ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 09/11/2014

Grantor: CDER IND/IDE Number: 68214 Serial Number: 0052

A Study of Icatibant in Patients With Acute Attacks of Hereditary Angioedema (FAST-3)

This study has been completed.

Sponsor:	Shire
Collaborators:	Shire
Information provided by (Responsible Party):	Shire
ClinicalTrials.gov Identifier:	NCT00912093

Purpose

This study is being conducted to evaluate the efficacy and safety of icatibant compared to placebo in patients experiencing acute attacks of hereditary angioedema (HAE).

Condition	Intervention	Phase
Hereditary Angioedema	Drug: Icatibant Drug: Placebo	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Phase III Randomized, Double-Blind,Placebo-Controlled, Multicenter Study of Icatibant for Subcutaneous Injection in Patients With Acute Attacks of Hereditary Angioedema (HAE)

Further study details as provided by Shire:

Primary Outcome Measure:

- Time to Onset of Symptom Relief for an Acute Attack, as Assessed by the Patient [Time Frame: Up to 120 hours post-dose] [Designated as safety issue: No]

Time to onset of symptom relief was calculated from study drug administration to onset of symptom relief, where onset of symptom relief was defined as the earliest of 3 consecutive measurements in which there was a 50% reduction from pretreatment in composite VAS score. Composite VAS score comprised 3 symptoms, including skin swelling, skin pain, and abdominal pain, for cutaneous and abdominal attacks and 5 symptoms, including skin swelling, skin pain, abdominal pain, difficulty swallowing, and voice change, for laryngeal attacks. Subjects who did not achieve symptom relief within the observation period were censored at the last observation time.

Secondary Outcome Measures:

- Time to Onset of Primary Symptom Relief [Time Frame: Up to 120 hours post-dose] [Designated as safety issue: No]
  Time to primary symptom relief was calculated from the time of study drug administration to the onset of primary symptom relief, where onset of primary symptom relief was determined using the subject-assessed VAS score for a single primary symptom (determined by edema location) and defined as the earliest of 3 consecutive non-missing measurements in which a pre-specified reduction from the pretreatment value was met. Subjects who did not achieve primary symptom relief within the observation period were censored at the last observation time.
- Time to Almost Complete Symptom Relief [Time Frame: Up to 120 Hours post treatment] [Designated as safety issue: No]
  Time to almost complete symptom relief was calculated from the time of study drug administration to almost complete symptom relief, where almost complete symptom relief was defined as the earliest of 3 consecutive non-missing measurements in which all VAS scores <10 mm. Subjects who did not achieve almost complete symptom relief within the observation period were censored at the last observation time.
- Time to Subject-Assessed Initial Symptom Improvement [Time Frame: Up to 120 hours post-dose] [Designated as safety issue: No]
  Time to initial symptom improvement was calculated from the time of study drug administration to initial symptom improvement as determined by the subject as the time they felt symptoms were starting to improve. Subjects who did not achieve initial symptom improvement within the observation period were censored at the last observation time.
- Time to Investigator-Assessed Initial Symptom Improvement [Time Frame: Up to 120 hours post-dose] [Designated as safety issue: No]
  Time to initial symptom improvement was calculated from the time of study drug administration to initial symptom improvement as determined by the investigator as the time they felt symptoms were starting to improve. Subjects who did not achieve initial symptom improvement within the observation period were censored at the last observation time.

Enrollment: 98
Study Start Date: June 2009
Primary Completion Date: July 2012
Study Completion Date: July 2012

Arms	Assigned Interventions
Placebo Comparator: Placebo Single subcutaneous injection of matching placebo	Drug: Placebo Single subcutaneous injection of matching placebo
Experimental: Icatibant Single subcutaneous injection of icatibant, 30 mg	Drug: Icatibant Single subcutaneous injection of icatibant, 30 mg Other Names: Firazyr

Detailed Description:

This Phase III study consisted of two parts: A controlled phase and an open label extension (OLE) phase.

The controlled phase describes the double blind part of the study and was intended to evaluate the efficacy and safety of icatibant compared with placebo for the first treated cutaneous and/or abdominal attack.

Patients with moderate to severe abdominal or cutaneous attacks were randomized to receive a single, blinded, subcutaneous injection of icatibant (30 mg) or placebo. After a protocol amendment, patients with mild to moderate laryngeal HAE attacks were also randomized to receive a single, blinded subcutaneous injection of icatibant (30 mg) or placebo in order to obtain blinded, controlled efficacy and safety data for this subset of subjects. Patients experiencing severe laryngeal attacks (post-amendment) or mild to severe laryngeal attacks (pre-amendment) were to receive open-label icatibant.

After treatment of the first attack in the controlled phase, patients were eligible to enter the OLE phase. In the OLE phase, patients who experienced angioedema attacks severe enough to warrant treatment were to be treated with s.c. icatibant as appropriate until the study was discontinued or the product was commercially available.

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. The patient is ≥18 years old at the time of informed consent.
2. The patient has a documented diagnosis of HAE type I or II. The diagnosis will be confirmed either by documented decreased C4 levels and/or immunogenic or functional C1-INH deficiency results (<50% of normal levels) consistent with HAE types I and II or by medical history.
3. The current HAE attack must be in the cutaneous, abdominal and/or laryngeal (inclusive of laryngeal and pharyngeal) areas.
4. Cutaneous or abdominal HAE attacks must be moderate to very severe as determined by investigator global assessment at pre-treatment assessments
5. The patient must report at least 1 VAS score ≥ 30mm
6. The patient commences treatment within 6 hours of the attack becoming at least mild (laryngeal) or moderate (non-laryngeal) in severity, but not more than 12 hours after the onset of the attack.
7. Women of childbearing potential must have a negative urine pregnancy test and must use appropriate methods to prevent pregnancy during their participation in the study.

Exclusion Criteria:

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

1. The patient has a diagnosis of angioedema other than HAE type I or II.
2. The patient has received previous treatment with icatibant.
3. The patient has participated in a clinical trial and has received treatment with another investigational medicinal product within the past 30 days.
4. The patient has received treatment with any pain medication since the onset of the current angioedema attack.
5. The patient has received replacement therapy (fresh frozen plasma [FFP], C1-INH products) less than 5 days (120 hours) from the onset of the current angioedema attack.
6. The patient is receiving treatment with angiotensin converting enzyme (ACE) inhibitors.
7. Evidence of coronary artery disease based on medical history or screening examination in particular unstable angina pectoris or severe coronary heart disease;

8. The patient has a serious concomitant illness or condition that, in the opinion of the Investigator, would be a contraindication for participation in the trial.
9. The patient is pregnant or breastfeeding.

Contacts and Locations

Locations

United States, Alabama
- Primary Care Associates of Alabaster
  - Alabaster, Alabama, United States, 35007
- UAB Lung Health Center
  - Birmingham, Alabama, United States, 35294

United States, Arizona
- Medical Research of AZ A Division of Allergy & Immunology Assoc
  - Scottsdale, Arizona, United States, 85251

United States, Arkansas
- Little Rock Allergy & Asthma Clinic, PA
  - Little Rock, Arkansas, United States, 72205

United States, California
- Allergy and Asthma Insititute of the Valley
  - Granada Hills, California, United States, 91344
- University of California San Diego
  - La Jolla, California, United States, 92093
- UCLA - Clinical Immunology & Allergy
  - Los Angeles, California, United States, 90095
- Standford University
  - Stanford, California, United States, 94305
- Speciality Medical Clinic & Research Center
  - Stanford, California, United States, 27330

United States, Colorado
- Asthma & Allergy Associates, PC
  - Colorado Springs, Colorado, United States, 80907

United States, Florida
- Medical Associates of Brevard
  - Melbourne, Florida, United States, 32935
- University of South Florida Division of Allergy and Immunology
  - Tampa, Florida, United States, 33613

United States, Georgia
- Family Allergy and Asthma Center, PC
  - Atlanta, Georgia, United States, 30342

United States, Illinois
- Rush University Medical Center
  - Chicago, Illinois, United States, 60612
- Rush University Medical Center
  - Chicago, Illinois, United States, 60612

United States, Indiana
Research Institute of Deaconess Clinic
Evansville, Indiana, United States, 47713
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Reno, Nevada, United States, 89503
United States, New Jersey
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Cincinnati, Ohio, United States, 45267
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Valley Clinical Research Center
Bethlehem, Pennsylvania, United States, 18020
Penn State Hershey Medical Center
Hershey, Pennsylvania, United States, 17033
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Adelaide, Australia
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Woden, Australian Capital Territory, Australia
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Russian Federation

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State Enterprise State Scientific Centre
Moscow, Moscow, Russian Federation, 115478

State Healthcare Institution of City of Moscow
Moscow, Moscow, Russian Federation, 115446

Municipal Medical & Preventive Treatment Institution
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Ukraine

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Investigators

Study Director:	Alan Kimura, M.D., PhD	Shire

More Information

Responsible Party:	Shire
Study ID Numbers:	HGT-FIR-054 2009-015606-19 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration Canada: Health Canada Australia: Department of Health and Ageing Therapeutic Goods Administration Hungary: National Institute of Pharmacy Israel: Ministry of Health Romania: National Medicines Agency Russia: Ministry of Health of the Russian Federation South Africa: Medicines Control Council Ukraine: State Pharmacological Center - Ministry of Health

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Study Results

Participant Flow

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant, 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase
Randomized-Icatibant (Blinded Treatment)-Laryngeal	Subjects with mild to moderate laryngeal attacks of HAE randomized to receive a single subcutaneous injection of icatibant, 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Laryngeal	Subjects with mild to moderate laryngeal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase
Open-Label Icatibant-Severe Laryngeal	Subjects with severe (post-amendment) or mild to severe (pre-amendment) laryngeal attacks of HAE treated with subcutaneous injection of icatibant, 30 mg in the controlled phase

The Controlled Phase

	Randomized-Icatibant (Blinded Treatment)-Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Randomized-Icatibant (Blinded Treatment)-Laryngeal	Randomized-Placebo (Blinded Treatment)-Laryngeal	Open-Label Icatibant-Severe Laryngeal
Started	43	45	3	2	5
Completed	43	43	3	2	4
Not Completed	0	2	0	0	1
Death	0	1	0	0	0
Medical Condition	0	1	0	0	0
Lost to Follow-up	0	0	0	0	1

The Open Label Extension (OLE) Phase

	Randomized-Icatibant (Blinded Treatment)-Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Randomized-Icatibant (Blinded Treatment)-Laryngeal	Randomized-Placebo (Blinded Treatment)-Laryngeal	Open-Label Icatibant-Severe Laryngeal
Started	38	35	3	2	4
Completed	38	35	3	2	4
Not Completed	0	0	0	0	0

Baseline Characteristics

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase
Randomized-Icatibant (Blinded Treatment)--Laryngeal	Subjects with mild to moderate laryngeal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Laryngeal	Subjects with mild to moderate laryngeal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

	Description
Open-Label Icatibant-Severe Laryngeal	Subjects with severe (post-amendment) or mild to severe (pre-amendment) laryngeal attacks of HAE treated with subcutaneous injection of icatibant 30 mg in the controlled phase

Baseline Measures

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Randomized-Icatibant (Blinded Treatment)--Laryngeal	Randomized-Placebo (Blinded Treatment)-Laryngeal	Open-Label Icatibant-Severe Laryngeal	Total
Number of Participants	43	45	3	2	5	98
Age, Continuous [units: years] Mean (Standard Deviation)	36.1 (13.69)	36.6 (11.18)	40.3 (6.66)	50.0 (22.63)	41.6 (11.78)	37.0 (12.46)
Gender, Male/Female [units: participants]						
Female	27	29	2	1	2	61
Male	16	16	1	1	3	37
Race/Ethnicity, Customized [units: participants]						
American Indian or Alaska Native	0	0	0	0	0	0
Asian	0	0	0	0	0	0
Black or African American	3	0	0	0	0	3
Native Hawaiian or Other Pacific	0	0	0	0	0	0
White	38	40	3	2	4	87
Other	2	5	0	0	1	8
Region of Enrollment [units: participants]						
United States	26	32	2	2	3	65
Hungary	3	1	0	0	0	4
Canada	1	0	0	0	0	1
Ukraine	0	1	0	0	0	1
Romania	3	1	1	0	0	5

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Randomized-Icatibant (Blinded Treatment)--Laryngeal	Randomized-Placebo (Blinded Treatment)-Laryngeal	Open-Label Icatibant-Severe Laryngeal	Total
Australia	2	3	0	0	0	5
Russian Federation	2	1	0	0	0	3
South Africa	2	1	0	0	1	4
Israel	4	5	0	0	1	10
Weight (kg) [units: participants]						
<= 50 kg	4	2	0	0	0	6
>50-75 kg	16	20	1	2	0	39
>75-100 kg	14	13	1	0	3	31
>100 kg	9	10	1	0	2	22

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Time to Onset of Symptom Relief for an Acute Attack, as Assessed by the Patient
Measure Description	Time to onset of symptom relief was calculated from study drug administration to onset of symptom relief, where onset of symptom relief was defined as the earliest of 3 consecutive measurements in which there was a 50% reduction from pretreatment in composite VAS score. Composite VAS score comprised 3 symptoms, including skin swelling, skin pain, and abdominal pain, for cutaneous and abdominal attacks and 5 symptoms, including skin swelling, skin pain, abdominal pain, difficulty swallowing, and voice change, for laryngeal attacks. Subjects who did not achieve symptom relief within the observation period were censored at the last observation time.
Time Frame	Up to 120 hours post-dose
Safety Issue?	No

Analysis Population Description

Non-laryngeal Intent-to-Treat (nl-ITT) population included all subjects with non-laryngeal attacks of HAE randomized to treatment. Subjects were analyzed according to the randomized treatment regardless of the treatment actually received. This was the primary analysis population for efficacy.

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

Measured Values

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal
Number of Participants Analyzed	43	45
Time to Onset of Symptom Relief for an Acute Attack, as Assessed by the Patient [units: Hours] Median (95% Confidence Interval)	2.0 (1.5 to 3.0)	19.8 (6.1 to 26.3)

Statistical Analysis 1 for Time to Onset of Symptom Relief for an Acute Attack, as Assessed by the Patient

Statistical Analysis Overview	Comparison Groups	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal, Randomized-Placebo (Blinded Treatment)-Non-laryngeal
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Peto-Peto Wilcoxon]
	Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Time to Onset of Primary Symptom Relief
Measure Description	Time to primary symptom relief was calculated from the time of study drug administration to the onset of primary symptom relief, where onset of primary symptom relief was determined using the subject-assessed VAS score for a single primary symptom (determined by edema location) and defined as the earliest of 3 consecutive non-missing measurements in which a pre-specified reduction from the pretreatment value was met. Subjects who did not achieve primary symptom relief within the observation period were censored at the last observation time.

Time Frame	Up to 120 hours post-dose
Safety Issue?	No

Analysis Population Description

Non-laryngeal Intent-to-Treat (nl-ITT) population included all subjects with non-laryngeal attacks of HAE randomized to treatment. Subjects were analyzed according to the randomized treatment regardless of the treatment actually received. This was the primary analysis population for efficacy.

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

Measured Values

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal
Number of Participants Analyzed	43	45
Time to Onset of Primary Symptom Relief [units: Hours] Median (95% Confidence Interval)	1.5 (1.0 to 2.0)	18.5 (3.6 to 23.9)

Statistical Analysis 1 for Time to Onset of Primary Symptom Relief

Statistical Analysis Overview	Comparison Groups	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal, Randomized-Placebo (Blinded Treatment)-Non-laryngeal
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Peto-Peto Wilcoxon]
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Time to Almost Complete Symptom Relief
Measure Description	Time to almost complete symptom relief was calculated from the time of study drug administration to almost complete symptom relief, where almost complete symptom relief was defined as the earliest of 3 consecutive non-missing measurements in which all VAS scores <10 mm. Subjects who did not achieve almost complete symptom relief within the observation period were censored at the last observation time.
Time Frame	Up to 120 Hours post treatment
Safety Issue?	No

Analysis Population Description

Non-laryngeal Intent-to-Treat (nl-ITT) population included all subjects with non-laryngeal attacks of HAE randomized to treatment. Subjects were analyzed according to the randomized treatment regardless of the treatment actually received. This was the primary analysis population for efficacy.

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

Measured Values

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal
Number of Participants Analyzed	43	45
Time to Almost Complete Symptom Relief [units: Hours] Median (95% Confidence Interval)	8.0 (5.0 to 42.5)	36.0 (29.0 to 50.9)

Statistical Analysis 1 for Time to Almost Complete Symptom Relief

Statistical Analysis Overview	Comparison Groups	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal, Randomized-Placebo (Blinded Treatment)-Non-laryngeal
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.012
	Comments	[Not specified]
	Method	Other [Peto Peto Wilcoxon]
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Time to Subject-Assessed Initial Symptom Improvement
Measure Description	Time to initial symptom improvement was calculated from the time of study drug administration to initial symptom improvement as determined by the subject as the time they felt symptoms were starting to improve. Subjects who did not achieve initial symptom improvement within the observation period were censored at the last observation time.
Time Frame	Up to 120 hours post-dose
Safety Issue?	No

Analysis Population Description

Non-laryngeal Intent-to-Treat (nl-ITT) population included all subjects with non-laryngeal attacks of HAE randomized to treatment. Subjects were analyzed according to the randomized treatment regardless of the treatment actually received. This was the primary analysis population for efficacy.

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

Measured Values

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal
Number of Participants Analyzed	43	45
Time to Subject-Assessed Initial Symptom Improvement [units: Hours] Median (95% Confidence Interval)	0.8 (0.5 to 1.0)	3.5 (1.9 to 5.4)

Statistical Analysis 1 for Time to Subject-Assessed Initial Symptom Improvement

Statistical Analysis Overview	Comparison Groups	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal, Randomized-Placebo (Blinded Treatment)-Non-laryngeal
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Peto-Peto Wilcoxon]
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Time to Investigator-Assessed Initial Symptom Improvement
Measure Description	Time to initial symptom improvement was calculated from the time of study drug administration to initial symptom improvement as determined by the investigator as the time they felt symptoms were starting to improve. Subjects who did not achieve initial symptom improvement within the observation period were censored at the last observation time.
Time Frame	Up to 120 hours post-dose
Safety Issue?	No

Analysis Population Description

Non-laryngeal Intent-to-Treat (nl-ITT) population included all subjects with non-laryngeal attacks of HAE randomized to treatment. Subjects were analyzed according to the randomized treatment regardless of the treatment actually received. This was the primary analysis population for efficacy.

Reporting Groups

	Description
Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of icatibant 30 mg in the controlled phase
Randomized-Placebo (Blinded Treatment)-Non-laryngeal	Subjects with moderate to severe cutaneous or abdominal attacks of HAE randomized to receive a single subcutaneous injection of matching placebo in the controlled phase

Measured Values

	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal	Randomized-Placebo (Blinded Treatment)-Non-laryngeal
Number of Participants Analyzed	43	45
Time to Investigator-Assessed Initial Symptom Improvement [units: Hours] Median (95% Confidence Interval)	0.8 (0.6 to 1.3)	3.4 (2.6 to 6.0)

Statistical Analysis 1 for Time to Investigator-Assessed Initial Symptom Improvement

Statistical Analysis Overview	Comparison Groups	Randomized-Icatibant (Blinded Treatment)--Non-laryngeal, Randomized-Placebo (Blinded Treatment)-Non-laryngeal
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Peto-Peto Wilcoxon]
	Comments	[Not specified]

Reported Adverse Events

Time Frame	Treatment emergent adverse events occurring within 16 days of study drug administration are included in the analysis
Additional Description	Subjects were analyzed according to the treatment actual received

Reporting Groups

	Description
Controlled Phase - Icatibant (Randomized)	Subjects who were randomized to treatment and received a single subcutaneous injection of icatibant 30 mg in the controlled phase
Controlled Phase -Placebo (Randomized)	Subjects who were randomized to treatment and received a single subcutaneous injection of matching placebo in the controlled phase

	Description
Controlled Phase - Icatibant (Open Label)	Subjects who were not randomized and received a single subcutaneous injection of icatibant 30 mg in the controlled phase
Open Label Extension - Icatibant (Open Label)	Subjects who treated with icatibant 30 mg in the open label extension phase

Serious Adverse Events

	Controlled Phase - Icatibant (Randomized)		Controlled Phase -Placebo (Randomized)		Controlled Phase - Icatibant (Open Label)		Open Label Extension - Icatibant (Open Label)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	0/46 (0%)		5/46 (10.87%)		0/6 (0%)		7/82 (8.54%)	
Cardiac disorders								
Arrhythmia	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	1/82 (1.22%)	1
Myocardial infarction	0/46 (0%)	0	1/46 (2.17%)	1	0/6 (0%)	0	0/82 (0%)	0
Congenital, familial and genetic disorders								
Hereditary angioedema	0/46 (0%)	0	2/46 (4.35%)	2	0/6 (0%)	0	3/82 (3.66%)	3
General disorders								
Non-Cardiac Chest Pain	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	1/82 (1.22%)	1
Hepatobiliary disorders								
Cholecystitis	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	1/82 (1.22%)	1
Infections and infestations								
Gastroenteritis	0/46 (0%)	0	1/46 (2.17%)	1	0/6 (0%)	0	0/82 (0%)	0
Respiratory, thoracic and mediastinal disorders								

	Controlled Phase - Icatibant (Randomized)		Controlled Phase -Placebo (Randomized)		Controlled Phase - Icatibant (Open Label)		Open Label Extension - Icatibant (Open Label)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Pneumonia	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	1/82 (1.22%)	1
Pulmonary Embolism	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	1/82 (1.22%)	1
Surgical and medical procedures								
Tracheostomy	0/46 (0%)	0	1/46 (2.17%)	1	0/6 (0%)	0	0/82 (0%)	0

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

	Controlled Phase - Icatibant (Randomized)		Controlled Phase -Placebo (Randomized)		Controlled Phase - Icatibant (Open Label)		Open Label Extension - Icatibant (Open Label)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	8/46 (17.39%)		12/46 (26.09%)		0/6 (0%)		23/82 (28.05%)	
Congenital, familial and genetic disorders								
Hereditary angioedema	5/46 (10.87%)	5	9/46 (19.57%)	9	0/6 (0%)	0	11/82 (13.41%)	17
Infections and infestations								
Upper Respiratory Tract Infection	0/46 (0%)	0	0/46 (0%)	0	0/6 (0%)	0	5/82 (6.1%)	7
Nervous system disorders								
Headache	3/46 (6.52%)	4	3/46 (6.52%)	3	0/6 (0%)	0	9/82 (10.98%)	12

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Shire’s agreements with investigators vary. All agreements provide Shire the right to embargo communications regarding trial results prior to public release for a period ≤180 days from the time submitted to Shire for review. Shire does not prohibit publication, but can require the removal of confidential information (excluding trial results) and can request postponement of a single-center publication until after disclosure of the trial’s multi-center publication.

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