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.

SPONSOR is committed to publicly disclosing all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to the SPONSOR product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.

Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- 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>Name of sponsor/company:</th>
<th>Shire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of finished product:</td>
<td>Firazyr®</td>
</tr>
<tr>
<td>Name of active ingredient:</td>
<td>icatibant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual Study Table Referring to Part of the Dossier</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>(for National Authority Use only)</th>
</tr>
</thead>
</table>

**Title of the study:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Study Evaluating the Safety and Efficacy of Icatibant as a Treatment for Angiotensin-Converting Enzyme Inhibitor (ACE-I)-Induced Angioedema in Adults

**Investigator(s):** A total of 54 investigators at 59 sites participated in the study. The coordinating investigator was [redacted] DO.

**Study center(s):** Subjects were screened at 59 sites in the United States (US; 48 sites), the United Kingdom (UK; 5 sites), Israel (4 sites), and Canada (2 sites).

**Publications (references):** Not applicable.

**Study period:**
- Date of first subject’s consent: 02 December 2013
- Date of last subject’s last protocol-defined assessment: 22 August 2015

**Phase of development: 3**

**Objectives:**

**Primary Efficacy Objective:** To compare the efficacy of icatibant with placebo in the treatment of angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema based on the Time to Meeting Discharge Criteria (TMDC) endpoint.

**Key Secondary Efficacy Objective:** To compare the efficacy of icatibant with placebo in the treatment of ACE-I-induced angioedema based on the Time to Onset of Symptom Relief (TOSR) endpoint.

**Safety Objective:** To assess the safety and tolerability of icatibant treatment in subjects experiencing an attack of ACE-I-induced angioedema.

**Pharmacokinetic Objective:** To characterize the pharmacokinetic properties of icatibant and its major metabolites (M1 and M2 [amino acids 1-5 and amino acids 7-10, respectively]) in subjects with ACE-I-induced angioedema.
Methodology:
This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the safety and efficacy of icatibant as a treatment for ACE-I-induced angioedema in adults.

Eligible subjects were randomized at a 1:1 ratio to receive a single subcutaneous (SC) injection of either 30 mg icatibant or placebo. Angioedema-associated upper airway symptom assessments were performed for all subjects at baseline and at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours post treatment. Subjects were required to stay in the emergency department (ED) or hospital (hospital refers to any inpatient unit, intensive care unit, general clinical research center, monitored bed, etc.) for a minimum of 8 hours for monitoring and safety tests to be performed. A subject was discharged at 8 hours after treatment if he/she achieved the TMDC endpoint during the 8-hour time period and was deemed clinically stable and dischargeable by the investigator. If the subject had not achieved the TMDC endpoint, he/she remained in the ED or hospital until the subject achieved this endpoint and, in the judgment of the investigator, was clinically stable and could be discharged. During this time, airway symptom assessments were performed every 2 hours from >8 to 24 hours after treatment and every 3 hours starting from >24 hours after treatment. At discharge, subjects were instructed to call the investigator immediately if they were experiencing any symptoms of concern or recurrence of angioedema symptoms or were hospitalized or required an ED visit for any reason.

Subjects could be treated with corticosteroids, antihistamines, and/or epinephrine at any time following study drug administration, at the discretion of the investigator or ED/attending physician.

Adverse events (AEs) were recorded from the time of consent until Day 3 with a window of +2 days, after study drug administration (or until the event has resolved, stabilized, or an outcome was reached, whichever came first). A safety follow-up phone call was performed on Day 3 (+2 days) to query and collect any AEs that occurred following discharge and to determine if there was any recurrence of angioedema attack symptoms. If a subject was discharged from the hospital on or after Day 3, the safety follow-up phone call was performed approximately 2 days after the subject was discharged.

Number of subjects (planned and analyzed):
A total of 118 treated subjects (59 per treatment group) were planned for this study.

A total of 121 (61 icatibant; 60 placebo) subjects were randomized and included in the intent-to-treat (ITT) population. Three subjects did not receive study drug; therefore the modified ITT (mITT) and safety populations included 118 (60 icatibant, 58 placebo) subjects. The Per-Protocol (PP) population consisted of all subjects in the ITT population excluding subjects not receiving study drug and those with significant protocol deviations that may impact efficacy. Overall, 10 (8.3%) subjects (4 [6.6%] icatibant; 6 [10.0%] placebo) had a significant protocol deviation that resulted in exclusion from the PP population. Therefore, 108 (89.3%) subjects (56 [91.8%] icatibant, 52 [86.7%] placebo) were included in the PP population.

Diagnosis and main criteria for inclusion:
Subjects, 18 years of age or older, who presented with ACE-I-induced angioedema of the head and/or neck region were enrolled in the study. To be eligible for the study, the subject had to experience an attack that was at least moderate in severity for at least 1 of the primary efficacy symptom assessments (difficulty breathing, difficulty swallowing, voice changes, tongue swelling). The duration of the attack had to be less than 12 hours at enrollment to allow study drug to be given within 12 hours of the onset of the attack.
Investigational product, dose, mode of administration, and batch number(s):
Icatibant at a dose of 30 mg was administered as a single SC injection. The batch and/or lot numbers of product used in this study were: and .

Reference product(s), dose, mode of administration, and batch number(s):
Placebo was administered as a single SC injection. This study was double-blinded; therefore, the icatibant and placebo were packaged identically under the same lot numbers.

Duration of treatment:
The duration of participation was up to 5 days (safety follow-up telephone call on Day 3 [+2 days]). In the event that a subject was discharged on or after Day 3, his or her duration of participation was extended to approximately 2 days after the subject’s discharge date.

Criteria for evaluation:
Primary Efficacy Endpoint: The TMDC was based on investigator assessment of angioedema-associated upper airway symptoms. The TMDC endpoint was calculated from the time of study drug administration to the earliest time point at which the symptoms of difficulty breathing and difficulty swallowing were absent (score=0) and the symptoms of voice change and tongue swelling were mild or absent (scores of 0 or 1).

Key Secondary Efficacy Endpoint: The TOSR was based on investigator assessment of angioedema-associated upper airway symptoms. The TOSR endpoint was calculated from the time of study drug administration to the earliest time point at which the individual symptoms with pretreatment scores of 2 (moderate) or more had improved by at least 1 severity grade and the individual symptoms with pretreatment scores of 0 or 1 (absent or mild) are scored again at 0 or 1.

Other Secondary Efficacy Endpoints: The other secondary efficacy endpoints included: TMDC and TOSR calculated for each of the individual symptoms of angioedema-associated upper airway compromise; occurrence of airway intervention (intubation, tracheotomy, cricothyrotomy) due to the ACE-I-induced angioedema attack; occurrence of admission to the hospital (inpatient) or intensive care unit (ICU) due to the ACE-I-induced angioedema attack; use of medications for the treatment of symptoms of the ACE-I-induced angioedema attack following study drug administration (corticosteroids, antihistamines, epinephrine); and achievement of the TMDC endpoint at 4, 6, and 8 hours post-treatment.

Safety Endpoints: The safety and tolerability of icatibant were evaluated through the assessment of AEs, injection site reactions, clinical laboratory testing (hematology, serum chemistry, and urinalysis), vital sign measurements, electrocardiogram (ECG) recordings, and physical examination findings.

Pharmacokinetic Endpoints: The primary pharmacokinetic parameters of icatibant and its major metabolites M1 and M2 (ie, C, AUC) were estimated based on population pharmacokinetic modeling.
Statistical methods:

Sample Size:

Using the log-rank test for evaluating the equality of survival curves and assuming a 0.05 2-sided significance level, a total of 100 subjects, 50 subjects per treatment group, would yield at least 95% power to detect a difference in the primary efficacy endpoint and at least 90% power to detect a difference in the key secondary efficacy endpoint given similar distributions of events as observed in a previous study. Assuming 15% of subjects did not achieve the endpoint, a total of 118 subjects, 59 subjects per treatment group, would be needed.

Primary Efficacy:

The difference in TMDC was tested by the following hypothesis:

\[ H_0: \frac{\lambda_{Icatibant}}{\lambda_{Placebo}} = 1 \quad \text{versus} \quad H_1: \frac{\lambda_{Icatibant}}{\lambda_{Placebo}} \neq 1 \]

Where \( \lambda_{Icatibant} \) referred to the hazard rate to achieve the TMDC endpoint under icatibant and \( \lambda_{Placebo} \) referred to the hazard rate to achieve TMDC endpoint under placebo. Thus, the null hypothesis \( H_0 \) stated that there was no difference between the 2 treatment groups (or hazard ratio was equal to 1). Estimated hazard ratios greater than 1 indicated that subjects receiving icatibant met the TMDC endpoint faster than the subjects receiving placebo. The test was performed using a weighted log-rank test called the Peto-Prentice test with a global 2-sided significance level of 5% after adjusting for stratification factors (race: Black vs other and the attack severity: moderate vs severe/very severe) in the ITT population.

Key Secondary Efficacy:

The TOSR was analyzed using the same method as the primary efficacy endpoint.

Other Secondary Endpoints:

The TMDC and TOSR endpoints were calculated for each of the individual symptoms of angioedema-associated upper airway compromise (difficulty breathing, difficulty swallowing, voice changes, and tongue swelling), and the treatment difference was tested using the Peto-Prentice test with a global 2-sided significance level of 5% after adjusting for race (Black or African American vs other races) and symptom specific pretreatment severity (mild/moderate vs severe/very severe).

The number and proportion of subjects with and without an occurrence of an airway intervention post-treatment due to the ACE-I-induced angioedema attack were summarized by treatment group, and the treatment difference was tested using a Fisher’s exact test.

The number and proportion of subjects with and without an occurrence of admission to the hospital (inpatient) or ICU post-treatment due to the ACE-I-induced angioedema attack were summarized by treatment group, and the treatment difference was tested using a Fisher’s exact test. The duration of stay in the hospital or ICU was summarized using descriptive statistics by treatment group.

The number and proportion of subjects with and without the use of conventional medications for the treatment of symptoms of the ACE-I-induced angioedema attack following study drug administration were summarized by treatment group, and the treatment difference was tested using a Fisher’s exact test.

The number and proportion of subjects who achieved and did not achieve the TMDC endpoint by 4, 6, and 8 hours post-treatment were summarized by treatment group, and the treatment difference was tested using a
Fisher’s exact test.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0. The number and percentage of subjects with an AE, as well as the total number of AEs, were summarized by system organ class (SOC), preferred term (PT), and treatment group. This was repeated for related AEs, SAEs, related SAEs, and AEs related to the ACE-I-induced angioedema attack. The number and percentage of subjects with AEs were also summarized by SOC, PT, and treatment group by severity, in which the subject’s most severe event within a category was counted. The number and percentage of subjects with AEs were also summarized by SOC, PT, and treatment group by closest relationship to treatment, in which the subject’s closest relationship to treatment event within a category was counted.

The number and percentage of subjects with any injection site reactions by type and any severe reactions by type were summarized by treatment group. The number and percentage of subjects with injection site reactions were also summarized by maximum severity at any time point and for each study time point by treatment group.

Changes in laboratory values and vital signs were summarized by study time point and treatment group. Number and percentage of subjects with normal or abnormal not clinically significant and abnormal clinically significant ECG results, or ECG not performed, were summarized by study time point and treatment group.

Pharmacokinetics:

Plasma concentrations were summarized using descriptive statistics.

Compartmental modeling using population methods and nonlinear mixed-effects modeling was used to define individual subject profiles and, if possible, parameter estimates. The structural pharmacokinetic model was developed and validated using pharmacokinetic information previously obtained from healthy adult subjects and adult subjects with hereditary angioedema. The model evaluated the impact of key covariates (ie, age, sex, disease state) on the disposition of icatibant. Population pharmacokinetic modeling was performed with nonlinear mixed-effects modeling software (eg, Phoenix NLME module, Pharsight Corp.).

Results:

Demographics and Baseline Characteristics:

The two treatment groups were well balanced with respect to demographics and baseline characteristics. The mean age was 61 years. About half of the subjects were female (51.2%). The majority of subjects were Black or African American (69.4%) and 13.2% of subjects enrolled at a site outside of the US. The majority of subjects were experiencing an attack of ACE-I-induced angioedema of moderate intensity (71.9%). The most frequently taken ACE inhibitor was lisinopril (69.4%).

Overall, 110 (90.9%) subjects were treated with conventional medications prior to receiving the study drug. The treatment groups were similar with respect to conventional medications use. Overall, the mean time from attack onset to conventional medication administration was 3.9 ± 2.4 hours and the mean time from conventional medication administration to study drug administration was 3.7 ± 2.4 hours. The mean time from attack onset to study drug administration was 7.6 ± 2.7 hours.
**Name of sponsor/company:**
Shire

**Name of finished product:**
Firazyr®

**Name of active ingredient:**
icatibant

**Efficacy results:**

**Primary Endpoint**
For the primary efficacy endpoint, TMDC, 60 (98.4%) icatibant subjects and 58 (96.7%) placebo subjects met the discharge criteria. TMDC was not statistically different between treatment groups (p=0.633). The median time to TMDC was 4.03 hours for the icatibant group and 4.00 hours for the placebo group.

![Time to TMDC](chart1.png)

**Key Secondary Endpoint**
For the key secondary efficacy endpoint, TOSR, 60 (98.4%) icatibant subjects and 58 (96.7%) placebo subjects experienced symptom relief. TOSR was not statistically different between treatment groups (p=0.570). The median time to TOSR was 2.00 hours for the icatibant group and 1.55 hours for the placebo group.

![Time to TOSR](chart2.png)

No treatment differences in TMDC or TOSR were observed when analyzed by age, sex, race, attack severity, weight, BMI, and geographic region.
Other Secondary Endpoints

There was no difference between the treatment groups in TMDC or TOSR for the individual symptoms of difficulty breathing, difficulty swallowing, voice changes, or tongue swelling.

There was no difference between the treatment groups for the occurrence of airway intervention (p=1.000). One (1.7%) icatibant subject and no placebo subjects required an airway intervention.

The occurrence of admission to the hospital (inpatient) or ICU post-treatment was not statistically different between treatment groups (p=1.000). A total of 22 (45.8%) icatibant subjects and 22 (45.8%) placebo subjects were admitted to the hospital or ICU. The mean duration of hospitalization was 30.10 hours for the icatibant group and 20.67 hours for the placebo group.

A total of 35 (58.3%) icatibant subjects and 35 (60.3%) placebo subjects used a medication to treat symptoms of the attack following study drug administration. This difference was not statistically significant (p =0.853). The most frequently used medication were antihistamines (43.3% icatibant; 50.0% placebo) and corticosteroids (41.7% icatibant; 48.3% placebo).

There was no statistically significant difference between the treatment groups in the achievement of meeting the discharge criteria at 4, 6, and 8 hours post-treatment.

Pharmacokinetic results:

Observed plasma concentrations, at 0.75 and 2 hours post a single SC administration of icatibant were 613 ± 198 and 484 ± 194 ng/mL for icatibant, 98.7 ± 52.6 and 182 ± 82.1 ng/mL for M1, and 116 ± 56.7 and 223 ± 94.2 ng/mL for M2, respectively. The corresponding molar ratios between M1 to icatibant and M2 to icatibant are approximately 0.821 and 1.05 at 2 hours post-dose, indicating that similar molar levels of icatibant, M1 and M2 are available in the bloodstream.

The estimated exposure to icatibant and its 2 metabolites as evaluated by AUC₀₋₆, AUC₀₋₂₄, Cₘ₅₉, C₆₀, are comparable. The apparent total clearance (CL/F) following a single SC administration is similar among icatibant, M1, and M2. Apparent volume of distribution was estimated as 40.8 ± 16.0, 33.8 ± 12.9, and 30.7 ± 12.0 L for icatibant, M1, and M2, respectively. Compared to icatibant which has Tₘ₉₉ values ranging from 0.70 to 1.30 hours, M1 and M2 are slowly formed with individual Tₘ₉₉ values ranging from 1.80 to 3.40 hours post-dose and are more slowly eliminated with terminal half-life values ranging from 4.14 to 7.61 hours post-dose.

No clinically meaningful effect of age, sex, or race on the estimated exposure to icatibant, M1, and M2 as evaluated by Cₘ₉₉, Tₘ₉₉, AUC₀₋₆, AUC₀₋₂₄ were noticed in this population.

Safety results:

There were a total of 70 TEAEs in 27 (45.0%) icatibant subjects and 40 TEAEs 21 (36.2%) placebo subjects. The most frequently occurring (≥ 5%) TEAEs were angioedema (9 events in 7 [11.7%] subjects), headache (7 events in 7 [11.7%] subjects), and dysphonia (4 events in 3 [5.0%] subjects) in icatibant subjects, and headache (4 events in 4 [6.9%] subjects), dyspnea (3 events in 3 [5.2%] subjects), and nausea (3 events in 3 [5.2%] subjects) in placebo subjects.

There were a total of 28 treatment-related TEAEs in 11 (18.3%) icatibant subjects and 16 TEAEs 8 (13.8%) placebo subjects. Treatment-related TEAEs experienced by 2 or more subjects included angioedema (3 events in 3 [5.0%] subjects), dysphonia (3 events in 2 [3.3%] subjects), blood uric acid increased (2 events in 2 [3.3%] subjects),
subjects), and neutrophil percentage increased (2 events in 2 [3.3%] subjects) for icatibant subjects and nausea (2 events in 2 [3.4%] subjects) in placebo subjects.

The majority of TEAEs reported by subjects during the study were mild or moderate in severity. One icatibant subject experienced laryngeal edema and one placebo subject experienced dysphonia that was assessed as severe in intensity; neither was assessed as treatment-related.

The percentage of subjects with any injection site reaction was greater in the icatibant group (39 [65%] subjects) than the placebo group (18 [31.0%] subjects). The most frequently noted injection site reaction in the icatibant group was erythema (31 [51.7%] subjects). No injection site reactions were assessed as severe.

There were no deaths and no discontinuations due to a TEAE in this study. One icatibant subject experienced laryngeal edema, 1 icatibant subject experienced hypoxia, and 1 placebo subject experienced rash pruritic that were reported as treatment-emergent SAEs; none of which was assessed as treatment-related. In addition, 1 subject, who did not receive study drug, experienced angioedema that was reported as an SAE assessed as not related to study drug.

No clinically meaningful changes were observed in laboratory values, vital signs, or ECGs.

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.

Date of report: 06 December 2015