throughout the protocol for consistency with these modifications.

Amendment 3 to Protocol 0624-209 includes the following changes.

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **17 September 2014**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
For subjects who weigh less than 25 kg, the Screening Visit must occur at least 14 days before Dosing Visit 1		Schedule 1 and Section 6.9
Doses of study drug administered at the subject's home will be administered by the Investigator or sub-Investigator		Protocol Synopsis, Schedule 1, and Sections 3.0 and 5.3
During the study, subjects who weigh less than 25 kg will have approximately 140 mL of blood collected for clinical safety laboratory testing (hematology, chemistry, coagulation, and virology), PK/PD assessments, and immunogenicity (C1 INH antibody) testing		Section 6.9

Other administrative and clarifying revisions have been made throughout the protocol for consistency with these modifications.

Amendment 2 to Protocol 0624-209 includes the following changes.

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **05 August 2014**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The SAE reporting procedure was revised to reflect that Investigators will report SAEs to PAREXEL International Pharmacovigilance, acting on behalf of Shire Pharmacovigilance		Emergency Contact Information, Schedule 2, and Sections 9.1.6, 9.1.7, 9.2.2, and 9.2.4
Sections regarding the discontinuation of subjects were revised to align with the Shire Phase 2-4 Protocol Template		Protocol Synopsis, Schedule 2, and Sections 3.0, 6.14, and 6.14.1
The total blood volume to be collected from subjects during the study was revised to approximately 200 mL		Section 6.9

Amendment 1 to Protocol 0624-209 includes the following major changes.

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **02 June 2014**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The Sponsor name and address were revised to reflect the acquisition of ViroPharma Incorporated by Shire plc		Title Page
The Sponsor Medical Monitor was changed to PPD, MD, PhD and a local Medical Monitor from PAREXEL International was added (PPD, MD, PhD)		Title Page
The Adverse Events and Data Handling Sections were revised to align with the Shire Phase 2-4 Protocol Template		Emergency Contact Information, Product Quality Complaints, and Sections 6.2, 9.0-9.2.7, and

	11.0-11.2
Adverse events will be collected from the time informed consent is signed	Schedule 1 and Sections 6.2 and 9.1
Angioedema attacks will not be reported as adverse events unless the attack meets the definition of a serious adverse event	Protocol Synopsis and Sections 3.0, 6.12, 6.12.2, 9.1, and 9.1.4
An inclusion criterion was added to stipulate that all subjects must be of Japanese descent	Protocol Synopsis and Section 4.1
An inclusion criterion was added to define a minimum body weight requirement for study entry (per PMDA request)	Protocol Synopsis and Section 4.1
If functional C1 INH testing is not performed as standard of care to diagnose HAE, a blood sample will be collected at screening to confirm a functional C1 INH concentration less than 50% of normal	Protocol Synopsis, Schedule 1, and Section 4.1
References to a second study diary were removed because the data collected were redundant with data captured by other study procedures	Protocol Synopsis, Schedule 1, Schedule 2, and Sections 3.0, 6.0, and 6.11
Treatment of breakthrough attacks is recommended to occur at the investigational site whenever possible so that clinical assessments can be completed as specified in the protocol	Protocol Synopsis and Sections 3.0 and 6.12.1
Other treatments for angioedema attacks (eg, another C1 INH product, tranexamic acid, fresh frozen plasma) are not permitted at the investigational site unless a subject does not adequately respond following treatment with CINRYZE	Protocol Synopsis and Section 6.12.1
The CINRYZE utilized in this study will be manufactured using US source plasma, and CINRYZE will be reconstituted with United States Pharmacopeia (USP) Sterile Water for Injection	Protocol Synopsis and Sections 5.3 and 8.2

Other administrative and clarifying revisions have been made throughout the protocol for consistency with these modifications.

APPENDIX 2 RECOMMENDED PROCEDURES FOR THE MANAGEMENT OF SUSPECTED VENOUS THROMBOEMBOLISM OR OTHER THROMBOTIC OR THROMBOEMBOLIC EVENTS