Clinical trial results:
Open-Label, Single-Dose Study to Evaluate the Response and Pharmacokinetics/Pharmacodynamics of Different Doses of CINRYZE® [C1 Inhibitor (Human)] For Treatment of Acute Angioedema Attacks in Children Less Than 12 Years of Age With Hereditary Angioedema

Summary

EudraCT number	2011-000369-11
Trial protocol	HU DE
Global end of trial date	15 July 2013

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	25 April 2015

Trial information

Trial identification

Sponsor protocol code	0624-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01095510
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard Wayne,, Pennsylvania, United States, 19087
Public contact	Daniella Tierens, ViroPharma SPRL, +32 2791 76 29,
Scientific contact	Daniella Tierens, ViroPharma SPRL, +32 2791 76 29,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000568-PIP01-09
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	15 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study were to evaluate
(1) The dose response.
(2) The Pharmacokinetics (PK) /Pharmacodynamics (PD) of intravenous (IV) administration of CINRYZE (C1 esterase inhibitor [human]) for the treatment of acute angioedema attacks in children above and below 25 kilogram (kg) and less than 12 years of age with Hereditary angioedema (HAE) and
(3) To determine the safety and tolerability following IV administration of CINRYZE in this study population.

Protection of trial subjects:

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

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)	9
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were not enrolled in the lower body weight category (10-25 kg) 1000 Units (U) dose group despite substantial recruitment efforts.

Pre-assignment

Screening details:

Of 12 subjects screened, 9 subjects were enrolled and treated. The reason for 3 subjects were screen failures in 3 subjects was that they did not meet the inclusion criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	500 U CINRYZE (10-25 kg Body Weight)

Arm description:

Single IV dose of 500 Unit (U) CINRYZE.

Arm type	Experimental
Investigational medicinal product name	CINRYZE® 500 U
Investigational medicinal product code	VP 20624
Other name	C1 esterase inhibitor (human)
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV dose of 500 U CINRYZE.

Arm title	1000 U CINRYZE (>25 kg Body Weight)

Arm description:

Single IV dose of 1000 U CINRYZE.

Arm type	Experimental
Investigational medicinal product name	CINRYZE®1000 U
Investigational medicinal product code	VP 20624
Other name	C1 esterase inhibitor (human)
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV dose of 1000 U CINRYZE.

Arm title	1500 U CINRYZE (>25 kg Body Weight)

Arm description:

Single IV dose of 1500 U CINRYZE.

Arm type	Experimental
Investigational medicinal product name	CINRYZE® 1500 U
Investigational medicinal product code	VP 20624
Other name	C1 esterase inhibitor (human)
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Single IV dose of 1500 U CINRYZE.

Number of subjects in period 1	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)
Started	3	3	3
Completed	3	3	3

Baseline characteristics

Reporting groups	
Reporting group title	500 U CINRYZE (10-25 kg Body Weight)
Reporting group description:	
Single IV dose of 500 Unit (U) CINRYZE.	
Reporting group title	1000 U CINRYZE (>25 kg Body Weight)
Reporting group description:	
Single IV dose of 1000 U CINRYZE.	
Reporting group title	1500 U CINRYZE (>25 kg Body Weight)
Reporting group description:	
Single IV dose of 1500 U CINRYZE.	

Reporting group values	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)
Number of subjects	3	3	3
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	7	9	10
full range (min-max)	6 to 9	7 to 9	8 to 11
Gender categorical			
Units: Subjects			
Female	3	3	2
Male	0	0	1

Reporting group values	Total		
Number of subjects	9		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	8		
Male	1		

End points

End points reporting groups

Reporting group title	500 U CINRYZE (10-25 kg Body Weight)
Reporting group description:	
Single IV dose of 500 Unit (U) CINRYZE.	
Reporting group title	1000 U CINRYZE (>25 kg Body Weight)
Reporting group description:	
Single IV dose of 1000 U CINRYZE.	
Reporting group title	1500 U CINRYZE (>25 kg Body Weight)
Reporting group description:	
Single IV dose of 1500 U CINRYZE.	

Primary: Presence of Unequivocal Beginning of Relief of the Defining Attack Symptom

End point title	Presence of Unequivocal Beginning of Relief of the Defining Attack Symptom[1]
End point description:	
Intent-to-treat efficacy (ITT-E) population included all subjects with baseline and at least one post-infusion investigator assessment of the hereditary angioedema (HAE) attack.	
End point type	Primary
End point timeframe:	
Within 4 hours following treatment	

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: Only descriptive statistics were done, no inferential statistical analyses were performed.

End point values	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: subjects				
Yes	3	3	3	
No	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Unequivocal Beginning of Relief of the Defining Attack Symptom

End point title	Time to Unequivocal Beginning of Relief of the Defining Attack Symptom
End point description:	
ITT-E population.	
End point type	Secondary

End point timeframe:
Within 4 hours following treatment

End point values	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: hours				
median (full range (min-max))	1.25 (0.25 to 1.75)	0.25 (0.25 to 0.5)	0.5 (0.25 to 2.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Resolution of the Attack

End point title	Time to Complete Resolution of the Attack
End point description: ITT-E population.	
End point type	Secondary
End point timeframe: Within 1 week following treatment	

End point values	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: hours				
median (full range (min-max))	13.58 (11.48 to 37.35)	10 (1.57 to 22.33)	29.07 (1.58 to 102.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in C1 Inhibitor (C1 INH) Antigen and Functional C1 INH Concentrations

End point title	Change in C1 Inhibitor (C1 INH) Antigen and Functional C1 INH Concentrations

End point description:

No subject agreed to the additional but optional blood sampling necessary to obtain a PK profile for antigenic and functional C1 INH levels (additional blood samples collected through 8 hours post-infusion on Day 1, and on Days 3, 5, and 8). Hence this endpoint was then planned not to be analysed.

End point type	Secondary

End point timeframe:

Pre-dose, 2, 4, 8 hours post dose on Day 1; Day 2, 3, 5, 8

End point values	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Not applicable				

Notes:

[2] - Data was not reported due to change in planned analysis.

[3] - Data was not reported due to change in planned analysis.

[4] - Data was not reported due to change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected through 1 week following the dose of study drug.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	500 U CINRYZE (10-25 kg Body Weight)
Reporting group description: Single IV dose of 500 U CINRYZE	
Reporting group title	1000 U CINRYZE (>25 kg Body Weight)
Reporting group description: Single IV dose of 1000 U CINRYZE	
Reporting group title	1500 U CINRYZE (>25 kg Body Weight)
Reporting group description: Single IV dose of 1500 U CINRYZE	

Serious adverse events	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	500 U CINRYZE (10-25 kg Body Weight)	1000 U CINRYZE (>25 kg Body Weight)	1500 U CINRYZE (>25 kg Body Weight)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2010	•Exclusion criterion was added to exclude pregnant or breastfeeding females •This amendment addressed a comment from an Independent Reviewing Authority (IRA), which requested that the protocol explicitly exclude pregnant females from study participation
20 December 2010	•The time from onset of symptoms of an acute HAE attack to initiation of study drug treatment was increased from 4 hours to 8 hours •Information on the reconstitution of CINRYZE was updated to include the use of Mix2Vial transfer system •Throughout the protocol, the trademark symbol "™" was replaced with the registration symbol "®"
29 June 2011	•Monitoring for potential thrombotic events (Venous thromboembolism (VTE), both Deep vein thrombosis (DVT) and Pulmonary embolism (PE)) •Added urinalysis with microscopy (if subject able to provide specimen; Groups 1-4) on Day 1 (pre-dose) and Day 2, and Complete blood count (CBC) with White blood cell (count) (WBC) count differential, platelet count (Groups 3 and 4, only) •Revised total blood volume collected to approximately 26 milliliter (mL) (from 22 mL) for Groups 1 and 2 •Specified that 41 mL of blood collected for subjects with minimum PK assessments, and 77 mL (from 51 mL) for subjects with all additional PK assessments in Groups 3 and 4 •Inclusion criteria: removed history of C1 INH gene mutation •Exclusion criteria: -timeframe of within 7 days prior to dosing for any prior HAE attack and specified "for the treatment or prevention of an HAE attack" with regard to receipt of any C1 INH product within 7 days prior to dosing -added suspect alternate explanation for symptoms other than acute HAE attack, and history of narcotic-seeking behavior and/or drug/alcohol abuse •Added information on thrombogenicity from preclinical data with Cetor and CINRYZE, and Thrombotic/thromboembolic events (T/TE) events from previous studies •Stopping and restarting rules were added for T/TE events and anaphylactic reaction •Laryngeal attack definition was expanded as pharyngeal or oral swelling that resulted in airway compromise •Vital signs to be measured immediately post completion of the infusion •Added dietary and electrolyte supplements as prior and concomitant medications •To report all SAEs occurring up to 30 days after the last dose to the Sponsor and IRA and SAEs with an onset greater than 30 days after last dose if considered related to study drug •Serum BUN and creatinine measurements were added to Days 3 and 5 if the subjects had the optional PK visit
13 December 2012	•Inclusion Criteria: The requirement for subjects to have a history of swelling of the face, extremities, gastrointestinal tract, genitourinary tract, or larynx was removed. •Ethical Conduct of the Study, was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Change in C1 INH antigen and functional C1 INH concentrations endpoint was not analysed as no subjects agreed to additional and optional blood sampling.

Notes: