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

Summary

EudraCT number	2014-001213-12
Trial protocol	GB
Global end of trial date	22 August 2015

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	HGT-FIR-096

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Study Physician, Shire, +1 1 866-842-5335,
Scientific contact	Study Physician, Shire, +1 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to compare the efficacy of icatibant with placebo in the treatment of angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema based on the time to meeting discharge criteria (TMDC) endpoint.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) 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	02 December 2013
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: 105
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Israel: 1
Worldwide total number of subjects	121
EEA total number of subjects	5

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	70

From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 59 sites in the United States, United Kingdom, Israel and Canada.

Pre-assignment

Screening details:

Overall 121 subjects were randomized, of which 118 received the study medication, and 117 completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Icatibant 30 mg

Arm description:

Subjects received a single dose of icatibant 30 milligram (mg) subcutaneous (SC) injection within 12 hours after the onset of the angiotensin-converting enzyme inhibitor (ACE-I) induced angioedema attack.

Arm type	Experimental
Investigational medicinal product name	Icatibant
Investigational medicinal product code	
Other name	Firazyr
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of icatibant 30 mg SC injection within 12 hours after the onset of the ACE-I induced angioedema attack.

Arm title	Placebo

Arm description:

Subjects received a single dose of placebo matched to icatibant SC injection within 12 hours after the onset of the ACE-I induced angioedema attack.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of placebo matched to icatibant 30 mg SC injection within 12 hours after the onset of the ACE-I induced angioedema attack.

Number of subjects in period 1	Icatibant 30 mg	Placebo
Started	61	60
Completed	60	57
Not completed	1	3
Consent withdrawn by subject	1	-
Physician decision	-	1
Unspecified	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Icatibant 30 mg
Reporting group description:	
Subjects received a single dose of icatibant 30 milligram (mg) subcutaneous (SC) injection within 12 hours after the onset of the angiotensin-converting enzyme inhibitor (ACE-I) induced angioedema attack.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of placebo matched to icatibant SC injection within 12 hours after the onset of the ACE-I induced angioedema attack.	

Reporting group values	Icatibant 30 mg	Placebo	Total
Number of subjects	61	60	121
Age categorical			
Units: Subjects			

Age Continuous			
Age was calculated as the difference between date of birth and date of informed consent, rounded to 1 decimal place.			
Units: years			
arithmetic mean	60.9	61.8	
standard deviation	± 12.1	± 13.4	-
Gender, Male/Female			
Units: subjects			
Female	27	35	62
Male	34	25	59

End points

End points reporting groups

Reporting group title	Icatibant 30 mg
Reporting group description:	
Subjects received a single dose of icatibant 30 milligram (mg) subcutaneous (SC) injection within 12 hours after the onset of the angiotensin-converting enzyme inhibitor (ACE-I) induced angioedema attack.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of placebo matched to icatibant SC injection within 12 hours after the onset of the ACE-I induced angioedema attack.	
Subject analysis set title	Metabolite M1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received a single dose of icatibant 30 mg sc injection within 12 hours after the onset of the ACE-I induced angioedema attack and assessed for metabolite M1.	
Subject analysis set title	Metabolite M2
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received a single dose of icatibant 30 mg sc injection within 12 hours after the onset of the ACE-I induced angioedema attack and assessed for metabolite M2.	

Primary: Time to Meeting Discharge Criteria (TMDC)

End point title	Time to Meeting Discharge Criteria (TMDC)
End point description:	
TMDC was based on the investigator-assessed angioedema-associated upper airway symptom assessments. It was calculated from the time of study drug administration to the earliest time point at which the symptoms of difficulty breathing and difficulty swallowing were absent and the symptoms of voice change and tongue swelling were mild or absent and all subsequent assessments continued to satisfy these conditions. These symptoms were evaluated by the investigator using a 5-point grading scale (0=absent, 1=mild, 2=moderate, 3=severe, and 4=very severe). TMDC was analysed using Kaplan-Meier estimates. Intent-to-treat (ITT) population included all randomized subjects.	
End point type	Primary
End point timeframe:	
Day 0 up to Day 5	

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: days				
median (inter-quartile range (Q1-Q3))	4.03 (2.03 to 6)	4 (1.03 to 6)		

Statistical analyses

Statistical analysis title	TMDC

Statistical analysis description:

A total of 121 subjects were analysed, however 3 subjects did not receive the study medication and were censored at time 0.

Comparison groups	Icatibant 30 mg v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633 [1]
Method	Adjusted Peto-Prentice

Notes:

[1] - Test was performed using a weighted log-rank test called the Peto-Prentice test with a global 2-sided significance level of 5 percent (%) after adjusting for stratification factors (race, and severity) in the ITT population.

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAE) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAE) and Treatment-emergent Serious Adverse Events (TESAEs)[2]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs were defined as adverse events/serious adverse events that started or worsened after the study drug treatment. Safety population included all subjects who received the study drug.

End point type	Primary

End point timeframe:

From start of study drug administration (Day 0) up to follow-up (Day 5)

Notes:

[2] - 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 planned to report and inferential statistics were not planned.

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)				
Participants with TEAEs	27	21		
Participants with TESAEs	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Injection Site Reaction

End point title	Number of Subjects with Treatment Emergent Injection Site Reaction[3]

End point description:

Injection site reaction included erythema, swelling, cutaneous pain, burning sensation, itching and warm sensation. Safety population included all subjects who received the study drug.

End point type	Primary

End point timeframe:

Day 0 to Day 5

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 planned to report and inferential statistics were not planned.

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)				
Erythema	31	13		
Swelling	17	13		
Cutaneous pain	10	7		
Burning sensation	15	7		
Itching	13	6		
Warm sensation	16	8		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Clinically Significant Changes in Laboratory Evaluation, Vital Signs, Electrocardiogram (ECG) and Physical Examination

End point title	Number of Subjects with Clinically Significant Changes in Laboratory Evaluation, Vital Signs, Electrocardiogram (ECG) and Physical Examination[4]

End point description:

Safety population included all subjects who received the study drug.

End point type	Primary

End point timeframe:

Day 0 to Day 5

Notes:

[4] - 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 planned to report and inferential statistics were not planned.

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief (TOSR)

End point title	Time to Onset of Symptom Relief (TOSR)

End point description:

TOSR was calculated for the individual symptoms with pre-treatment scores of 2 (moderate) or more improved by at least 1 severity grade and the individual symptoms with pretreatment scores of 0 or 1 (absent or mild) were scored again at 0 or 1 and all the subsequent assessments continued to satisfy this condition. Time-to-event data were summarized using Kaplan-Meier estimates. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: days				
median (inter-quartile range (Q1-Q3))	2 (0.58 to 3.08)	1.55 (0.5 to 3.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experienced Airway Intervention due to ACE-I-induced Angioedema

End point title	Number of Subjects Experienced Airway Intervention due to ACE-I-induced Angioedema

End point description:

Airway Intervention included intubation, tracheotomy, cricothyrotomy. Modified Intent to treat (mITT) population included all randomized participants who received the study drug.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Admitted to Hospital or Intensive Care Unit (ICU)

End point title	Number of Subjects Admitted to Hospital or Intensive Care Unit (ICU)

End point description:

Number of subjects with and without an occurrence of admission to the hospital (inpatient) or ICU post-treatment due to the ACE-I-induced angioedema attack were described. mITT population included all randomized subjects who received the study drug.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)	22	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experienced ACE-I-induced Angioedema Attack Following Study Drug Administration

End point title	Number of Subjects Experienced ACE-I-induced Angioedema Attack Following Study Drug Administration

End point description:

Number of subjects with the use of conventional medications (corticosteroids, antihistamines, epinephrine) for the treatment of symptoms of the ACE-I- induced angioedema attack following study drug administration were presented. mITT population included all randomized subjects who received the study drug.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: subjects				
number (not applicable)	35	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Time to Meeting Discharge Criteria (TMDC) at specified time points

End point title	Percentage of Subjects With Time to Meeting Discharge Criteria (TMDC) at specified time points

End point description:

mITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

4, 6, and 8 hours post treatment

End point values	Icatibant 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: percentage of subjects				
number (not applicable)				
At 4 hours post treatment	55	60.3		
At 6 hours post treatment	78.3	75.9		
At 8 hours post treatment	91.7	91.4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Serum Concentration (Cmax) of Icatibant and its Metabolites (M1 and M2)

End point title	Maximum Observed Serum Concentration (Cmax) of Icatibant and its Metabolites (M1 and M2)[5]

End point description:

Cmax is the peak plasma concentration of a drug after administration. Pharmacokinetic (PK) analysis included all subjects in the safety population who received study drug and provided evaluable plasma drug concentrations.

End point type	Other pre-specified

End point timeframe:

0.75 and 2 hours post-dose

Notes:

[5] - 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: Descriptive statistics were planned to report and inferential statistics were not planned.

End point values	Icatibant 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Icatibant: 0.75 hours	613 (± 198)			
Icatibant: 2 hours	484 (± 194)			
Metabolite M1: 0.75 hours	98.7 (± 52.6)			
Metabolite M1: 2 hours	182 (± 82.1)			
Metabolite M2: 0.75 hours	116 (± 56.7)			
Metabolite M2: 2 hours	223 (± 94.2)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under the Plasma Concentration Versus Time Curve (AUC[0-24]) of Icatibant and its Metabolites (M1 and M2)

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC[0-24]) of Icatibant and its Metabolites (M1 and M2)[6]

End point description:

Area under the plasma concentration-time curve from time zero to 24 hours post-dose (AUC[0-24]). PK analysis included all subjects in the safety population who received study drug and provided evaluable plasma drug concentrations.

End point type	Other pre-specified

End point timeframe:

0.75 and 2 hours post-dose

Notes:

[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: Descriptive statistics were planned to report and inferential statistics were not planned.

End point values	Icatibant 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hours*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Icatibant	2530 (± 786)			
Metabolite M1	2890 (± 813)			
Metabolite M2	3180 (± 931)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to Day 5

Adverse event reporting additional description:

Injection site reactions were reported separately from general reports of adverse events as they were considered as adverse events of special interest.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received a single dose of placebo matched to icatibant SC injection within 12 hours after the onset of the ACEI induced angioedema attack.

Reporting group title	Icatibant 30 mg

Reporting group description:

Subjects received a single dose of icatibant 30 mg SC injection within 12 hours after the onset of the ACE-I-induced angioedema attack.

Serious adverse events	Placebo	Icatibant 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 58 (1.72%)	2 / 60 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			

subjects affected / exposed	1 / 58 (1.72%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Icatibant 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 58 (18.97%)	14 / 60 (23.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 58 (6.90%)	7 / 60 (11.67%)	
occurrences (all)	4	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 58 (5.17%)	0 / 60 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	2 / 58 (3.45%)	3 / 60 (5.00%)	
occurrences (all)	2	4	
Dyspnoea			
subjects affected / exposed	3 / 58 (5.17%)	1 / 60 (1.67%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 58 (3.45%)	7 / 60 (11.67%)	
occurrences (all)	4	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	-Added a new exclusion criterion. -Text were made to clarify an existing exclusion criterion and several operational aspects of the study and to describe the secondary packaging of the study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported