ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 06/30/2014

EASSI - Evaluation of the Safety of Self-Administration With Icatibant

This study has been completed.

Sponsor:	Shire
Collaborators:	Jerini AG
Information provided by (Responsible Party):	Shire
ClinicalTrials.gov Identifier:	NCT00997204

Purpose

This study is being conducted to explore the clinical safety, local tolerability, convenience and effectiveness of self-treatment of hereditary angioedema (HAE) attacks with subcutaneous injections of icatibant.

Condition	Intervention	Phase
Hereditary Angioedema	Drug: Icatibant	Phase 3

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety Study
Official Title: Open Label, Multicenter Study to Evaluate Safety, Local Tolerability, Convenience, and Efficacy of a Self-Administered Subcutaneous Formulation of Icatibant for the Treatment of Acute Attacks of Hereditary Angioedema

Further study details as provided by Shire:

Primary Outcome Measure:

- Number of Participants With Adverse Events in Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant [Time Frame: 7 days from the beginning of each phase] [Designated as safety issue: Yes]

  Clinical safety of self-treatment of acute HAE attacks with s.c. injections of icatibant was assessed by calculating the number of AEs occurred during the study. Only those adverse events occurring up to the earlier of 7 days from the start of the naive phase, study discontinuation and start of the self-

administration phase are assessed. The Local Tolerability Assessment tool was used. Subjects and Investigators graded erythema/reddening, swelling, burning, pruritus/itching, warm sensation, and skin pain on a 0 to 3 severity scale.

Secondary Outcome Measures:

- Clinical Efficacy of Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant, Time to Symptom Relief Using VAS Score for a Single Primary Symptom by Patient Cohort [Time Frame: 48 hours post-dose] [Designated as safety issue: No]

  Subjects assessed angioedema attack symptoms using the visual analogue scale (VAS) for skin pain, skin swelling and abdominal pain. The VAS is a continuous scale comprised of a 100 mm in length line, anchored by 2 verbal descriptors, one for each symptom extreme 0 (no pain) and 100 (worst pain). The respondent is asked to place a mark on the VAS line (any where between 0 and 100 mm) at the point that represents their pain intensity. The score is determined by measuring the distance (mm) on the line between the "no pain" anchor and the patient's mark, providing a range of scores from 0-100. A higher score indicates greater pain intensity. Score interpretation is: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm). Symptom relief is defined as at least a 50% reduction in a pre-dose VAS score of 30 mm or greater. The time to onset of symptom relief is defined as the first of 3 consecutive assessments at which symptom relief was observed.

Enrollment: 151
Study Start Date: September 2009
Primary Completion Date: June 2011
Study Completion Date: September 2011

Arms	Assigned Interventions
Experimental: Icatibant- Naive Treatment Phase Single subcutaneous injection of icatibant, 30 mg	Drug: Icatibant Single subcutaneous injection of icatibant, 30 mg Other Names: Brand name, Firazyr®
Experimental: icatibant- Self administration Phase Single subcutaneous injection of icatibant, 30 mg	Drug: Icatibant Single subcutaneous injection of icatibant, 30 mg Other Names: Brand name, Firazyr®

Detailed Description:

This Phase IIIb study was multi-center and open-label with a single dose level. Subjects with a documented diagnosis of HAE Type I or II were eligible to participate in this trial. Eligible subjects included those who had received treatment for HAE with icatibant in previous clinical trials, or subjects who had been previously treated with the marketed product Firazyr® and subjects who were naïve to icatibant treatment.

All subjects were trained on the method of self-administration at their enrollment visit (Visit 1).For the training sessions, a syringe pre-filled with 3 mL placebo solution was used in place of icatibant. Comprehensive educational material and instructions including pictograms were developed for the subjects to illustrate the method of self-administration and use of the Patient Diary. The training material provided additional information on how to self-diagnose an HAE attack and how to decide on the necessity to treat.In addition, instructions were provided on what to do in case of a laryngeal attack.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. Males and females 18 years of age at the time of informed consent
2. Documented diagnosis of HAE Type I or II based on ALL of the following criteria:
    - Family and/or medical history
    - Characteristic attack manifestations, recurrent attacks
    - Historical functional C1-INH <50% normal values
3. Women of childbearing potential must use consistently and correctly a highly effective, adequate method of birth control (failure rate less than 1% per year) - sexual abstinence or have a vasectomised partner during the duration of the study. Hormonal contraception can be continued if verified by a physician that it doesn't affect the course of HAE attacks.
4. Mental and physical condition allowing patients to complete baseline assessment, to self-administer icatibant and to follow other study procedures.
5. Ability to provide signed written informed consent after all aspects of the study have been explained and discussed with the patient.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study.

1. Participation in a clinical trial of another investigational medicinal product within the past month (except a previous icatibant study).
2. Diagnosis of angioedema other than Type I or Type II HAE.
3. Evidence of symptomatic coronary artery disease based on medical history, in particular, unstable angina pectoris or severe coronary heart disease.
4. Congestive heart failure (NYHA Class 3 and 4).
5. Stroke within the past 6 months.
6. Treatment with angiotensin converting enzyme (ACE) inhibitor.
7. Pregnancy and/or breast-feeding.
8. In the opinion of the investigator: mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study.
9. In the opinion of the investigator: unlikely to comply with the protocol, for example, uncooperative attitude, inability to return for follow-up visits, or unlikely to complete the study for any reason.
10. In the opinion of the investigator: inability to manage study medication or self-administration of an injection.

Contacts and Locations

Locations

Argentina

Hospital Britanico Unidad de Alergia

Buenos Aires, Buenos Aires, Argentina, C1035AAT

Austria

Universitätsklinik für Dermatologie und Venerologie

Graz, Austria, 8036

Denmark
- Odense Universitetshospital-OUH
  - Odense, I og Alergicentret, Denmark

France
- Centre Hospitalier Universitaire/ Service de Dermatologie
  - Angers, Angers Cedex 09, France, 49933
- Hospital Edouaed Herriot
  - Lyon, Cedex 03, France, 69437
- Clinique Universitaire de Medicine/ Centre National de reference
  - Grenoble, Grenoble Cedex 09, France, 38043
- Hopital Claude Huriex/ Service de medicine interne
  - Lille, Lille Cedex, France, 59037
- Hopital Europeen Georges Pompidou Immunologie Clinique
  - Paris, Paris Cedex 15, France, 75015

Germany
- Universitätsmedizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie, Charité
  - Berlin, Germany, 10117
- Universitäts-Hals-Nasen-Ohren-Klinik Essen, Universität Duisburg-Essen
  - Essen, Germany, 45127
- Hautklinik und Poliklinik, Universitätsmedizin der Johannes Gutenberg-Universität
  - Mainz, Germany, 55101
- Klinkum der Johann Wolfgang Goethe-Universitat
  - Frankfurt am Main, Frankfurt am Main, Germany, 60590

Israel
- Bnai-Zion M.C. Clinical Immunology and Allergy Division
  - Haifa, Israel, 31048
- Tel Aviv Sourasky Medical Center - Allergy Unit
  - Tel Aviv, Israel, 64239
- The Chaim Sheba Medical Center, The Allergy and Clinical Immunology Unit
  - Tel Hashomer, Israel, 52621

Italy
- Universita degli Studi di Napoli 'Federico II'
  - Napoli,, Italy, 80131
- Ospedale Luigi Sacco
  - Milano, Milano, Italy, 20157

Spain
- Hospital Universitario Vall de Hebrón / Sección de Alergia, Escola Infermeria
  - Barcelona, Spain, 08035
- Hospital Universitario La Paz, Servicio de Alergia
  - Madrid, Spain, 28046
- Hospital Universitario La Fe, Servicio de Alergia
  - Valencia, Spain, 46009
- Hospital General Universitario Gregorio Maranon
  - Madrid, Madrid, Spain, 28007

Switzerland

Luzerner Kantonsspital
Luzern, Switzerland
Universitätsspital Zürich / Dermatologische Klinik
Zurich, Switzerland, 8091
United Kingdom
Southmead Hospital, Department of Immunology
Bristol, United Kingdom, BS10 5NB
Barts & The London NHS Trust, Pathology and Pharmacy Building
London, United Kingdom, E1 2ES
Derriford Combined Laboratory, Department of Clinical Immunology & Allergy
Plymouth, United Kingdom, PL6 8DH

Investigators

Study Director:	Anja D. Lachmann, Dr.	Jerini AG

More Information

Responsible Party:	Shire
Study ID Numbers:	JE049-3101 2008-000071-25 [EudraCT Number]
Health Authority:	Austria: Agency for Health and Food Safety Germany: Federal Institute for Drugs and Medical Devices United Kingdom: Medicines and Healthcare Products Regulatory Agency Israel: Ethics Commission Switzerland: Swissmedic Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Italy: Ministry of Health Spain: Agencia Española de Medicamentos y Productos Sanitarios Denmark: Danish Medicines Agency

---

Study Results

Participant Flow

Pre-Assignment Details	Patients were screened for entry based on their known medical histories (HAE attacks) and previous exposure to a treatment (naïve or not). 151 were enrolled and trained in the self-administration. 47 of these subjects did not have an acute attack of HAE treated with icatibant during this study and were included in the untreated population.

Reporting Groups

	Description
Naive Subjects/ Naive Treatment Phase	Patients who had never received icatibant before this phase, got treatment of Acute HAE Attack with SC icatibant (30 mg)Administered at Site by Health Care Provider.
Non-Naive Subjects/ Self-administration Phase	Subjects who had received treatment for HAE with icatibant in previous clinical trials or had been previously treated with the marketed product Firazyr®, got Treatment of Acute HAE Attack with SC icatibant (30 mg)Self-Administered.

Naive Treatment Phase

	Naive Subjects/ Naive Treatment Phase	Non-Naive Subjects/ Self-administration Phase
Started	25	79 [1]
Completed	19	0
Not Completed	6	79

[1] Non-naive patients participated in the study but they were not treated in the naive treatment phase

Self-administration Phase

	Naive Subjects/ Naive Treatment Phase	Non-Naive Subjects/ Self-administration Phase
Started	19	78 [1]
Completed	19	77
Not Completed	0	1

[1] 1 subject did not self-administered icatibant but had a HCP to perform. the data were not included.

Baseline Characteristics

Reporting Groups

	Description
Non-Naive Patients	Patients who previously treated with icatibant in clinical studies or with commercial Firazyr® and got the treatment during the self-administered phase
Naive Patients	Patients who had never received icatibant and treated in both the Naive treatment phase and the Self-administered phase

Baseline Measures

	Non-Naive Patients	Naive Patients	Total
Number of Participants	79	25	104
Age, Continuous [units: years] Mean (Standard Deviation)	40.607 (13.044)	44.68 (16.53)	41.58 (13.98)
Gender, Male/Female [units: participants]			
Female	52	16	68
Male	27	9	36
Region of Enrollment [units: participants]			
France	6	0	6
Argentina	18	5	23
Spain	9	2	11
Denmark	5	0	5
Austria	9	5	14
Israel	15	0	15
Germany	9	5	14
Italy	1	1	2
Switzerland	1	1	2
United Kingdom	6	6	12

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Adverse Events in Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant
Measure Description	Clinical safety of self-treatment of acute HAE attacks with s.c. injections of icatibant was assessed by calculating the number of AEs occurred during the study. Only those adverse events occurring up to the earlier of 7 days from the start of the naive phase, study discontinuation and start of the self-administration phase are assessed. The Local Tolerability Assessment tool was used. Subjects and Investigators graded erythema/reddening, swelling, burning, pruritus/itching, warm sensation, and skin pain on a 0 to 3 severity scale.
Time Frame	7 days from the beginning of each phase

Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Naive Subjects Administered Icatibant by Health Care Provider	The first HAE attack of naïve subjects enrolled in the study was treated at the study site, where a Health Care Provider administered icatibant to the subject. 3 subjects (of the original 25 enrolled in the naive treatment phase)self-administered icatibant while observed bu HCP, as opposed to having the HCP perform the injection. these data were not included in the naive treatment safety analyses.
Subjects Who Self-administered Icatibant (Naive)	Naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.
Subjects Who Self-administered Icatibant (Non-naive)	Non-Naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.

Measured Values

	Naive Subjects Administered Icatibant by Health Care Provider	Subjects Who Self-administered Icatibant (Naive)	Subjects Who Self-administered Icatibant (Non-naive)
Number of Participants Analyzed	22	19	78
Number of Participants With Adverse Events in Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant [units: participants]	11	6	27

2. Secondary Outcome Measure:

Measure Title	Clinical Efficacy of Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant, Time to Symptom Relief Using VAS Score for a Single Primary Symptom by Patient Cohort

Measure Description	Subjects assessed angioedema attack symptoms using the visual analogue scale (VAS) for skin pain, skin swelling and abdominal pain. The VAS is a continuous scale comprised of a 100 mm in length line, anchored by 2 verbal descriptors, one for each symptom extreme 0 (no pain) and 100 (worst pain). The respondent is asked to place a mark on the VAS line (any where between 0 and 100 mm) at the point that represents their pain intensity. The score is determined by measuring the distance (mm) on the line between the “no pain” anchor and the patient’s mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity. Score interpretation is: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm). Symptom relief is defined as at least a 50% reduction in a pre-dose VAS score of 30 mm or greater. The time to onset of symptom relief is defined as the first of 3 consecutive assessments at which symptom relief was observed.
Time Frame	48 hours post-dose
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Naive Subjects Administered Icatibant by Health Care Provider	The first HAE attack of naïve subjects enrolled in the study was treated at the study site, where a Health Care Provider administered icatibant to the subject.
Subjects Who Self-administered Icatibant (Naive)	Naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.
Subjects Who Self-administered Icatibant (Non-naive)	Non-naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.

Measured Values

	Naive Subjects Administered Icatibant by Health Care Provider	Subjects Who Self-administered Icatibant (Naive)	Subjects Who Self-administered Icatibant (Non-naive)
Number of Participants Analyzed	22	19	78
Clinical Efficacy of Self-treatment of Acute HAE Attacks With s.c. Injections of Icatibant, Time to Symptom Relief Using VAS Score for a Single Primary Symptom by Patient Cohort [units: Hours] Median (Inter-Quartile Range)	2.0 (1.0 to 4.2)	3.1 (2.0 to 4.0)	2.0 (1.0 to 5.3)

Reported Adverse Events

Time Frame	7 days from the beginning of each phase
Additional Description	[Not specified]

Reporting Groups

	Description
Naive Subjects Administered Icatibant by Health Care Provider	The first HAE attack of naïve subjects enrolled in the study was treated at the study site, where a Health Care Provider administered icatibant to the subject.
Subjects Who Self-administered Icatibant (Naive)	Naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.
Subjects Who Self-administered Icatibant (Non-naive)	Non-naive subjects self-administered the study drug at home or other site convenient to the subject, but not at the investigational site, nor under HCP-supervision.

Serious Adverse Events

	Naive Subjects Administered Icatibant by Health Care Provider	Subjects Who Self-administered Icatibant (Naive)	Subjects Who Self-administered Icatibant (Non-naive)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/22 (0%)	0/19 (0%)	0/78 (0%)

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Naive Subjects Administered Icatibant by Health Care Provider	Subjects Who Self-administered Icatibant (Naive)	Subjects Who Self-administered Icatibant (Non-naive)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	7/22 (31.82%)	6/19 (31.58%)	21/78 (26.92%)
Congenital, familial and genetic disorders			
Hereditary Angioedema [A] †	6/22 (27.27%)	3/19 (15.79%)	19/78 (24.36%)
General disorders			
Edema Peripheral [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Feeling Hot [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Local Swelling [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)

	Naive Subjects Administered Icatibant by Health Care Provider	Subjects Who Self-administered Icatibant (Naive)	Subjects Who Self-administered Icatibant (Non-naive)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Localized edema [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Investigations			
Blood pressure increased [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Nervous system disorders			
Headache [A] †	1/22 (4.55%)	1/19 (5.26%)	2/78 (2.56%)
Respiratory, thoracic and mediastinal disorders			
Laryngeal edema [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Pharyngeal erythema [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)
Skin and subcutaneous tissue disorders			
Skin Lesion [A] †	0/22 (0%)	1/19 (5.26%)	0/78 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

Results Point of Contact:

Name/Official Title: Alan Kimura, MD,PhD
Organization: Shire Human Genetic Therapies, Inc
Phone: 781-482-0738
Email: akimura@shire.com