Clinical trial results:
A Multicenter, Open-Label, Non-Randomized Study to Assess the Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Administration of Icatibant in Children and Adolescents with Hereditary Angioedema

Summary

EudraCT number	2011-003825-81
Trial protocol	DE HU ES IT AT
Global end of trial date	12 March 2018

Results information

Result version number	v1 (current)
This version publication date	27 September 2018
First version publication date	27 September 2018

Trial information

Trial identification

Sponsor protocol code	HGT-FIR-086

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01386658
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000408-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate the pharmacokinetics (PK), tolerability, and safety of a single subcutaneous (SC) dose of icatibant in children and adolescents with hereditary angioedema (HAE).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	32
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	15
Adolescents (12-17 years)	17
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 27 study centers in the United States, Germany, Israel, Spain, Argentina, Australia, Austria, Canada, Colombia, Hungary, and Italy between 27 January 2012 (first subject first visit) and 12 March 2018 (last subject last visit).

Pre-assignment

Screening details:

A total of 32 subjects were enrolled and received treatment.

Period 1

Period 1 title	Initial Icatibant Exposure
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Prepubertal

Arm description:

Prepubertal subjects received a single subcutaneous (SC) injection of 0.4 milligram per kilogram (mg/kg) icatibant (up to a maximal dose of 30 mg) in the abdominal region.

Arm type	Experimental
Investigational medicinal product name	Icatibant
Investigational medicinal product code	JE049
Other name	Firazyr
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of icatibant in the abdominal region.

Arm title	Pubertal/Postpubertal

Arm description:

Pubertal/postpubertal subjects received a SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.

Arm type	Experimental
Investigational medicinal product name	Icatibant
Investigational medicinal product code	JE049
Other name	Firazyr
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of icatibant in the abdominal region.

Number of subjects in period 1	Prepubertal	Pubertal/Postpubertal
Started	11	21
Completed	11	9
Not completed	0	12
Consent withdrawn by subject	-	9
Lack of adherence and poor compliance	-	3

Period 2

Period 2 title	Icatibant Exposure 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pubertal/Postpubertal: Exposure 2

Arm description:

Subjects received a single SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region by health care practitioner or caregiver/self, after initial exposure to icatibant during acute HAE attacks or in between attacks during Period 1 of the study.

Arm type	Experimental
Investigational medicinal product name	Icatibant
Investigational medicinal product code	JE049
Other name	Firazyr
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of icatibant in the abdominal region.

Number of subjects in period 2	Pubertal/Postpubertal: Exposure 2
Started	9
Completed	9

Period 3

Period 3 title	Icatibant Exposure 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pubertal/Postpubertal: Exposure 3

Arm description:

Subjects received a single SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region by health care practitioner or caregiver/self, after initial 2 exposures to icatibant during acute HAE attacks or in between attacks during Period 1 of the study.

Arm type	Experimental
Investigational medicinal product name	Icatibant
Investigational medicinal product code	JE049
Other name	Firazyr
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of icatibant in the abdominal region.

Number of subjects in period 3	Pubertal/Postpubertal: Exposure 3
Started	9
Completed	9

Baseline characteristics

Reporting groups	
Reporting group title	Prepubertal
Reporting group description:	
Prepubertal subjects received a single subcutaneous (SC) injection of 0.4 milligram per kilogram (mg/kg) icatibant (up to a maximal dose of 30 mg) in the abdominal region.	
Reporting group title	Pubertal/Postpubertal
Reporting group description:	
Pubertal/postpubertal subjects received a SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.	

Reporting group values	Prepubertal	Pubertal/Postpubertal	Total
Number of subjects	11	21	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8.6	14.3	
standard deviation	± 2.97	± 1.66	-
Gender categorical Units: Subjects			
Female	5	8	13
Male	6	13	19
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	11	20	31
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	10	19	29
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Prepubertal
Reporting group description:	
Prepubertal subjects received a single subcutaneous (SC) injection of 0.4 milligram per kilogram (mg/kg) icatibant (up to a maximal dose of 30 mg) in the abdominal region.	
Reporting group title	Pubertal/Postpubertal
Reporting group description:	
Pubertal/postpubertal subjects received a SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.	
Reporting group title	Pubertal/Postpubertal: Exposure 2
Reporting group description:	
Subjects received a single SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region by health care practitioner or caregiver/self, after initial exposure to icatibant during acute HAE attacks or in between attacks during Period 1 of the study.	
Reporting group title	Pubertal/Postpubertal: Exposure 3
Reporting group description:	
Subjects received a single SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region by health care practitioner or caregiver/self, after initial 2 exposures to icatibant during acute HAE attacks or in between attacks during Period 1 of the study.	
Subject analysis set title	Pubertal/postpubertal: with acute attack
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with acute attack received a SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.	
Subject analysis set title	Pubertal/postpubertal: without acute attack
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects without acute attack received a SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.	

Primary: Time to Peak Concentration (Tmax) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Time to Peak Concentration (Tmax) of a Single Subcutaneous (SC) Dose of Icatibant[1][2]
End point description:	
Time to peak concentration (Tmax) of a single SC dose of icatibant was reported. Pharmacokinetic (PK) population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.	
End point type	Primary
End point timeframe:	
Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	11	10	
Units: Hour (h)				
arithmetic mean (standard deviation)				
Hour (h)	0.42 (± 0.13)	0.55 (± 0.19)	0.57 (± 0.17)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Maximum Plasma Concentration (Cmax) of a Single Subcutaneous (SC) Dose of Icatibant[3][4]

End point description:

Maximum plasma concentration (Cmax) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	11	10	
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Nanogram per milliliter (ng/mL)	659 (± 158)	805 (± 125)	761 (± 133)	

Statistical analyses

No statistical analyses for this end point

Primary: Total Plasma Clearance (CL/F) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Total Plasma Clearance (CL/F) of a Single Subcutaneous (SC) Dose of Icatibant[5][6]

End point description:

Total plasma clearance (CL/F) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	11	10	
Units: Milliliters per minute (mL/min)				
arithmetic mean (standard deviation)				
Milliliters per minute (mL/min)	10.8 (± 4.63)	13.1 (± 3.42)	19.3 (± 4.84)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to 4 Hours Post-dose (AUC0-4) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to 4 Hours Post-dose (AUC0-4) of a Single Subcutaneous (SC) Dose of Icatibant[7][8]

End point description:

Area under the plasma concentration-time curve from time zero to 4 hours post-dose (AUC0-4) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	11	10	
Units: Hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Hour*nanogram per milliliter (h*ng/mL)	1241 (± 319)	1448 (± 304)	1335 (± 211)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to 6 Hours Post-dose (AUC0-t) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to 6 Hours Post-dose (AUC0-t) of a Single Subcutaneous (SC) Dose of Icatibant[9][10]

End point description:

Area under the plasma concentration-time curve from time zero to 6 hours post-dose (AUC0-t) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	11	10	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
h*ng/mL	1289 (± 325)	1573 (± 372)	1398 (± 225)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of a Single Subcutaneous (SC) Dose of Icatibant[11][12]

End point description:

Area under the plasma concentration-time curve from time zero to infinity (AUC0-inf) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	11	10	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
h*ng/mL	1243 (± 244)	1710 (± 569)	1416 (± 229)	

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution (Vz/F) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Volume of Distribution (Vz/F) of a Single Subcutaneous (SC) Dose of Icatibant[13][14]

End point description:

Volume of distribution (Vz/F) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	11	10	
Units: Liters (L)				
arithmetic mean (standard deviation)				
Liters (L)	12.5 (± 5.28)	23.5 (± 13.9)	25.4 (± 8.87)	

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-life (t1/2) of a Single Subcutaneous (SC) Dose of Icatibant

End point title	Elimination Half-life (t1/2) of a Single Subcutaneous (SC) Dose of Icatibant[15][16]

End point description:

Elimination half-life (t1/2) of a single SC dose of icatibant was reported. PK population consisted of subjects who were treated with icatibant and had sufficient icatibant plasma concentration-time measurements to derive primary PK parameters. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-dose; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours post-dose on Day 1

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK analysis was performed for prepubertal subjects with an acute attack of HAE and pubertal/postpubertal subjects with or without an acute attack of HAE.

End point values	Prepubertal	Pubertal/postpubertal: with acute attack	Pubertal/postpubertal: without acute attack	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	11	10	
Units: Hour (h)				
arithmetic mean (standard deviation)				
Hour (h)	0.80 (± 0.04)	1.34 (± 0.96)	0.90 (± 0.10)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes in Vital Signs[17]

End point description:

Vital signs included pulse rate, blood pressure, respiration rate, and temperature. The number of subjects who reported clinically significant changes in vital signs were reported. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

Pre-dose up to 97 days post-dose

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Electrocardiograms (ECGs)

End point title	Number of Subjects With Clinically Significant Changes in Electrocardiograms (ECGs)[18]

End point description:

A standard 12-lead ECG was performed after 10 minutes at rest when the subject was seated or supine following treatment. The number of subjects who reported clinically significant changes in ECGs were reported. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

6 - 8 hours post-dose on Day 1

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Clinical Laboratory Evaluations

End point title	Number of Subjects With Clinically Significant Changes in Clinical Laboratory Evaluations[19]

End point description:

Clinical laboratory evaluations included clinical chemistry (including liver function tests), hematology, urinalysis. The number of subjects who reported clinically significant changes in clinical laboratory evaluations were reported. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

Pre-dose up to 97 days post-dose

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Reported Presence of Anti-icatibant Antibodies

End point title	Number of Subjects who Reported Presence of Anti-icatibant Antibodies[20]

End point description:

The number of subjects who reported anti-icatibant antibodies were reported. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

Pre-dose up to 97 days post-dose

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs)[21]

End point description:

An AE was any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in a clinical study, whether or not considered investigational product related. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

From the start of study drug administration up to 97 days post-dose

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	2	11		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Reported Injection Site Reactions (ISR) for Icatibant Exposure Number 1

End point title	Number of Subjects who Reported Injection Site Reactions (ISR) for Icatibant Exposure Number 1[22]

End point description:

The number of subjects with injection site reactions (erythema, swelling, burning sensation, itching/pruritus, warm sensation, cutaneous pain, or other) that occured after initial icatibant administration was reported. Safety population consisted of subjects who were treated with icatibant at

least once during the study.

End point type	Primary

End point timeframe:

1 h post-dose on Day 1 up to 9 days post-dose

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Any Reaction	9	20		
Any Severe Reaction	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Reported Injection Site Reactions (ISR) for Icatibant Exposure Number 2 and 3

End point title	Number of Subjects who Reported Injection Site Reactions (ISR) for Icatibant Exposure Number 2 and 3[23]

End point description:

The number of subjects with injection site reactions (erythema, swelling, burning sensation, itching/pruritus, warm sensation, cutaneous pain, or other) that occurred after subsequent icatibant administration by study-site personnel (health care practitioner [HCP] administration) or by caregiver/self (caregiver administration) was reported. In the below table, ASR refers to any severe reaction and "n" indicates the number of subjects evaluable for this endpoint. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

1 h post-dose up to 9 days post-dose

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
HCP Administration: Any Reaction (n=1,1)	1	1		
HCP Administration: ASR (n=1,1)	0	0		
Caregiver Administration: Any Reaction (n=8,8)	8	7		
Caregiver Administration: ASR (n=8,8)	3	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Reproductive Hormones

End point title	Number of Subjects With Clinically Significant Changes in Reproductive Hormones[24]

End point description:

Reproductive hormone levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone in females, and FSH, LH, and testosterone in males were measured. The number of subjects with clinically significant changes in reproductive hormones was reported. Safety population consisted of subjects who were treated with icatibant at least once during the study.

End point type	Primary

End point timeframe:

Pre-dose up to 97 days post-dose

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: Subjects				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR) for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 1

End point title	Time to Onset of Symptom Relief (TOSR) for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 1

End point description:

TOSR was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there was at least a 20 percent(%) improvement in the average post-treatment symptom score with no worsening of any single component score for the initial icatibant exposure. The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. TOSR for subjects received initial icatibant administration was reported. In the below table, number of subjects analyzed indicates the subjects evaluable for this endpoint. Efficacy population consisted of subjects who were treated with icatibant attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 8.5 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR) for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 2 and 3

End point title	Time to Onset of Symptom Relief (TOSR) for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 2 and 3

End point description:

TOSR was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there was at least a 20% improvement in the composite (or average) post-treatment symptom score with no worsening of any single component score. The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. In the below table, HCP refers to health care practitioner administration and "n" indicates the number of subjects evaluable for this endpoint. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 12 hours post-dose

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Hour (h)				
median (confidence interval 95%)				
HCP Administration (n=1,1)	4.0 (4.0 to 4.0)	1.0 (1.0 to 1.0)		
Caregiver Administration (n=8,7)	1.0 (1.0 to 2.3)	1.1 (1.0 to 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR) for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 1

End point title	Time to Onset of Symptom Relief (TOSR) for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 1

End point description:

TOSR was defined as the earliest time at which the post-treatment score improved by at least one level. Subjects of 4 years age and older self-assessed their HAE-related pain using the FPS-R instrument. FPS-R is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (0=no pain to 10=very much pain). TOSR for subjects who received initial icatibant administration was reported. In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 52 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	0.9 (0.8 to 1.0)	1.0 (0.6 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR) for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 2 and 3

End point title	Time to Onset of Symptom Relief (TOSR) for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 2 and 3

End point description:

TOSR was defined as the earliest time at which the post-treatment score improved by at least one level. Subjects of 4 years age and older self-assessed their HAE-related pain using the FPS-R instrument. FPS-R is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (0=no pain to 10=very much pain). TOSR for subjects who received subsequent icatibant administration by HCP administration or by caregiver/ self-administration was reported. In the below table, HCP refers to health care practitioner administration and "n" indicates the number of subjects with FPS-R data. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 28 hours post-dose

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Hour (h)				
median (confidence interval 95%)				
HCP Administration (n=1,1)	3.0 (3.0 to 3.0)	1.0 (1.0 to 1.0)		
Caregiver Administration (n=7,7)	1.0 (1.0 to 1.2)	1.1 (1.0 to 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR) for Faces, Legs, Activity, Cry, and Consolability (FLACC) Scores

End point title	Time to Onset of Symptom Relief (TOSR) for Faces, Legs, Activity, Cry, and Consolability (FLACC) Scores[25]

End point description:

TOSR was defined as the earliest time at which a 20% improvement was seen in the total post-treatment score. Subjects of 4 years age and young underwent investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC comportmental pain scale. Each of the 5 categories was scored from 0 to 2. Face(F): 0 (no particular expression/smile) - 2 (frequent to constant frown clenched jaw quivering chin); Legs(L): 0 (normal position/relaxed) - 2 (kicking/legs drawn up); Activity(A): 0 (lying quietly, normal position, moves easily) - 2 (arched rigid/jerking); Cry(C): 0 (No cry [awake/asleep]) - 2 (crying steadily/screams/sobs or frequent complaints); Consolability(C): 0 (content/relaxed) - 2 (difficult to console/comfort), resulting in a total score between 0 and 10. In the below table, the number of subjects analyzed signifies subjects with FLACC data. Efficacy population was analyzed.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 8.5 hours post-dose

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects of 4 years age and younger.

End point values	Prepubertal			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	1.0 (1.0 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Symptoms for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 1

End point title	Time to Minimum Symptoms for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 1

End point description:

Time to minimum symptom was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which all symptoms were either mild or absent for the investigator-reported symptom score. The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. Time to minimum symptom for subjects who received initial icatibant administration was reported. In the below table, the number of subjects analyzed signifies those evaluable for this measure. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 8.5 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	1.9 (1.0 to 2.0)	1.0 (1.0 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Symptoms for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 2 and 3

End point title	Time to Minimum Symptoms for Composite Investigator-Assessed Symptom Scores for Icatibant Exposure Number 2 and 3

End point description:

Time to minimum symptom was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which all symptoms were either mild or absent for the investigator-reported symptom score. The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. Time to minimum symptom for subjects who received subsequent icatibant administration by HCP administration or by caregiver/ self-administration was reported. In the below table, HCP refers to health care practitioner administration, "99999" indicates that the data was not calculated due to less number of subjects, "88888" indicates that the data was not calculated due to analysis method limitation and "n" indicates the number of subjects evaluable for this endpoint. Efficacy population was analyzed.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 12 hours post-dose

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Hour (h)				
median (confidence interval 95%)				
HCP Administration (n=0,0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Caregiver Administration (n=7,7)	1.2 (1.0 to 2.0)	2.2 (1.0 to 88888)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Symptom for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 1

End point title	Time to Minimum Symptom for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 1

End point description:

Time to minimum symptoms was defined as the duration of time in hours from study drug administration to the earliest time at which post-treatment score improved to zero (or no pain). Subjects of 4 years of age and older self-assessed their HAE-related pain using the FPS-R instrument. FPS-R is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (0=no pain to 10=very much pain). Time to minimum symptom for subjects who received initial icatibant administration was reported. In the below table, the number of subjects analyzed signifies subjects with FPS-R data. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 52 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	2.4 (1.9 to 5.3)	3.8 (1.0 to 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Symptom for Faces Pain Scale-Revised (FPS-R) Scores for Icatibant Exposure Number 2 and 3

End point title	Time to Minimum Symptom for Faces Pain Scale-Revised (FPS-

	R) Scores for Icatibant Exposure Number 2 and 3

End point description:

Time to minimum symptoms was defined as the duration of time in hours from study drug administration to the earliest time at which post-treatment score improved to zero (or no pain). Subjects of 4 years of age and older self-assessed their HAE-related pain using the FPS-R instrument. FPS-R is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (0=no pain to 10=very much pain). Time to minimum symptom for subjects who received subsequent icatibant administration by HCP administration or by caregiver/ self-administration was reported. In the below table, HCP refers to health care practitioner administration and "n" indicates the number of subjects with FPS-R data. Efficacy population was analyzed.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 28 hours post-dose

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Hour (h)				
median (confidence interval 95%)				
HCP Administration (n=1,1)	3.0 (3.0 to 3.0)	5.8 (5.8 to 5.8)		
Caregiver Administration (n=7,7)	2.1 (1.0 to 4.0)	24.0 (3.8 to 24.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Symptom for Faces, Legs, Activity, Cry, and Consolability (FLACC) Scores

End point title	Time to Minimum Symptom for Faces, Legs, Activity, Cry, and Consolability (FLACC) Scores[26]

End point description:

Time to minimum symptoms was defined as the duration of time in hours from study drug administration to the earliest time at which the total post-treatment score improved to zero. Subjects of 4 years age and younger underwent investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC comportmental pain scale. Each of the 5 categories was scored from 0 to 2. (F) Face: 0 (no particular expression/smile) - 2 (frequent to constant frown clenched jaw quivering chin); (L) Legs: 0 (normal position/relaxed) - 2 (kicking/legs drawn up); (A) Activity: 0 (lying quietly, normal position, moves easily) - 2 (arched rigid/jerking); (C) Cry: 0 (No cry [awake/asleep]) - 2 (crying steadily/screams/sobs or frequent complaints); (C) Consolability: 0 (content/relaxed) - 2 (difficult to console/comfort), resulting in a total score between 0 and 10. In the below table, the number of subjects analyzed signifies subjects with FLACC data. Efficacy population was analyzed.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 8.5 hours post-dose

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects of 4 years age and younger.

End point values	Prepubertal			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	1.0 (1.0 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Use of Rescue Medication for the Treatment of Symptoms of the HAE Attack Following Study Drug Administration

End point title	Time to Use of Rescue Medication for the Treatment of Symptoms of the HAE Attack Following Study Drug Administration

End point description:

Rescue medication was any medication used after the administration of icatibant which, in the opinion of the investigator, was immediately necessary to alleviate acute symptoms which are judged by the investigator as resultant from the current HAE attack. Time to first use of rescue medication prior to the onset of symptom relief was calculated from the time of study drug administration to the first use of rescue medication prior to the onset of symptom relief. This analysis was not performed since as per protocol, "This analysis will only be performed if there are at least 5 subjects for a given attack who used rescue medication prior to attaining symptom relief". In the below table, the number of subjects analyzed signifies subjects who were evaluable for this measure. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From the start of study drug administration up to 52 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[27]	0[28]		
Units: Hour (h)				
median (confidence interval 95%)				
Hour (h)	(to)	(to)		

Notes:

[27] - This analysis was not performed.

[28] - This analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With Icatibant Exposure Number 1

End point title	Number of Subjects With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With Icatibant Exposure Number 1

End point description:

The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none (absence of symptoms), 1=mild (no to mild interference with daily activities), 2=moderate (moderate interference with daily activities), 3=severe (severe interference with daily activities) and 4=very severe (very severe interference with daily activities). The number of subjects with a worsened severity of HAE symptoms at 4 hours post-dose from 2 hours post-dose were reported. In the below table, "n" indicates the number of subjects evaluable for this endpoint. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From 2 hours post-dose to 4 hours post-dose

End point values	Prepubertal	Pubertal/Postpubertal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Subjects				
Abdominal Tenderness	0	1		
Nausea	0	0		
Vomiting	0	0		
Diarrhea	0	0		
Skin Pain	0	0		
Erythema	0	0		
Skin Irritation	0	0		
Skin Swelling	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With Icatibant Exposure Number 2 and 3

End point title	Number of Subjects With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With Icatibant Exposure Number 2 and 3

End point description:

The investigator used a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale: 0=none (absence of symptoms), 1=mild (no to mild interference with daily activities), 2=moderate (moderate interference with daily activities), 3=severe (severe interference with daily activities) and 4=very severe (very severe interference with daily activities). The number of subjects with a worsened severity of HAE symptoms at 4 hours post-dose from 2 hours post-dose were reported. In the below table, HCPA refers to health care practitioner administration, CA refers to caregiver/ self-administration and "n" indicates the number of subjects evaluable for this endpoint. Efficacy population consisted of subjects who were treated with icatibant for their first and any additional attacks during the study.

End point type	Secondary

End point timeframe:

From 2 hours post-dose to 4 hours post-dose

End point values	Pubertal/Postpubertal: Exposure 2	Pubertal/Postpubertal: Exposure 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
HCPA: Abdominal Tenderness (n=1,1)	0	0		
CA: Abdominal Tenderness (n=8,8)	0	1		
HCPA: Nausea (n=1,1)	0	0		
CA: Nausea (n=8,8)	0	0		
HCPA: Vomiting (n=1,1)	0	0		
CA: Vomiting (n=8,8)	0	0		
HCPA: Diarrhea (n=1,1)	0	0		
CA: Diarrhea (n=8,8)	0	1		
HCPA: Skin Pain (n=1,1)	0	0		
CA: Skin Pain (n=8,8)	0	0		
HCPA: Erythema (n=1,1)	0	0		
CA: Erythema (n=8,8)	0	0		
HCPA: Skin Irritation (n=1,1)	0	0		
CA: Skin Irritation (n=8,8)	0	0		
HCPA: Skin Swelling (n=1,1)	0	0		
CA: Skin Swelling (n=8,8)	0	0		
HCPA: Dysphagia (n=1,1)	0	0		
CA: Dysphagia (n=8,8)	0	0		
HCPA: Voice Change (n=1,1)	0	0		
CA: Voice Change (n=8,8)	0	0		
HCPA: Breathing Difficulties (n=1,1)	0	0		
CA: Breathing Difficulties (n=8,8)	0	0		
HCPA: Stridor (n=1,1)	0	0		
CA: Stridor (n=8,8)	0	0		
HCPA: Asphyxia (n=1,1)	0	0		
CA: Asphyxia (n=8,8)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration up to 187 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Prepubertal
Reporting group description:	
Prepubertal subjects received a single SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region.	
Reporting group title	Pubertal/Post-pubertal
Reporting group description:	
Pubertal/postpubertal subjects received an SC injection of 0.4 mg/kg icatibant (up to a maximal dose of 30 mg) in the abdominal region; and subjects after initial exposure to icatibant during acute HAE attacks or in between attacks during Period 1 of the study, who subsequently experienced an acute hereditary angioedema (HAE) attack continued to receive treatment with icatibant as a single SC administration per attack for a total of 3 eligible icatibant exposures.	

Serious adverse events	Prepubertal	Pubertal/Post-pubertal	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Prepubertal	Pubertal/Post-pubertal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	8 / 21 (38.10%)	
Investigations			
Nitrite urine present			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Epiphyseal fracture			

subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	5	
Conjunctivitis allergic			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	9	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	4	
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2011	- Safety assessments were amended to include ECG evaluations. - An investigator assessment utilizing a comportmental pain scale (FLACC) was added for the evaluation of abdominal symptoms of acute HAE in children below 4 years of age.
06 March 2012	- Determination of Tanner stage was eliminated in favor of simply stratifying subjects by pubertal status. - Clarifications were made to inclusion criterion pertaining to the definition of C1-INH deficiency. - Clarification to exclusion criterion was made to ensure that the text clearly prohibits subjects from participating in another concurrent interventional clinical study and to exclude subjects with a physical condition that interfered with pubertal status determination.
19 June 2013	- The number of adolescent subjects participating in the study remained at 20; however, 10 subjects were to be treated with icatibant during an HAE attack while the other 10 subjects were to be treated without an attack. - The number of prepubertal subjects was reduced from 16 to 10. - Adolescent subjects, including both those treated during an attack or not, could be offered further open-label treatment with icatibant for any subsequent HAE attacks that occurred at least 7 days after prior treatment.
18 March 2016	- A parent/legal guardian/caregiver was allowed to administer or the subject (under the supervision of a parent/legal guardian/caregiver) was allowed to self-administer the investigational product after having received appropriate training.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported