



## Clinical trial results:

### **A Phase 3, Multicenter, Randomized, Single-Blind, Dose-Ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age with Hereditary Angioedema**

#### **Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-002453-29 |
| Trial protocol           | GB DE IT RO    |
| Global end of trial date | 04 May 2017    |

#### **Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 19 November 2017 |
| First version publication date | 19 November 2017 |

#### **Trial information**

##### **Trial identification**

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 0624-301 |
|-----------------------|----------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02052141 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### **Sponsors**

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

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:

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**Results analysis stage**

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 08 September 2017 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 04 May 2017       |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of this study was to assess the relative efficacy of 2 dose levels of CINRYZE (500 units (U) and 1000 U) administered by intravenous (IV) injection every 3 or 4 days to prevent angioedema attacks in children 6 to 11 years of age.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for 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                          | 20 March 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | United States: 5 |
| Country: Number of subjects enrolled | Germany: 3       |
| Country: Number of subjects enrolled | Mexico: 3        |
| Country: Number of subjects enrolled | Romania: 1       |
| Worldwide total number of subjects   | 12               |
| EEA total number of subjects         | 4                |

Notes:

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**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)                     | 12 |
| 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:

The study was conducted in 10 study centers in the United States, European Union, Mexico, and Israel between 20 March 2014 (first subject first visit) and 04 May 2017 (last subject last visit).

### Pre-assignment

Screening details:

A total of 16 subjects were screened and of them, 12 were enrolled into the baseline observational period (12 weeks) and were randomized to receive the treatment in sequence A-B and B-A during this crossover study without a washout period.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Intervention Period 1   |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Subject                 |

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | Treatment A-B (500 U/1000 U CINRYZE) |

Arm description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | CINRYZE                       |
| Investigational medicinal product code | SHP616                        |
| Other name                             | C1 Esterase Inhibitor (Human) |
| Pharmaceutical forms                   | Injection                     |
| Routes of administration               | Intravenous use               |

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Treatment B-A (1000 U/500 U CINRYZE) |
|------------------|--------------------------------------|

Arm description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | CINRYZE                       |
| Investigational medicinal product code | SHP616                        |
| Other name                             | C1 Esterase Inhibitor (Human) |
| Pharmaceutical forms                   | Injection                     |
| Routes of administration               | Intravenous use               |

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

| Number of subjects in period 1 | Treatment A-B (500 U/1000 U CINRYZE) | Treatment B-A (1000 U/500 U CINRYZE) |
|--------------------------------|--------------------------------------|--------------------------------------|
|                                |                                      |                                      |
| Started                        | 5                                    | 7                                    |
| Completed                      | 5                                    | 7                                    |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Intervention Period 2   |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Subject                 |

## Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | Treatment A-B (500 U/1000 U CINRYZE) |

### Arm description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | CINRYZE                       |
| Investigational medicinal product code | SHP616                        |
| Other name                             | C1 Esterase Inhibitor (Human) |
| Pharmaceutical forms                   | Injection                     |
| Routes of administration               | Intravenous use               |

### Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Treatment B-A (1000 U/500 U CINRYZE) |
|------------------|--------------------------------------|

### Arm description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | CINRYZE                       |
| Investigational medicinal product code | SHP616                        |
| Other name                             | C1 Esterase Inhibitor (Human) |
| Pharmaceutical forms                   | Injection                     |
| Routes of administration               | Intravenous use               |

### Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

| Number of subjects in period 2 | Treatment A-B (500 U/1000 U CINRYZE) | Treatment B-A (1000 U/500 U CINRYZE) |
|--------------------------------|--------------------------------------|--------------------------------------|
|                                |                                      |                                      |
| Started                        | 5                                    | 7                                    |
| Completed                      | 5                                    | 7                                    |

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | Treatment A-B (500 U/1000 U CINRYZE) |
| Reporting group description:<br>Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods. |                                      |
| Reporting group title  | Treatment B-A (1000 U/500 U CINRYZE) |
| Reporting group description:<br>Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.    |                                      |

| Reporting group values   | Treatment A-B (500 U/1000 U CINRYZE) | Treatment B-A (1000 U/500 U CINRYZE) | Total |
|--|--------------------------------------|--------------------------------------|-------|
| Number of subjects   | 5                                    | 7                                    | 12    |
| Age categorical<br>Units: Subjects   |                                      |                                      |       |
| Age continuous   |                                      |                                      |       |
| Age was calculated as the difference between date of birth and date of informed consent, truncated to years. |                                      |                                      |       |
| Units: years   |                                      |                                      |       |
| arithmetic mean  | 10.2                                 | 9.4                                  |       |
| standard deviation   | ± 0.84                               | ± 1.51                               | -     |
| Gender categorical<br>Units: Subjects  |                                      |                                      |       |
| Female   | 2                                    | 5                                    | 7     |
| Male   | 3                                    | 2                                    | 5     |
| Ethnicity (NIH/OMB)<br>Units: Subjects   |                                      |                                      |       |
| Hispanic or Latino   | 2                                    | 2                                    | 4     |
| Not Hispanic or Latino   | 3                                    | 5                                    | 8     |
| Unknown or Not Reported  | 0                                    | 0                                    | 0     |

## End points

### End points reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Treatment A-B (500 U/1000 U CINRYZE) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Treatment B-A (1000 U/500 U CINRYZE) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Treatment A-B (500 U/1000 U CINRYZE) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Treatment B-A (1000 U/500 U CINRYZE) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Treatment A (500 U CINRYZE) |
|----------------------------|-----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Subjects received 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 1 in sequence A-B and intervention period 2 in sequence B-A). Each intervention period was of 12 weeks.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Treatment B (1000 U CINRYZE) |
|----------------------------|------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 2 in sequence A-B and intervention period 1 in sequence B-A). Each intervention period was of 12 weeks.

### Primary: Normalized Number of Angioedema Attacks Per Month in a Treatment Period

|                 |   |
|-----------------|---|
| End point title | Normalized Number of Angioedema Attacks Per Month in a 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. Attacks that began then appeared to resolve and then reappeared without a symptom-free calendar day reported after the appearance of resolution were considered 1 attack. Any events of swelling due to trauma or symmetrical nonpainful swelling of the lower extremities were not considered an angioedema attack. 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 start of treatment up to 12 weeks during each treatment period



| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Angioedema attacks            |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Angioedema attacks                   | 1.2 ( $\pm$ 1.53)                 | 0.7 ( $\pm$ 1.35)                  |  |  |

## Statistical analyses

| Statistical analysis title  | Statistical analysis 1                                     |
|---|--|
| Statistical analysis description:   |  |
| Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12. |  |
| Comparison groups   | Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE) |
| Number of subjects included in analysis   | 24   |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.03   |
| Method  | Paired t-test  |
| Parameter estimate  | Mean difference  |
| Point estimate  | -0.4   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | -0.71  |
| upper limit   | -0.1   |
| Variability estimate  | Standard deviation   |
| Dispersion value  | 0.58   |

## Secondary: Cumulative Attack-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

|   |   |
|---|---|
| End point title   | Cumulative Attack-severity of Angioedema Attacks Normalized Per Month in a Treatment Period |
| End point description:  |   |
| Severity of the angioedema attack sign/symptom at each location was characterized as None: no symptom; Mild: noticeable symptom but easily tolerated by the subject and did not interfere with routine activities; Moderate: symptom interfered with the subject's ability to attend school or participate in family life and social/recreational activities; Severe: symptom significantly limited the subject's ability to attend school or participate in family life and social/recreational activities. Cumulative attack severity score was the sum of the maximum symptom severity recorded for each angioedema attack in a treatment period. Cumulative attack-severity score normalized per month was reported here. |   |
| End point type  | Secondary   |

End point timeframe:

From start of treatment up to 12 weeks during each treatment period

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Score on a scale              |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Score on a scale                     | 2.0 ( $\pm$ 2.91)                 | 1.4 ( $\pm$ 2.68)                  |  |  |

## Statistical analyses

| Statistical analysis title   | Statistical analysis 1                                     |
|--|--|
| Statistical analysis description:<br>Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12. |  |
| Comparison groups  | Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE) |
| Number of subjects included in analysis  | 24   |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| P-value  | = 0.05   |
| Method   | Paired t-test  |
| Parameter estimate   | Mean difference  |
| Point estimate   | -0.7   |
| Confidence interval  |  |
| level  | 90 %   |
| sides  | 2-sided  |
| lower limit  | -1.2   |
| upper limit  | -0.11  |
| Variability estimate   | Standard deviation   |
| Dispersion value   | 1.06   |

## Secondary: Cumulative Daily-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

|                 |  |
|-----------------|--|
| End point title | Cumulative Daily-severity of Angioedema Attacks Normalized Per Month in a Treatment Period |
|-----------------|--|

End point description:

Severity of the angioedema attack sign/symptom at each location was characterized as None: no symptom; Mild: noticeable but easily tolerated by the subject and did not interfere with routine activities; Moderate: interfered with the subject's ability to attend school or participate in family life and social/recreational activities; Severe: significantly limited the subject's ability to attend school or participate in family life and social/recreational activities. Cumulative daily-severity score was the sum of the severity scores recorded for every day of reported symptoms in a treatment period. Cumulative daily-severity score normalized per month was reported here.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From start of treatment up to 12 weeks during each intervention period |           |

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Score on a scale              |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Score on a scale                     | 4.1 ( $\pm$ 5.01)                 | 2.2 ( $\pm$ 3.50)                  |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Statistical analysis 1                                     |
| Statistical analysis description:   |  |
| Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12. |  |
| Comparison groups   | Treatment B (1000 U CINRYZE) v Treatment A (500 U CINRYZE) |
| Number of subjects included in analysis   | 24   |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.04   |
| Method  | Paired t-test  |
| Parameter estimate  | Mean difference  |
| Point estimate  | -1.9   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | -3.31  |
| upper limit   | -0.38  |
| Variability estimate  | Standard deviation   |
| Dispersion value  | 2.82   |

## Secondary: Normalized Number of Angioedema Attacks Per Month Requiring Acute Treatment in a Treatment Period

|                 |   |
|-----------------|---|
| End point title | Normalized Number of Angioedema Attacks Per Month Requiring Acute Treatment in a 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. Attacks that began then appeared to resolve and then reappeared without a symptom-free calendar day reported after the appearance of resolution were considered 1

attack. Any events of swelling due to trauma or symmetrical nonpainful swelling of the lower extremities were not considered an angioedema attack. The number of attacks requiring acute treatment 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 start of treatment up to 12 weeks during each intervention period |           |

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Angioedema attacks            |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Angioedema attacks                   | 0.7 (± 1.5)                       | 0.4 (± 1.27)                       |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Statistical analysis 1                                     |
| Statistical analysis description:   |  |
| Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12. |  |
| Comparison groups   | Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE) |
| Number of subjects included in analysis   | 24   |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.07   |
| Method  | Paired t-test  |
| Parameter estimate  | Mean difference  |
| Point estimate  | -0.2   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | -0.41  |
| upper limit   | -0.03  |
| Variability estimate  | Standard deviation   |
| Dispersion value  | 0.37   |

## Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Dose Group

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Dose Group |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a subject participating in a

clinical study with the sponsor's product, regardless of causal relationship. TEAEs were defined as events that started or worsened on or after the date and time of the first dose of investigational product and up to 7 days after the last dose of investigational product.

|  |           |
|--|-----------|
| End point type                               | Secondary |
| End point timeframe:                         |           |
| From start of study treatment up to 25 weeks |           |

| End point values            | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|-----------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type          | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed | 12                                | 12                                 |  |  |
| Units: Subject              |                                   |                                    |  |  |
| Subjects                    | 10                                | 11                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of C1 Esterase Inhibitor (C1 INH) Antigen

|   |  |
|---|--|
| End point title   | Plasma Concentration of C1 Esterase Inhibitor (C1 INH) Antigen |
| End point description:  |  |
| C1 INH antigen concentration in plasma was determined using an automated nephelometric assay.   |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Pre-dose and 1 hour (h) post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period |  |

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Gram per liter (g/L)          |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Week 1: Pre-dose 1 (n=12,11)         | 0.0945 (±<br>0.03294)             | 0.0736 (±<br>0.02885)              |  |  |
| Week 1: 1 h post-dose 1 (n=11,11)    | 0.1819 (±<br>0.04331)             | 0.2084 (±<br>0.08757)              |  |  |
| Week 6: Pre-dose 12 (n=12,12)        | 0.0965 (±<br>0.03129)             | 0.1068 (±<br>0.03098)              |  |  |
| Week 6: 1 h post-dose 12 (n=10,11)   | 0.1631 (±<br>0.04188)             | 0.2543 (±<br>0.05499)              |  |  |
| Week 12: Pre-dose 24 (n=12,11)       | 0.0823 (±<br>0.02758)             | 0.1002 (±<br>0.04420)              |  |  |
| Week 12: 1 h post-dose 24 (n=12,10)  | 0.1621 (±<br>0.02990)             | 0.2396 (±<br>0.04511)              |  |  |

|                                   |                    |                    |  |  |
|-----------------------------------|--------------------|--------------------|--|--|
| Week 12: 2 h post-dose 24 (n=3,2) | 0.1440 (± 0.00400) | 0.2070 (± 0.01838) |  |  |
| Week 12: 4 h post-dose 24 (n=2,2) | 0.1440 (± 0.01131) | 0.1770 (± 0.02970) |  |  |
| Week 12: 8 h post-dose 24 (n=2,3) | 0.1280 (± 0.00990) | 0.1790 (± 0.03100) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: C1 Esterase Inhibitor (C1 INH) Functional Activity in Plasma

|                 |  |
|-----------------|--|
| End point title | C1 Esterase Inhibitor (C1 INH) Functional Activity in Plasma |
|-----------------|--|

End point description:

The functional activity of C1 INH in plasma samples was determined by a chromogenic assay.

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

End point timeframe:

Pre-dose and 1 h post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Units per milliliter (U/mL)   |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Week 1: Pre-dose 1 (n=12,11)         | 0.290 (± 0.0914)                  | 0.210 (± 0.1282)                   |  |  |
| Week 1: 1 h post-dose 1 (n=12,11)    | 0.575 (± 0.1358)                  | 0.725 (± 0.3100)                   |  |  |
| Week 6: Pre-dose 12 (n=12,12)        | 0.297 (± 0.1375)                  | 0.336 (± 0.0933)                   |  |  |
| Week 6: 1 h post-dose 12 (n=11,11)   | 0.570 (± 0.1190)                  | 0.865 (± 0.1550)                   |  |  |
| Week 12: Pre-dose 24 (n=12,11)       | 0.255 (± 0.1108)                  | 0.362 (± 0.1897)                   |  |  |
| Week 12: 1 h post-dose 24 (n=12,10)  | 0.531 (± 0.1330)                  | 0.803 (± 0.1906)                   |  |  |
| Week 12: 2 h post-dose 24 (n=3,3)    | 0.497 (± 0.0635)                  | 0.613 (± 0.2601)                   |  |  |
| Week 12: 4 h post-dose 24 (n=3,3)    | 0.497 (± 0.0058)                  | 0.590 (± 0.1803)                   |  |  |
| Week 12: 8 h post-dose 24 (n=3,3)    | 0.430 (± 0.0458)                  | 0.643 (± 0.0723)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Complement C4

|  |                                       |
|--|---------------------------------------|
| End point title  | Plasma Concentration of Complement C4 |
| End point description:<br>Concentration of Complement C4 in plasma was determined using an automated nephelometric assay.  |                                       |
| End point type   | Secondary                             |
| End point timeframe:<br>Pre-dose and 1 h post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period |                                       |

| End point values                     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type                   | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed          | 12                                | 12                                 |  |  |
| Units: Milligram per liter (mg/L)    |                                   |                                    |  |  |
| arithmetic mean (standard deviation) |                                   |                                    |  |  |
| Week 1: Pre-dose 1 (n=12,11)         | 105.1 (± 39.38)                   | 71.2 (± 29.63)                     |  |  |
| Week 1: 1 h post-dose 1 (n=12,11)    | 99.7 (± 36.73)                    | 71.4 (± 33.20)                     |  |  |
| Week 6: Pre-dose 12 (n=12,12)        | 97.3 (± 37.26)                    | 121.3 (± 41.50)                    |  |  |
| Week 6: 1 h post-dose 12 (n=11,11)   | 88.0 (± 27.75)                    | 111.7 (± 41.75)                    |  |  |
| Week 12: Pre-dose 24 (n=12,11)       | 83.3 (± 21.63)                    | 111.6 (± 50.28)                    |  |  |
| Week 12: 1 h post-dose 24 (n=12,10)  | 79.2 (± 20.21)                    | 90.7 (± 27.72)                     |  |  |
| Week 12: 2 h post-dose 24 (n=3,3)    | 86.7 (± 4.93)                     | 94.3 (± 32.04)                     |  |  |
| Week 12: 4 h post-dose 24 (n=3,3)    | 89.3 (± 12.66)                    | 103.7 (± 32.35)                    |  |  |
| Week 12: 8 h post-dose 24 (n=3,3)    | 99.3 (± 11.02)                    | 114.7 (± 30.75)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with C1 Esterase Inhibitor (C1 INH) Antibodies in Plasma

|  |   |
|--|---|
| End point title  | Number of Subjects with C1 Esterase Inhibitor (C1 INH) Antibodies in Plasma |
| End point description:<br>The presence of C1 INH antibodies in plasma samples was determined using a proprietary enzyme-linked-immunosorbent-assay. Number of subjects with C1 INH Antibodies was reported here. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Pre-dose, 1 week post treatment (Week 13, Week 25) and 1 month post treatment follow-up (Week 28)  |   |

| <b>End point values</b>     | Treatment A<br>(500 U<br>CINRYZE) | Treatment B<br>(1000 U<br>CINRYZE) |  |  |
|-----------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type          | Subject analysis set              | Subject analysis set               |  |  |
| Number of subjects analysed | 5                                 | 7                                  |  |  |
| Units: Subject              |                                   |                                    |  |  |
| Subjects                    | 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 Week 25

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Treatment B (1000 U CINRYZE) |
|-----------------------|------------------------------|

Reporting group description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 2 in sequence A-B and intervention period 1 in sequence B-A). Each intervention period was of 12 weeks.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Treatment A (500 U CINRYZE) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects received 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 1 in sequence A-B and intervention period 2 in sequence B-A). Each intervention period was of 12 weeks.

| Serious adverse events                            | Treatment B (1000 U CINRYZE) | Treatment A (500 U CINRYZE) |  |
|---|------------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events |                              |                             |  |
| subjects affected / exposed                       | 0 / 12 (0.00%)               | 0 / 12 (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                            | Treatment B (1000 U CINRYZE) | Treatment A (500 U CINRYZE) |  |
|---|------------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                              |                             |  |
| subjects affected / exposed                           | 11 / 12 (91.67%)             | 10 / 12 (83.33%)            |  |
| Vascular disorders                                    |                              |                             |  |
| Vascular pain   |                              |                             |  |
| subjects affected / exposed                           | 0 / 12 (0.00%)               | 1 / 12 (8.33%)              |  |
| occurrences (all)                                     | 0                            | 1                           |  |
| General disorders and administration site conditions  |                              |                             |  |
| Facial pain   |                              |                             |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1  | 0 / 12 (0.00%)<br>0  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>9  | 1 / 12 (8.33%)<br>9  |  |
| Infusion site pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 1 / 12 (8.33%)<br>19 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)         | 0 / 12 (0.00%)<br>0  | 2 / 12 (16.67%)<br>2 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1  | 0 / 12 (0.00%)<br>0  |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)  | 2 / 12 (16.67%)<br>2 | 0 / 12 (0.00%)<br>0  |  |
| Psychiatric disorders<br>Irritability<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 12 (8.33%)<br>7  | 1 / 12 (8.33%)<br>7  |  |
| Injury, poisoning and procedural complications<br>Arthropod bite<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1  | 0 / 12 (0.00%)<br>0  |  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Face injury  |                      |                      |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1   | 0 / 12 (0.00%)<br>0   |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1   | 1 / 12 (8.33%)<br>1   |  |
| Head injury<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1   | 1 / 12 (8.33%)<br>1   |  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |  |
| Lip injury<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |  |
| Multiple injuries<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |  |
| Post-Traumatic neck syndrome<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1   | 0 / 12 (0.00%)<br>0   |  |
| Sunburn<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1   | 0 / 12 (0.00%)<br>0   |  |
| Congenital, familial and genetic disorders<br>Hereditary angioedema<br>subjects affected / exposed<br>occurrences (all) | 8 / 12 (66.67%)<br>25 | 9 / 12 (75.00%)<br>41 |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 12 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |  |
| Headache  |                       |                       |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 12 (16.67%)<br>5 | 1 / 12 (8.33%)<br>1 |  |
| Eye disorders                                    |                      |                     |  |
| Eye pain   |                      |                     |  |
| subjects affected / exposed                      | 0 / 12 (0.00%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 0                    | 1                   |  |
| Gastrointestinal disorders                       |                      |                     |  |
| Abdominal discomfort                             |                      |                     |  |
| subjects affected / exposed                      | 0 / 12 (0.00%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 0                    | 1                   |  |
| Abdominal pain                                   |                      |                     |  |
| subjects affected / exposed                      | 2 / 12 (16.67%)      | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 2                    | 2                   |  |
| Constipation                                     |                      |                     |  |
| subjects affected / exposed                      | 1 / 12 (8.33%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                   |  |
| Dental caries                                    |                      |                     |  |
| subjects affected / exposed                      | 0 / 12 (0.00%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 0                    | 1                   |  |
| Diarrhoea  |                      |                     |  |
| subjects affected / exposed                      | 1 / 12 (8.33%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 1                    | 2                   |  |
| Nausea   |                      |                     |  |
| subjects affected / exposed                      | 2 / 12 (16.67%)      | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 2                    | 2                   |  |
| Toothache  |                      |                     |  |
| subjects affected / exposed                      | 1 / 12 (8.33%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 4                    | 1                   |  |
| Vomiting   |                      |                     |  |
| subjects affected / exposed                      | 1 / 12 (8.33%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Skin and subcutaneous tissue disorders           |                      |                     |  |
| Angioedema                                       |                      |                     |  |
| subjects affected / exposed                      | 1 / 12 (8.33%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                   |  |
| Erythema   |                      |                     |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Erythema marginatum                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 12 (16.67%) | 2 / 12 (16.67%) |  |
| occurrences (all)                               | 12              | 12              |  |
| Prurigo   |                 |                 |  |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Pruritus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Coccydynia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Myalgia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 1               | 2               |  |
| Infections and infestations                     |                 |                 |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Gingivitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| H1n1 influenza                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Hordeolum                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed             | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 1               | 0               |  |
| Nasopharyngitis                         |                 |                 |  |
| subjects affected / exposed             | 2 / 12 (16.67%) | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 3               | 1               |  |
| Paronychia                              |                 |                 |  |
| subjects affected / exposed             | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 1               | 0               |  |
| Sinusitis                               |                 |                 |  |
| subjects affected / exposed             | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 0               | 1               |  |
| Tinea pedis                             |                 |                 |  |
| subjects affected / exposed             | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 0               | 1               |  |
| Tonsillitis                             |                 |                 |  |
| subjects affected / exposed             | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 0               | 1               |  |
| Upper respiratory tract infection       |                 |                 |  |
| subjects affected / exposed             | 2 / 12 (16.67%) | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 4               | 1               |  |
| Viral pharyngitis                       |                 |                 |  |
| subjects affected / exposed             | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 0               | 1               |  |
| Viral upper respiratory tract infection |                 |                 |  |
| subjects affected / exposed             | 6 / 12 (50.00%) | 2 / 12 (16.67%) |  |
| occurrences (all)                       | 8               | 3               |  |
| Metabolism and nutrition disorders      |                 |                 |  |
| Decreased appetite                      |                 |                 |  |
| subjects affected / exposed             | 0 / 12 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                       | 0               | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 09 October 2013 | Blood sample collection for post-treatment immunogenicity assessments, the post-dose time point was changed to Dose 12. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported