# Clinical trial results:
# A Phase 2, Randomized, Double-Blind, Multicenter, Dose-Ranging, Crossover Study to Evaluate the Safety and Efficacy of Subcutaneous Administration of CINRYZE® (C1 Esterase Inhibitor [Human]) With Recombinant Human Hyaluronidase (rHuPH20) for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema

## Summary

| | |
|---|---|
| EudraCT number | 2012-000083-24 |
| Trial protocol | HU ES DE SE |
| Global end of trial date | 13 September 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 September 2018 |
| First version publication date | 14 June 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0624-206 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01756157 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Shire Development LLC |
| Sponsor organisation address | 735 Chesterbrook Boulevard Wayne, Pennsylvania, United States, 19087 |
| Public contact | Danielle Tierens, Shire, +32 27917629, |
| Scientific contact | Danielle Tierens, Shire, +32 27917629, |

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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 13 September 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 September 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

1. To evaluate the efficacy of 1000 units (U) and 2000 U doses of CINRYZE (C1 Esterase Inhibitor [Human]) With Recombinant Human Hyaluronidase (rHuPH20) administered by subcutaneous (SC) injection to prevent angiodema attacks.
2. To assess the safety and tolerability of CINRYZE with rHuPH20 administered by SC injection.

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). Prior to the initiation of any study procedures, the investigators obtained written informed consent from each subject or the assent of the child or minor and written informed consent (permission) from the parent/legal guardian.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 04 February 2013 |
| 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 | Sweden: 2 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | United States: 36 |
| Worldwide total number of subjects | 47 |
| EEA total number of subjects | 11 |

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) | 1 |
| Adults (18-64 years) | 45 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 24 sites (United States=20, Europe=4) between 04 February 2013 (first subject dosed) and 13 September 2013 (last subject contact). Of 52 screened subjects, 47 were randomized and treated. The reasons for screen failure were violation of eligibility criteria by 4 subjects and consent withdrawal by 1 subject.

### Pre-assignment

Screening details:

Due to emergence of, and unexpected incidence and titer of, non-neutralizing anti-rHuPH20 antibodies in some subjects after administration of CINRYZE+rHuPH20, sponsor decided to stop dosing subjects with rHuPH20 and thus close the study. However, the study was completed with collection of safety data as outlined in the protocol.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (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** | Treatment sequence A/B |

Arm description:

Subjects received Treatment A in Period 1 and Treatment B in Period 2, as a single 20 milliliter (mL) SC injection per dose.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | rHuPH20 |
| Investigational medicinal product code | |
| Other name | Recombinant human hyaluronidase |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received Treatment A in Period 1 and Treatment B in Period 2, as a single 20 mL SC injection per dose.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.

| | |
|---|---|
| Investigational medicinal product name | CINRYZE |
| Investigational medicinal product code | |
| Other name | C1 esterase inhibitor (human) |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received Treatment A in Period 1 and Treatment B in Period 2, as a single 20 mL SC injection per dose.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.

| | |
|---|---|
| **Arm title** | Treatment sequence B/A |

Arm description:

Subjects received Treatment B in Period 1 and Treatment A in Period 2, as a single 20 mL SC injection per dose.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CINRYZE |
| Investigational medicinal product code | |
| Other name | C1 esterase inhibitor (human) |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received Treatment B in Period 1 and Treatment A in Period 2, as a single 20 mL SC injection per dose.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.

| | |
|---|---|
| Investigational medicinal product name | rHuPH20 |
| Investigational medicinal product code | |
| Other name | Recombinant human hyaluronidase |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received Treatment B in Period 1 and Treatment A in Period 2, as a single 20 mL SC injection per dose.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.

| **Number of subjects in period 1** | Treatment sequence A/B | Treatment sequence B/A |
|---|---|---|
| Started | 23 | 24 |
| Completed | 22 | 22 |
| Not completed | 1 | 2 |
| Consent withdrawn by subject | 1 | - |
| Lost to follow-up | - | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Treatment sequence A/B |
| Reporting group description: | |
| Subjects received Treatment A in Period 1 and Treatment B in Period 2, as a single 20 milliliter (mL) SC injection per dose.<br>Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.<br>Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.<br>A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2. | |
| Reporting group title | Treatment sequence B/A |
| Reporting group description: | |
| Subjects received Treatment B in Period 1 and Treatment A in Period 2, as a single 20 mL SC injection per dose.<br>Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.<br>Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.<br>A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2. | |

| **Reporting group values** | Treatment sequence A/B | Treatment sequence B/A | Total |
|---|---|---|---|
| Number of subjects | 23 | 24 | 47 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| Intent-to-treat safety (ITT-S) population included all subjects who received any amount of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 39.7 | 38.3 | |
| standard deviation | ± 13.7 | ± 15.7 | - |
| Gender categorical | | | |
| ITT-S population. | | | |
| Units: Subjects | | | |
| Female | 15 | 18 | 33 |
| Male | 8 | 6 | 14 |

## End points

### End points reporting groups

| Reporting group title | Treatment sequence A/B |
|---|---|

Reporting group description:

Subjects received Treatment A in Period 1 and Treatment B in Period 2, as a single 20 milliliter (mL) SC injection per dose.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2.

| Reporting group title | Treatment sequence B/A |
|---|---|

Reporting group description:

Subjects received Treatment B in Period 1 and Treatment A in Period 2, as a single 20 mL SC injection per dose.
Treatment B: 2000 U CINRYZE with 48,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
Treatment A: 1000 U CINRYZE with 24,000 U rHuPH20 twice weekly (every 3 or 4 days) for 8 weeks.
A washout period of at least 7 days and no more than 30 days was maintained between the last dose in Period 1 and the first dose in Period 2.

| Subject analysis set title | Intent-to-treat efficacy (ITT-E) population |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

ITT-E population (N=22) included all subjects who completed both randomized treatment periods and fulfilled a priori defined evaluability criteria.

| Subject analysis set title | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects received Treatment A (1000 U CINRYZE with 24,000 U rHuPH20 twice weekly [every 3 or 4 days] for 8 weeks) as a single 20 mL SC injection per dose in each treatment period.

| Subject analysis set title | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects received Treatment B (2000 U CINRYZE with 48,000 U rHuPH20 twice weekly [every 3 or 4 days] for 8 weeks) as a single 20 mL SC injection per dose in each treatment period.

### Primary: Normalized Number of Angioedema Attacks During the Treatment Period

| End point title | Normalized Number of Angioedema Attacks During the Treatment Period[1] |
|---|---|

End point description:

Angioedema attack was defined as the subject-reported indication of symptoms or signs such as swelling or pain at any location following a report of no swelling or pain on the previous day. Manifestations of an attack that progress from one site to another, prior to complete resolution, was considered a single attack. Attacks that began to regress and then worsened before complete resolution was also considered one attack. Subjects who were dosed but did not have any attacks in the period were assigned a value of zero. The number of attacks was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.

| End point type | Primary |
|---|---|

End point timeframe:

From Visit 1 (Week 1) up to Visit 16 (Week 8) during each treatment period

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: EudraCT database does auto-addition of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[2] | 22[3] | | |
| Units: angioedema attacks | | | | |
| arithmetic mean (confidence interval 95%) | 1.58 (0.88 to 2.29) | 0.97 (0.41 to 1.53) | | |

Notes:

[2] - ITT-E population

[3] - ITT-E population

| Attachments (see zip file) | Statistical Analyses_Primary_Angioedema Attacks/0624- |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cumulative Attack-severity During the Treatment Period

| End point title | Cumulative Attack-severity During the Treatment Period |
|---|---|

End point description:

Cumulative Attack-severity score was the sum of the maximum symptom severity recorded for each angioedema attack, which was determined on the last day of symptoms and recorded as None=0, Mild=1, Moderate=2, and Severe=3 and summing over the unique attacks, yields a Cumulative Attack-severity score.
None: no angioedema attack symptom;
Mild: the angioedema attack symptom was noticeable to the subject but was easily tolerated and did not interfere with routine activities;
Moderate: the angioedema attack symptom interfered with work/school or the ability to participate in family life and social activities;
Severe: the angioedema attack symptom significantly limited the subject's ability to attend work/school or participate in family life and social activities.
Cumulative attack-severity was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.
The scores ranged from 0 to 168 and higher scores represent worse symptoms.

| End point type | Secondary |
|---|---|

End point timeframe:

From Visit 1 (Week 1) up to Visit 16 (Week 8) during each treatment period

| End point values | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[4] | 22[5] | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 3.14 (± 3.79) | 1.81 (± 2.55) | | |

Notes:

[4] - ITT-E population

[5] - ITT-E population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative Daily-severity During the Treatment Period

| End point title | Cumulative Daily-severity During the Treatment Period |
|---|---|

End point description:

Cumulative Daily-severity score was the sum of the severity scores recorded for every day of reported symptoms during the treatment period.
Severity scores were recorded as None=0, Mild=1, Moderate=2, and Severe=3.
None: no angioedema attack symptom;
Mild: the angioedema attack symptom was noticeable to the subject but was easily tolerated and did not interfere with routine activities;
Moderate: the angioedema attack symptom interfered with work/school or the ability to participate in family life and social activities;
Severe: the angioedema attack symptom significantly limited the subject's ability to attend work/school or participate in family life and social activities.
Cumulative daily severity was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.
The scores ranged from 0 to 168 and higher scores represent worse symptoms.

| End point type | Secondary |
|---|---|

End point timeframe:

From Visit 1 (Week 1) up to Visit 16 (Week 8) during each treatment period

| **End point values** | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[6] | 22[7] | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 4.63 (± 5.79) | 2.81 (± 4.42) | | |

Notes:

[6] - ITT-E population

[7] - ITT-E population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative Symptomatic Days During the Treatment Period

| End point title | Cumulative Symptomatic Days During the Treatment Period |
|---|---|

End point description:

Cumulative symptomatic days was defined as the sum of the symptomatic days of each angioedema attack reported during the treatment period. Subjects who were dosed but did not have any attacks in the period were assigned a value of zero. Cumulative symptomatic days was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.

| End point type | Secondary |
|---|---|

End point timeframe:

From Visit 1 (Week 1) up to Visit 16 (Week 8) during each treatment period

| End point values | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[8] | 22[9] | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 3.06 (± 3.51) | 2.14 (± 3.3) | | |

Notes:

[8] - ITT-E population

[9] - ITT-E population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Angioedema Attacks Requiring Acute Treatment During the Treatment Period

| End point title | Number of Angioedema Attacks Requiring Acute Treatment During the Treatment Period |
|---|---|

End point description:

Angioedema attack was defined as the subject-reported indication of symptoms or signs such as swelling or pain at any location following a report of no swelling or pain on the previous day. Manifestations of an attack that progress from one site to another, prior to complete resolution, was considered a single attack. Attacks that began to regress and then worsened before complete resolution was also considered one attack. Subjects who were dosed but did not have any attacks in the period were assigned a value of zero. The number of attacks was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.

| End point type | Secondary |
|---|---|

End point timeframe:

From Visit 1 (Week 1) up to Visit 16 (Week 8) during each treatment period

| End point values | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[10] | 22[11] | | |
| Units: angioedema attacks | | | | |
| arithmetic mean (standard deviation) | 0.99 (± 1.51) | 0.43 (± 0.89) | | |

Notes:

[10] - ITT-E population

[11] - ITT-E population

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time of first dose of study drug up to 7 days after the last dose of study drug within each treatment period (8 weeks)

Adverse event reporting additional description:

Treatment-emergent adverse events included adverse events (AEs) that were not present at baseline (that is, prior to the first dose of study drug) but started during or after the first administration of study drug in each treatment period, and AEs that were present at baseline but worsened in frequency and/or severity.
ITT-S population.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) |

Reporting group description:

Subjects received Treatment A (1000 U CINRYZE with 24,000 U rHuPH20 twice weekly [every 3 or 4 days] for 8 weeks) as a single 20 mL SC injection per dose in each treatment period.

| | |
|---|---|
| Reporting group title | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) |

Reporting group description:

Subjects received Treatment B (2000 U CINRYZE with 48,000 U rHuPH20 twice weekly [every 3 or 4 days] for 8 weeks) as a single 20 mL SC injection per dose in each treatment period.

| Serious adverse events | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 46 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Treatment A (1000 U CINRYZE + 24000 U rHuPH20) | Treatment B (2000 U CINRYZE + 48000 U rHuPH20) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 44 (95.45%) | 46 / 46 (100.00%) | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Hereditary angioedema | | | |
| subjects affected / exposed | 32 / 44 (72.73%) | 28 / 46 (60.87%) | |
| occurrences (all) | 108 | 69 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 3 / 46 (6.52%) | |
| occurrences (all) | 2 | 3 | |
| General disorders and administration site conditions | | | |
| Injection site reactions | | | |
| subjects affected / exposed | 37 / 44 (84.09%) | 40 / 46 (86.96%) | |
| occurrences (all) | 1113 | 1212 | |
| Injection site extravasation | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 9 / 46 (19.57%) | |
| occurrences (all) | 15 | 32 | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 1 / 46 (2.17%) | |
| occurrences (all) | 5 | 1 | |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Injury associated with device | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 46 (2.17%) | |
| occurrences (all) | 2 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 46 (4.35%) | |
| occurrences (all) | 3 | 2 | |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 1 / 46 (2.17%) | |
| occurrences (all) | 4 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 October 2012 | 1. Added the evaluation of subject experience with self administration of study drug as secondary objective<br>2. Included prophylactic treatment with other C1 inhibitor (INH) therapy in inclusion criteria<br>3. Excluded subjects who received androgen therapy within 7 days prior to the first dose of study drug in Period 1<br>4. Clarified additional study staff to be unblinded for the purposes of pharmacokinetic/pharmacodynamic (PK/PD) assessments and review of drug accountability<br>5. Added recording of details regarding any therapy received during the previous 12 months hereditary angioedema (HAE) management and delineated other C1 INH therapy as part of prophylaxis<br>6. Added upper extremity examinations for monitoring venous thromboembolism<br>7. Sample collection was modified for PK/PD, C1 INH and rHuPH20 antibodies<br>8. Included an additional study diary (Angioedema Activity Score)<br>9. Added a self-administration survey to gather information regarding the ease of syringe use, "injection button" use, training, and overall long-term use<br>10. An exploratory endpoint of response status (responder/non-responder) during each treatment period was added<br>11. Added an additional Angioedema Quality of Life (AE-QoL) questionnaire<br>12. Changed from target of achieving 36 to 34 subjects<br>13. Suspected unexpected serious adverse reactions (SUSARs) were to be reported to relevant competent authorities<br>14. Added the recommendation that the subject be in a semi-reclined (semi-Fowler) position during the injection<br>15. Added a section to indicate that for the purposes of this study, rHuPH20 antibodies were considered laboratory events of special interest<br>16. Subjects to be trained (and supervised) in self-administration of SC CINRYZE in Period 2<br>17. Added preliminary results of an ex vivo thrombogenicity study, new safety data regarding the development of rHuPH20 antibodies in an unrelated development program, updated PK/PD and safety data from Study 0624-204 (NCT01426763) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|

| | | |
|---|---|---|
| 01 August 2013 | Following discussions with the Food and drug administration (FDA) in August 2013, study drug (CINRYZE with rHuPH20) dosing was discontinued in this study as a precaution related to the emergence of, and unexpected incidence and titer of, non-neutralizing anti-rHuPH20 antibodies in some subjects. As a result, on 01 August 2013, the Sponsor decided to close the study. These antibodies had not been associated with any adverse clinical effects and were of unknown clinical significance. Data from the study continued to be collected and analyzed to inform ongoing safety assessment and design of future HAE studies.<br>The Sponsor continued to follow subjects who developed anti-rHuPH20 antibodies in accordance with guidance from the FDA and to report anti-rHuPH20 antibody findings in an expedited manner. | - |

Notes:

## Limitations and caveats

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

Results of time to first angioedema attack and effects of C1 INH and C4 levels on clinical outcome during treatment period were not reported due to early termination of the study.

Notes: