This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
# STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>COMPANY NAME:</th>
<th>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</th>
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</thead>
<tbody>
<tr>
<td>ViroPharma Incorporated</td>
<td>(For National Authority Use Only)</td>
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<tr>
<th>NAME OF_finished_PRODUCT:</th>
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<tr>
<td>CINRYZE®</td>
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<th>NAME_of_ACTIVE_INGREDIENT:</th>
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<td>C1 esterase inhibitor (human)</td>
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**STUDY TITLE:** A phase 4 study to evaluate the safety and effect of escalating doses of CINRYZE® (C1 inhibitor [human]) as prophylactic therapy in subjects with inadequately controlled hereditary angioedema attacks (Protocol 0624-400)

**INVESTIGATOR AND STUDY CENTER:** Multicenter trial (11 US sites)

**PUBLICATION (REFERENCE):** none

**STUDY PERIOD:**

- 31 August 2009 (first subject dosed)
- 24 May 2012 (last subject contact)

**CLINICAL PHASE:** Phase 4

**OBJECTIVES:** The objectives of this study were: (1) to assess the safety and tolerability of escalating doses of CINRYZE; (2) to assess the effect of an escalating dose algorithm for CINRYZE on angioedema attack rates; and (3) to assess the immunogenicity of CINRYZE.

**METHODOLOGY:** This open-label, multicenter, Phase 4 study assessed escalating doses of IV CINRYZE (1500 U, 2000 U, and 2500 U) as prophylactic therapy to lower the angioedema attack rate in subjects who were not adequately controlled while receiving the recommended CINRYZE dosing regimen (1000 U every 3 to 4 days via IV injection).

Subjects with qualifying angioedema attack rates, and who met other specified entry criteria, were entered into a 3-step dose-escalation algorithm. (The potential dose-escalation steps are provided in the STUDY DRUG section of the synopsis.) Each step consisted of 12 weeks of initial monitoring of subject safety while receiving the escalated prophylaxis therapy dose, followed by computation of the average monthly attack rate based on subject reports of any angioedema attack (regardless of intensity) and the actual duration of therapy for that step.

- If a subject was deemed a “success” (an average of ≤1.0 angioedema attack/month) at the most recent dosing step and the investigator and medical monitor determined that it was safe for the subject to continue on that dose, the subject entered the 3-month follow-up period at that dose level with continued safety monitoring. The subject could not re-enter the study for purposes of dose escalation during any “follow-up” period.
- If the subject was deemed a “failure” (an average of >1.0 angioedema attack/month), the next higher step of the dose-escalation algorithm was initiated for that subject provided that the investigator and medical monitor agreed that the subject was sufficiently compliant and that dose escalation was appropriate.

If at the end of step 3, the subject had an average of >1.0 angioedema attack/month, then the Week 12 visit represented completion of the study and the subjects were referred to the physician who managed their HAE for standard of care.

During the study, subjects or parents/caregivers used a study diary each day to document specific information about any angioedema attacks that occurred and the number of associated days of missed school/daycare or work. Subjects or parents/caregivers also received instruction on how to recognize symptoms associated with potential thrombotic events and to seek medical attention for these symptoms in addition to informing their principal investigator.

The first dose (Day 1 Visit) and the last dose (Week 12 Visit) of CINRYZE of each dose-escalation step were to be administered by qualified study personnel at the investigational site. In addition, at the end of dosing in the 3-month follow-up period, the last dose of CINRYZE was administered at the investigational site (Month 3 Visit). All other doses of study drug during the study were administered by qualified study personnel at the investigational site or by trained healthcare personnel (e.g., Visiting Nurses) in the subject’s home or place of work.
METHODOLOGY (continued): The investigator or designee was to monitor and document study compliance, tolerability of increased CINRYZE dose, and adverse events. For those subjects who were dosed by healthcare personnel at home or work, study personnel were to contact each subject or parent/caregiver by telephone at weekly intervals during each 12-week monitoring period and every other week during the 3-month follow-up period.

After a minimum of 6 months for those adequately controlled on the entry dose of this study (1500 U twice per week) and a maximum of 12 months of enrollment for subjects reaching the third tier of dose escalation (2500 U twice per week), subjects completed the study and their follow up was referred to the physician who managed their HAE care.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: To qualify for enrollment, a subject had to:

- Be ≥6 years of age and ≥25 kg body weight.
- Have a confirmed diagnosis of HAE with a documented history of swelling of the face, extremities, gastrointestinal tract, genitalia, or larynx and a history of at least one of the following:
  - C1 inhibitor (C1 INH) gene mutation
  - C4 level below the lower limit of the reference range
  - C1 inhibitor antigen level below the lower limit of the reference range
  - Functional C1 inhibitor level below the lower limit of the reference range
  - Family history of HAE (i.e., grandparent, parent, sibling)
- Have a history of >1.0 angioedema attack per month (average) of any severity during the 3 consecutive months prior to screening while receiving the recommended CINRYZE dosing of 1000 U every 3 to 4 days via IV injection.
- Have not had a history of abnormal blood clotting or other coagulopathy.
- Have not received any blood products (other than CINRYZE) within 60 days prior to screening.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED): Twenty (20) subjects were planned for enrollment. Twenty (20) subjects were enrolled and treated with IV CINRYZE and analyzed for safety: 20 subjects received 1500 U CINRYZE in dose-escalation Step 1; 13 subjects were dose-escalated to Step 2 and received 2000 U CINRYZE, 12 of whom were dose-escalated to Step 3 and received 2500 U CINRYZE. Sixteen (16) subjects (80%) completed treatment and 17 subjects (85%) completed the study.

DURATION OF TREATMENT: 2 times/week for 12 weeks in each dose-escalation step (Steps 1-3) and 2 times/week for 3 months in the follow-up period.
CINRYZE® (C1 esterase inhibitor [human])

**COMPANY NAME:**
ViroPharma Incorporated

**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**

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**NAME OF FINISHED PRODUCT:**
CINRYZE®

**NAME OF ACTIVE INGREDIENT:**
C1 esterase inhibitor (human)

**Volume:**

**Page:**

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**STUDY DRUG, DOSE, AND MODE OF ADMINISTRATION, LOT NUMBERS:**

CINRYZE was supplied as a lyophilized powder of 500 U (C1 INH)/vial for reconstitution with sterile water for injection. There were three potential dose-escalation steps:

- **Step 1:** 1500 U IV twice per week (starting dosing regimen for all subjects in study)
- **Step 2:** 2000 U IV twice per week
- **Step 3:** 2500 U IV twice per week

**NOTE:** No single dose could exceed 100 U per kg.

[The duration of dosing and algorithm for dose escalation is provided in the METHODOLOGY section of the synopsis.]

CINRYZE lot numbers were:

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**REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION, LOT NUMBER:**
None.

**SAFETY ASSESSMENTS:** Safety was monitored through the recording of AEs and any changes in physical examinations, vital signs, and clinical safety laboratory testing. Confirmed diagnoses of clinically significant thrombotic or thromboembolic events were to be reported as serious adverse events.

**EFFICACY ASSESSMENTS:** Efficacy assessments included the following: incidence of any angioedema attacks as determined by subject reported diary data, use of rescue therapy, hospitalization, and/or use of other therapy for treating an angioedema attack (e.g., androgens). Angioedema attacks included the following: (1) any attack of swelling or pain typical of an HAE event and subsequently recorded by the subject, study personnel, or home health care professionals, and (2) Actionable attacks, where “Actionable” was defined as seeking medical attention including any of the following interventions: IV fluids, narcotics, plasma administration, or C1 INH therapy.

**STATISTICAL METHODS:**

Safety: Descriptive statistics (e.g., N, mean, SE, SD, median, range) were reported for baseline, post-baseline, and change from baseline values in clinical laboratory (testing performed pre-dose on Day 1 of dose escalation Step 1 [baseline] and at Week 12 and follow-up Month 3 for each dose level) and vital signs (BP and HR measured immediately before and approximately 15 minutes after completion of each injection) parameters. Two summaries of AEs were provided: all treatment-emergent AEs (TEAEs) and all TEAEs related to study drug. Adverse events were coded using MedDRA (Medical Dictionary for Regulatory Activities) Version 15.0.
### Statistical Methods (continued):

#### Efficacy:
In this study, the calculation of angioedema attack rates included all reported attacks, regardless of severity, whether Actionable or not. Subject-reported HAE symptoms that occurred on consecutive days constituted one angioedema attack. The attack rate for a therapy period, nominally 84 days (12 weeks), was normalized to a monthly attack rate using the following formula:

\[
\text{Monthly attack rate} = \frac{30.4 \times \text{(# angioedema attacks in period)}}{\text{(days monitored in period)}}
\]

Thus, the calculated attack rate was based only on the formal observation interval (during which attacks were explicitly monitored). This same calculation was performed for Actionable attacks by substituting for the numerator the number of Actionable attacks in the observation period. Subjects observed to have an average monthly attack rate of \( \leq 1.0 \) per month at the end of any step (Week 12) were deemed a “success” based on the protocol definition.

### Study Population:
Enrolled and treated subjects, N=20
- Gender: Females, 14 (70%); Males, 6 (30%)
- Race: White/Caucasian, 18 (90%); Black/African American, 1 (5%); Other (Mexican), 1 (5%)
- Ethnicity: Hispanic/Latino, 2 (10%); Not Hispanic/Latino, 18 (90%)
- Age (Mean ± SD): 41.7 ± 15.3 years (range: 16-77 years)

### Safety Results:
No deaths were reported during this study. Two subjects experienced SAEs during the study; however, these events were considered by the investigator to be unrelated to study drug (cerebral hygroma for 1 subject; and HAE [verbatim: laryngeal angioedema attack], anemia [verbatim: anemia (worsening)], and bile duct stone [verbatim: worsening choledocholithiasis] for 1 subject). One of these subjects had study drug interrupted due to 2 SAEs while receiving 2000 U CINRYZE (due to hospitalization). No subject was discontinued from escalating doses of IV CINRYZE up to 2500 U due to an AE.

In addition, no subjects experienced a systemic thrombotic or thromboembolic TEAE during the study. Across all subjects, 90% (18/20) reported 1 or more TEAEs during the study: 75% (15/20) of subjects receiving 1500 U CINRYZE, 85% (11/13) of subjects receiving 2000 U CINRYZE, and 92% (11/12) of subjects receiving 2500 U CINRYZE. The most frequently reported TEAE following IV injection of CINRYZE across all dose levels was URTI, reported by 25% (5/20) of all subjects, followed in overall frequency by nasopharyngitis, reported by 15% (3/20) of all subjects.

The majority of TEAEs in this study (95%, 86/91 events) were considered by the investigator to be unrelated to study drug: 2 (10%) of the 20 subjects had a total of 5 events that were considered related to CINRYZE: catheter site pain (1 event at 1500 U, 1 event at 2500 U), dyspnea (2500 U, Day 173), and medical device complication (verbatim: blood clot in port; 1500 U, onset Day 81), reported by 1 subject and muscle spasms (2000 U, also related to concomitant use of imatinib on Days -483 to Day 253 for CML) reported by 1 subject. The medical device complication (blood clot in port) was treated locally with streptokinase with complete resolution. All of these events were mild in intensity and considered to be possibly related to study drug, with the exception of moderate catheter site pain during 1500 U dosing, which was considered to be definitely related to study drug. Both events of catheter site pain occurred only on the first day of dosing (for 1500 U and 2500 U), were characterized as a burning sensation/discomfort at port area, and resolved within 1 day.

Furthermore, the majority of TEAEs in this study were of mild or moderate intensity (85%, 77/91 events); 14 severe events (14/91, 15%) were reported by 7 subjects. All severe TEAEs with the exception of 1 event (muscle spasms; also related to concomitant use of imatinib on Duys -483 to Day 253 for CML) were considered by the investigator to be unrelated to study drug.
SAFETY RESULTS (continued): Results of clinical laboratory evaluations and vital signs measurements were generally unremarkable and did not suggest any treatment-emergent abnormalities related to the administration of CINRYZE.

Two subjects who had progressed through dose escalation Steps 1-3 (1500, 2000, and 2500 U, respectively) had C1 INH antibodies detected in plasma samples collected during the study. Both were deemed clinical failures. One subject had C1 INH antibodies detected at baseline (pre-dose Day 1) and in all samples collected at Week 12 of Steps 1 (1500 U), 2 (2000 U), and 3 (2500 U), respectively. The other subject had no detectable C1 INH antibodies at baseline (pre-dose Day 1), or at Week 12 of Step 1 (1500 U) and Step 2 (2000 U); subsequently, C1 INH antibodies were detected (ratio of 5.6) in the plasma sample collected at Week 12 of Step 3 (2500 U). An evaluation is ongoing to further characterize these C1 INH antibodies. No other subjects had detectable C1 INH antibodies in any of the samples analyzed.

EFFICACY RESULTS: All subjects enrolled in this study (n=20) had recurrent angioedema attacks despite therapy with CINRYZE 1000 U IV twice weekly; notably 3 of these subjects were receiving CINRYZE 1000 U IV thrice weekly. All of these refractory subjects started the study at an IV CINRYZE dose of 1500 U (Step 1); 13 subjects were dose escalated to 2000 U (Step 2), 12 of whom were further dose escalated to 2500 U (Step 3). Nine (45%) of the 20 subjects were deemed a success based on the protocol definition (i.e., an average of ≤1.0 angioedema attack/month at the end of any step [Week 12]) and continued on their final CINRYZE dose during follow-up at the investigator’s discretion: 4 subjects at Step 1 (1500 U) and 5 subjects at Step 3 (2500 U). Of note, 1 of these subjects was also a success at Step 2 (2000 U), based on the protocol definition; however, this subject was dose-escalated to Step 3, at the investigator’s clinical discretion. As outlined in the protocol efficacy assumptions, this study can be declared a success because greater than 4 subjects had an average of ≤1.0 angioedema attacks/month at the end of any step.

In addition to the per-protocol successes, based on the investigator’s clinical judgment, 2 subjects were also determined to be a success; both subjects had angioedema attack rates only slightly above the limits of protocol-defined success at their final dose level and continued on their final dose during follow-up at the investigator’s discretion: 1 subject at Step 1 (1500 U) and 1 subject at Step 3 (2500 U) had monthly average attack rates of 1.4 and 1.8, respectively. Therefore, based on the protocol-defined criteria and the investigator’s clinical judgment, 55% (11/20) of subjects were determined to be a success.

The sponsor reviewed data from all subjects who met the protocol definition of failure (n=9). Based on this review, 3 (15%) of the 20 subjects enrolled and treated in this study were assessed as a sponsor-determined success, which was defined as a reduction from historical angioedema attack rate of >1 at the end of any step (Week 12): 1 subject at Step 1 (1500 U) and 2 subjects at Step 3 (2500 U). Although 1 additional subject met this definition (reduction from historical rate of 3.3 to 1.9 during Step 3), the attacks remained severe and in 1 case involved the upper airway. Therefore, based on the protocol-defined criteria and both the investigator’s and sponsor’s clinical judgment, 70% (14/20) of subjects were determined to be a success.

Six (30%) of 20 subjects were deemed clinical failures (i.e., an average of >1.0 angioedema attack/month at the end of any step [Week 12]). Of note, 2 of these 6 subjects prematurely discontinued treatment and study: 1 subject during Step 1 (only received 9 doses of study drug); and 1 subject during Step 2 (only received 9 doses of study drug during Step 2).
### Individual Study Table Referring to Part of the Dossier

**COMPANY NAME:** ViroPharma Incorporated  
**NAME OF FINISHED PRODUCT:** CINRYZE®  
**NAME OF ACTIVE INGREDIENT:** C1 esterase inhibitor (human)  
**CONFIDENTIAL**

Mean (± SD) serum pre-dose (trough) complement concentrations (functional C1 INH, C1 INH antigen, and C4 complement) are presented below:

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<tr>
<th>Parameter (unit)</th>
<th>Pre-Dose Escalation (N=19)</th>
<th>IV CINRYZE</th>
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<tr>
<td></td>
<td></td>
<td>Step 1: 1500 U (N=19)</td>
</tr>
<tr>
<td>Functional C1 INH (U/mL)</td>
<td>0.129 ± 0.098</td>
<td>0.229 ± 0.052</td>
</tr>
<tr>
<td>Week 12</td>
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<td></td>
</tr>
<tr>
<td>C1 INH antigen (g/L)</td>
<td>0.161 ± 0.194</td>
<td>0.177 ± 0.046</td>
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<tr>
<td>Week 12</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>C4 complement (mg/L)</td>
<td>158 ± 80</td>
<td>172 ± 24</td>
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<tr>
<td>Week 12</td>
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In general, no correlation was observed between measured functional C1 INH, C1 INH antigen, or C4 complement and per-protocol, investigator-determined, or sponsored-determined success.

**CONCLUSIONS:**

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.
**COMPANY NAME:**
ViroPharma Incorporated

**NAME OF FINISHED PRODUCT:**
CINRYZE®

**NAME OF ACTIVE INGREDIENT:**
C1 esterase inhibitor (human)

**CONCLUSIONS (continued):**
This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

**Report Date:** 03 October 2012