



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) | EMA-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 | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 March 2010 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•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:<ul style="list-style-type: none">-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 | <ul style="list-style-type: none">•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: