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**

**COMPANY NAME:** ViroPharma Incorporated

**NAME OF FINISHED PRODUCT:** Cinryze®

**NAME OF ACTIVE INGREDIENT:** C1 Esterase Inhibitor (Human)

**STUDY TITLE:** An open-label, multiple-dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of subcutaneous versus intravenous administration of CINRYZE in adolescents and adults with hereditary angioedema (Protocol 0624-200)

**INVESTIGATOR AND STUDY CENTER:** Multicenter trial (6 U.S. sites)

**PUBLICATION (REFERENCE):** None

**STUDY PERIOD:** Initiation Date: 07 June 2010 (first subject dosed)  
Completion Date: 16 December 2010 (last subject contact)

**OBJECTIVES:**  
(1) to evaluate the safety and tolerability of multiple doses of CINRYZE administered by subcutaneous (SC) injection in adults and adolescents with hereditary angioedema (HAE);  
(2) to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of multiple doses of CINRYZE administered by SC injection in this study population; and  
(3) to assess the immunogenicity of CINRYZE following SC administration.

**METHODOLOGY:** This open-label, multiple-dose study was conducted to evaluate the safety/tolerability and PK/PD of SC versus IV administration of CINRYZE in adolescent and adult subjects with HAE. The study was conducted at 6 centers in the US. Following a screening visit within 21 days prior to study entry, subjects with HAE who met all other specified entry criteria were randomly assigned to one of two treatment sequences:

- CINRYZE 1000 U IV → 1000 U via SC injection (Sequence A/B)
- CINRYZE 1000 U IV → 2000 U via SC injection (Sequence A/C)

Each subject was to participate in two 18-day treatment periods, which were separated by a washout period of at least 14 days (starting after Day 18 of Period 1) during which no C1 INH therapy or other blood products were administered. Study drug was administered twice weekly for 2 weeks (i.e., on Days 1, 4, 8, and 11) in each treatment period. In Period 1, all subjects were to receive 1000 U CINRYZE as an IV infusion of 10 mL over ~10 minutes (Treatment A); in Period 2, SC CINRYZE was to be administered at separate sites in the abdomen as either 2 x 1.5 mL injections (3 mL total; 1000 U, Treatment B) or 4 x 1.5 mL injections (6 mL total; 2000 U, Treatment C).

Subjects remained outpatient throughout the study. Eligible subjects reported to the study center on Day 1 of each treatment period (the day of the first CINRYZE dose in each period) and were to remain in the study unit until after collection of the 8 hour PK sample. Subjects were to return to the study unit on Days 2, 3, 4, 6, 8, 11 (additional 8-hour PK profile), 12, 13, 14, 16, and 18 of each treatment period for PK/PD and safety assessments. PK/PD evaluations included assessment of antigenic and functional C1 INH levels (PK) and C4 complement (PD) levels. Safety was monitored through the recording of adverse events (AEs) and changes in physical examinations, 12-lead electrocardiogram (ECG, performed if clinically indicated), vital signs, and clinical laboratory testing (complete blood count [CBC], blood urea nitrogen [BUN], and creatinine); blood samples were also analyzed for the presence of C1 INH antibodies (Days 1 [pre-dose] and 18 of each treatment period).

Study personnel were to report any HAE attacks that occurred during the study as AEs, including those occurring during the washout period. General supportive care for management of acute HAE attacks (e.g., airway protection, IV fluids) was to follow standard practices at the investigational site or other site of care. If specific treatment with C1 INH was indicated (as determined by the investigator) the recommended treatment for use during the study was open-label CINRYZE 1000 U IV, followed by a second dose of 1000 U IV 1 hour later if needed.
If a subject had an HAE attack during Days 1-18 of one of the treatment periods, study treatment and study procedures were interrupted during that period. After recovery from the HAE attack, it was possible for the subject to re-enter the study after at least a 14-day washout period in which no C1 INH therapy or other blood products were administered, if mutually agreed by both the Sponsor and investigator. Otherwise, the subject was discontinued from the study. If the subject had another HAE attack during either treatment period, the subject was discontinued from the study.

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

- Be at least 12 years of age with a confirmed diagnosis of HAE and a history of at least one of the following:
  - C1 INH gene mutation
  - C4, C1 INH antigen, or functional C1 INH level below normal
- During the 3 consecutive months prior to screening, have a history of less than 1.0 HAE attack per month (average) treated with C1 INH therapy or any other blood products, ecallantide (Kalbitor®), icatibant (Firazyr®), antifibrinolytics (e.g., tranexamic acid), IV fluids, or narcotic analgesics.
- Have not received C1 INH therapy or any blood products (for treatment or prevention of an HAE attack) or ecallantide (Kalbitor®), icatibant (Firazyr®), or antifibrinolytics (e.g., tranexamic acid) within 14 days prior to the first dose of study drug in Period 1.
- Have had no change in androgen therapy (e.g., danazol, oxandrolone, stanozolol, testosterone) within 14 days prior to the first dose of study drug in Period 1.
- If female, agree not to start taking or change the dose of any hormonal contraceptive regimen or hormone replacement therapy (i.e., estrogen/progestin containing products) within 3 months prior to the first dose of study drug in Period 1.
- Have not received an immunization within 30 days prior to the first dose of study drug in Period 1.

**NUMBER OF SUBJECTS (PLANNED, ENROLLED, ANALYZED):** Twenty-four (24) subjects were planned for enrollment. Twenty-six (26) subjects were randomized and treated with CINRYZE (any amount) and analyzed for safety: 26, 13, and 12 subjects received 1000 U IV, 1000 U SC, and 2000 U SC CINRYZE, respectively, and were included in the safety population. Twenty-five (25) subjects completed treatment (1 subject did not receive treatment with 1000 U SC CINRYZE in Period 2) and 24 subjects completed the study. Subjects with evaluable PK/PD profiles were included in the PK/PD analyses.

**DURATION OF TREATMENT:** 2 times/week for 2 weeks in each of two treatment periods (i.e., on Days 1, 4, 8, and 11 of Periods 1 and 2).
Cinryze® (C1 esterase inhibitor [human])
Protocol 0624-200; Study Report DD0055

COMPANY NAME: VIROPHARMA INCORPORATED

NAME OF FINISHED PRODUCT: Cinryze®

NAME OF ACTIVE INGREDIENT: C1 Esterase Inhibitor (Human)

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: CINRYZE was supplied as a lyophilized powder of 500 U (C1 INH)/vial for reconstitution with sterile water for injection. Subjects were to receive 1000 U IV CINRYZE in Period 1 and 1000 U or 2000 U SC CINRYZE in Period 2, according to their randomized treatment sequence (A/B or A/C):
- Treatment A - IV infusion (1000 U, 10 mL) over ~10 minutes.
- Treatment B - 2 x 1.5 mL SC injections (1000 U in 3 mL total; 2 separate abdominal injection sites).
- Treatment C - 4 x 1.5 mL SC injections (2000 U in 6 mL total; 4 separate abdominal injection sites).

Periods 1 and 2 were separated by a washout period of at least 14 days (with no C1 INH or other blood products).

CINRYZE lot numbers were

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

PHARMACOKINETIC AND PHARMACODYNAMIC METHODS: Pharmacokinetic and pharmacodynamic parameters were calculated using observed or baseline-corrected concentrations versus actual time relative to Dose 1 of the treatment period and noncompartmental analyses in WinNonlin 5.3 (Pharsight, Cary, NC).

EFFICACY ASSESSMENTS: Not applicable.

SAFETY ASSESSMENTS: Safety was monitored by recording AEs and changes in physical examinations, 12-lead ECG (performed if clinically indicated), vital signs, and clinical laboratory testing.

STATISTICAL METHODS: Pharmacokinetics and Pharmacodynamics – Plasma concentration data and PK/PD parameters were summarized using descriptive statistics and nominal times including number of observations (N), mean, standard deviation (SD), minimum (min), median, maximum (max), coefficient of variation (CV%), and geometric mean (PK/PD parameters only). Linear correlation coefficients were estimated for plots of \( C_{\text{max}} \), \( R_{\text{max}} \), \( C_{\text{avg}} \), \( \text{AUC}_{0-72} \), and \( \text{AUC}_{0-\tau} \), values versus dose normalized to body weight (U/kg) values. Results of C1 INH antibody testing were reported for individual subjects, as appropriate.

Safety – Descriptive statistics (e.g., N, mean, standard error [SE], SD, median, range) were reported for baseline, post-baseline, and change from baseline values in clinical laboratory and vital signs parameters. Four summaries of AEs were presented by treatment period: all AEs, all AEs related to study drug, all treatment-emergent AEs (TEAEs), and all TEAEs related to study drug. Adverse events were coded using MedDRA (Medical Dictionary for Regulatory Activities) Version 14.0.

STUDY POPULATION: Randomized and treated subjects, N=26
Gender = Females, 15 (58%); Males, 11 (42%)
Race = White/Caucasian, 22 (85%); Black/African American, 4 (15%)
Ethnicity = Hispanic/Latino, 1 (4%); Not Hispanic/Latino, 25 (96%)
Age (Mean ± SD): 32.7 ± 14.7 years; 4 subjects <18 years of age (range: 12-16 years)
**COMPANY NAME:** ViroPharma Incorporated

**NAME OF FINISHED PRODUCT:** Cinryze®, Cinryze® (C1 esterase inhibitor [human])

**NAME OF ACTIVE INGREDIENT:** C1 Esterase Inhibitor (Human)

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1000 U IV</th>
<th>1000 U SC</th>
<th>2000 U SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 INH Antigen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (g/L)</td>
<td>0.100 ± 0.033</td>
<td>0.034 ± 0.032</td>
<td>0.050 ± 0.010</td>
</tr>
<tr>
<td>$C_{\text{avg}}$ (g/L)</td>
<td>0.049 ± 0.021</td>
<td>0.025 ± 0.024</td>
<td>0.040 ± 0.010</td>
</tr>
<tr>
<td>AUC$_{0-72}$ (g*h/L)</td>
<td>3.77 ± 1.56</td>
<td>1.84 ± 1.83</td>
<td>2.93 ± 0.69</td>
</tr>
<tr>
<td>AUC$_{0-\tau}$ (g*h/L)</td>
<td>4.08 ± 1.74</td>
<td>2.09 ± 2.06</td>
<td>3.35 ± 0.82</td>
</tr>
<tr>
<td>$K_{e1}$ (h$^{-1}$)</td>
<td>0.02 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>42.8 ± 24.1</td>
<td>64.0 ± 32.8</td>
<td>87.5 ± 60.3</td>
</tr>
<tr>
<td>$V_z$ or $V_z/F$ (mL/kg)</td>
<td>35.8 ± 21.0</td>
<td>151 ± 129</td>
<td>171 ± 126</td>
</tr>
<tr>
<td>F (%)</td>
<td>NA</td>
<td>22.3 (0.6 – 64.5)</td>
<td>35.0 (23.0 – 61.0)</td>
</tr>
<tr>
<td>Functional C1 INH Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (U/mL)</td>
<td>0.45 ± 0.14</td>
<td>0.15 ± 0.08</td>
<td>0.24 ± 0.11</td>
</tr>
<tr>
<td>$C_{\text{avg}}$ (U/mL)</td>
<td>0.23 ± 0.10</td>
<td>0.09 ± 0.07</td>
<td>0.18 ± 0.08</td>
</tr>
<tr>
<td>AUC$_{0-72}$ (U*h/mL)</td>
<td>17.7 ± 7.8</td>
<td>6.6 ± 5.1</td>
<td>13.7 ± 6.3</td>
</tr>
<tr>
<td>AUC$_{0-\tau}$ (U*h/mL)</td>
<td>19.2 ± 8.8</td>
<td>7.4 ± 5.6</td>
<td>15.5 ± 7.0</td>
</tr>
<tr>
<td>$K_{e1}$ (h$^{-1}$)</td>
<td>0.02 ± 0.01</td>
<td>0.01 ± 0.00</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>51.7 ± 29.2</td>
<td>68.9 ± 30.4</td>
<td>47.4 ± 16.9</td>
</tr>
<tr>
<td>$V_z$ or $V_z/F$ (mL/kg)</td>
<td>52.5 ± 24.3</td>
<td>297 ± 282</td>
<td>139 ± 70</td>
</tr>
<tr>
<td>F (%)</td>
<td>NA</td>
<td>22.8 (8.7 – 56.0)</td>
<td>31.5 (17.3 – 63.9)</td>
</tr>
</tbody>
</table>

**PHARMACODYNAMIC RESULTS:** Pharmacodynamic analyses were performed for all subjects with evaluable profiles.

**Steady-State (Day 11) Pharmacodynamic Parameters of C4 Complement in Subjects with HAE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1000 U IV</th>
<th>1000 U SC</th>
<th>2000 U SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{max}}$ (mg/L)</td>
<td>71 ± 31</td>
<td>37 ± 20</td>
<td>83 ± 56</td>
</tr>
<tr>
<td>AUC$_{0-72}$ (mg*h/L)</td>
<td>3870 ± 1994</td>
<td>1146 ± 997</td>
<td>4066 ± 1818</td>
</tr>
<tr>
<td>AUC$_{0-\tau}$ (mg*h/L)</td>
<td>4411 ± 2308</td>
<td>1356 ± 1164</td>
<td>4789 ± 2223</td>
</tr>
</tbody>
</table>
SAFETY RESULTS: No deaths or other serious adverse events (SAEs) occurred during the study. No subjects experienced a TEAE that was thrombotic or thromboembolic in nature during the study.

Across all subjects, 85% (22/26) reported 1 or more TEAEs during the study: 46% (12/26) of subjects receiving 1000 U IV CINRYZE, 77% (10/13) of subjects receiving 1000 U SC CINRYZE, and 92% (11/12) of subjects receiving 2000 U SC CINRYZE. During the IV CINRYZE period, the only TEAE reported in more than 1 subject was angioedema attack due to HAE (19%, 5/26).

As summarized below, the most frequently reported TEAEs following SC injection of CINRYZE were those associated with local tolerance at the injection site (i.e., injection site reactions), all of which were considered by the investigator to be related to study drug, with the exception of 1 event (injection site hematoma [bruising, 2000 U SC CINRYZE]). In both the 1000 U and 2000 U SC CINRYZE groups, injection site pain was the most commonly reported reaction.

### Treatment-Emergent Injection Site Reactions During SC CINRYZE Administration – Safety Population

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>CINRYZE 1000 U SC (n=13)</th>
<th>CINRYZE 2000 U SC (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain a</td>
<td>10 (77%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>4 (31%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Injection site hematoma b</td>
<td>1 (8%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>2 (15%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

a: Reported as burning, stinging, or pain.
b: Reported as bruising.

Among these injection site reactions, 93% (90/97 events) were of mild (52 events) or moderate (38 events) intensity; the remaining 7% were events of severe injection site pain (7 events in 3 subjects receiving 1000 U SC dosing). No severe injection site AEs were reported by subjects receiving 2000 U SC dosing, and no subjects discontinued treatment because of an injection site reaction.

With the exception of HAE, reported by 2 subjects (15%) receiving 1000 U SC CINRYZE and headache, reported by 2 subjects (17%) receiving 2000 U SC CINRYZE, all other TEAEs were reported by no more than 1 subject in either SC dose group.

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.
**COMPANY NAME:**
ViroPharma Incorporated

**NAME OF FINISHED PRODUCT:**
Cinryze®

**NAME OF ACTIVE INGREDIENT:**
C1 Esterase Inhibitor (Human)

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

**DATE OF THE REPORT:** 06 September 2011

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.