



## Clinical trial results:

**A Phase IIIb randomized, double-blind, placebo-controlled study with an open-label extension evaluating the efficacy, safety and immunogenicity of recombinant human C1 inhibitor for the treatment of acute attacks of angioedema in patients with HAE**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000049-19 |
| Trial protocol           | HU IT          |
| Global end of trial date | 07 March 2013  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 07 October 2018 |
| First version publication date | 07 October 2018 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | C1 1310 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01188564 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------|
| Sponsor organisation name    | Pharming Technologies BV                                                               |
| Sponsor organisation address | Darwinweg 24, Leiden, Netherlands, 2333CR                                              |
| Public contact               | Anurag Relan, Pharming Technologies BV, 31 715247400, medical-information@pharming.com |
| Scientific contact           | Anurag Relan, Pharming Technologies BV, 31 715247400, medical-information@pharming.com |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Interim           |
| Date of interim/final analysis                       | 26 September 2012 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 26 September 2012 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 07 March 2013     |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate efficacy and safety of rhC1INH at a dose of 50 U/kg when used for the treatment of acute angioedema attacks in patients with HAE.

Protection of trial subjects:

Any patient having received randomized treatment who does not achieve beginning of relief within 4 hours at the primary attack location (or if beginning of relief does not persist at the 4½ hour assessment) or experiencing oropharyngeal-laryngeal symptoms or a significant degree of pain, discomfort, or disability due to their HAE symptoms, was allowed to receive rescue medication (open-label rhC1INH).

Rescue medication was also allowed to be provided prior to 4 hours following randomized treatment in case of life-threatening oropharyngeal-laryngeal angioedema symptoms.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 30 January 2011 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                                               |
|--------------------------------------|-----------------------------------------------|
| Country: Number of subjects enrolled | Poland: 7                                     |
| Country: Number of subjects enrolled | Bulgaria: 1                                   |
| Country: Number of subjects enrolled | Hungary: 3                                    |
| Country: Number of subjects enrolled | Italy: 3                                      |
| Country: Number of subjects enrolled | United States: 38                             |
| Country: Number of subjects enrolled | Israel: 3                                     |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 7 |
| Country: Number of subjects enrolled | Romania: 9                                    |
| Country: Number of subjects enrolled | Serbia: 4                                     |
| Worldwide total number of subjects   | 75                                            |
| EEA total number of subjects         | 23                                            |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 71 |
| From 65 to 84 years                       | 3  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Consenting male or female patients  $\geq 13$  years of age ( $\geq 18$  years for patients outside the United States or Canada) with a clinically suspected and laboratory confirmed diagnosis of HAE were eligible for enrollment.

### Pre-assignment

Screening details:

The criteria for the diagnosis of HAE consisted of a medical history supported by central laboratory investigations including a functional C1INH level  $< 50\%$  of normal. In total: 227 patients screened, 75 enrolled (44 rhC1INH; 31 saline)

### Period 1

|                              |                            |
|------------------------------|----------------------------|
| Period 1 title               | RCT Phase (overall period) |
| Is this the baseline period? | Yes                        |
| Allocation method            | Randomised - controlled    |
| Blinding used                | Double blind               |
| Roles blinded                | Subject, Investigator      |

### Arms

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Are arms mutually exclusive?           | Yes                              |
| <b>Arm title</b>                       | rhC1INH                          |
| Arm description: -                     |                                  |
| Arm type                               | Active comparator                |
| Investigational medicinal product name | Recombinant Human C1 Inhibitor   |
| Investigational medicinal product code | rhC1INH                          |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Recombinant human C1INH supplied by Pharming Technologies B.V., reconstituted with sterile water for injection and administered by slow iv injection over a period of approximately 5 minutes at an approximate flow rate of 6 mL/minute. A dose consisted of rhC1INH 50 IU/kg for patients  $< 84$  kg, or a dose of rhC1INH 4200 IU (2 vials) for patients  $\geq 84$  kg

|                                        |                                  |
|----------------------------------------|----------------------------------|
| <b>Arm title</b>                       | Placebo (Saline)                 |
| Arm description: -                     |                                  |
| Arm type                               | Placebo                          |
| Investigational medicinal product name | Saline                           |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Normal saline (0.9% NaCl) for iv injection

| <b>Number of subjects in period 1</b> | rhC1INH | Placebo (Saline) |
|---------------------------------------|---------|------------------|
| Started                               | 44      | 31               |
| Completed                             | 43      | 31               |
| Not completed                         | 1       | 0                |
| Randomized, not treated               | 1       | -                |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | RCT Phase |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values    | RCT Phase | Total |  |
|---------------------------|-----------|-------|--|
| Number of subjects        | 75        | 75    |  |
| Age categorical           |           |       |  |
| Units: Subjects           |           |       |  |
| Adolescents (12-17 years) | 1         | 1     |  |
| Adults (18-64 years)      | 71        | 71    |  |
| From 65-84 years          | 3         | 3     |  |
| Age continuous            |           |       |  |
| Units: years              |           |       |  |
| median                    | 40.2      |       |  |
| standard deviation        | ± 13.75   | -     |  |
| Gender categorical        |           |       |  |
| Units: Subjects           |           |       |  |
| Female                    | 47        | 47    |  |
| Male                      | 28        | 28    |  |

## End points

### End points reporting groups

|                                |                  |
|--------------------------------|------------------|
| Reporting group title          | rhC1INH          |
| Reporting group description: - |                  |
| Reporting group title          | Placebo (Saline) |
| Reporting group description: - |                  |

### Primary: Time to Beginning of Relief of Symptoms in RCT phase

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title          | Time to Beginning of Relief of Symptoms in RCT phase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| End point description:   | <p>The primary efficacy endpoint was the time to beginning of relief of symptoms (based on Questions 1 and 2 of the TEQ, with persistence) at the primary attack location.</p> <p>The time to beginning of relief at the primary attack location was defined as the time between beginning of treatment administration and the first time point at which the patient reported the following:</p> <ul style="list-style-type: none"><li>• An answer of "A little better", "Better" or "Much better" to TEQ Question 1, and</li><li>• An answer of "Yes" to TEQ Question 2</li><li>• Persistence of improvement at the next assessment time (i.e., either the same or a better response to Question 1 and "Yes" to Question 2)</li></ul> |
| End point type           | Primary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| End point timeframe:     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Observation for 24 hours |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| End point values                 | rhC1INH         | Placebo (Saline) |  |  |
|----------------------------------|-----------------|------------------|--|--|
| Subject group type               | Reporting group | Reporting group  |  |  |
| Number of subjects analysed      | 44              | 31               |  |  |
| Units: Minutes                   |                 |                  |  |  |
| median (confidence interval 95%) | 90 (61 to 150)  | 152 (93 to 1440) |  |  |

### Statistical analyses

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Statistical analysis title              | RCT ITT                          |
| Comparison groups                       | rhC1INH v Placebo (Saline)       |
| Number of subjects included in analysis | 75                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | < 0.05                           |
| Method                                  | Logrank                          |
| Parameter estimate                      | Median difference (final values) |

|                      |                    |
|----------------------|--------------------|
| Confidence interval  |                    |
| sides                | 2-sided            |
| Variability estimate | Standard deviation |

## Secondary: Time to Minimal Symptoms in RCT phase

|                                                                                                                                                                                                                                                                          |                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| End point title                                                                                                                                                                                                                                                          | Time to Minimal Symptoms in RCT phase |
| End point description:<br>The key secondary efficacy endpoint was the time to minimal symptoms at all locations (Time to Minimal Symptoms [based on Question 3 of the TEQ]). The time to achieving minimal symptoms was defined as an answer of "Yes" to TEQ Question 3. |                                       |
| End point type                                                                                                                                                                                                                                                           | Secondary                             |
| End point timeframe:<br>24 hours                                                                                                                                                                                                                                         |                                       |

| End point values              | rhC1INH          | Placebo (Saline)  |  |  |
|-------------------------------|------------------|-------------------|--|--|
| Subject group type            | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed   | 44               | 31                |  |  |
| Units: Minutes                |                  |                   |  |  |
| median (full range (min-max)) | 303 (240 to 720) | 483 (300 to 1440) |  |  |

## Statistical analyses

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Statistical analysis title              | RCT ITT                        |
| Comparison groups                       | rhC1INH v Placebo (Saline)     |
| Number of subjects included in analysis | 75                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.05                         |
| Method                                  | Logrank                        |
| Parameter estimate                      | Mean difference (final values) |
| Confidence interval                     |                                |
| sides                                   | 2-sided                        |
| Variability estimate                    | Standard deviation             |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of the ICF till 90 days following each treated attack.

Adverse event reporting additional description:

Patients who received saline followed by rhC1INH as rescue medication are summarized in the saline column up to receipt of rescue medication and in the rhC1INH column afterwards. Saline at any time column only includes patients who received saline. Counting is by patient. Treatment emergent adverse event information for RCT is reported.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | rhC1INH |
|-----------------------|---------|

Reporting group description:

rhC1INH: One i.v. injection of rhC1INH at the dose of 50 U/kg, for patients up to 84 kg; one i.v. injection of rhC1INH at the dose of 4200U (2 vials) for patients of 84 kg body weight or greater

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Placebo (Saline) |
|-----------------------|------------------|

Reporting group description:

Placebo (Saline): One i.v. injection of saline (NaCl 0.9% w/v), equivalent in volume to the active treatment

| Serious adverse events                            | rhC1INH        | Placebo (Saline) |  |
|---------------------------------------------------|----------------|------------------|--|
| Total subjects affected by serious adverse events |                |                  |  |
| subjects affected / exposed                       | 1 / 56 (1.79%) | 0 / 18 (0.00%)   |  |
| number of deaths (all causes)                     | 0              | 0                |  |
| number of deaths resulting from adverse events    | 0              | 0                |  |
| Gastrointestinal disorders                        |                |                  |  |
| Abdominal hernia                                  |                |                  |  |
| subjects affected / exposed                       | 1 / 56 (1.79%) | 0 / 18 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0            |  |

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

| Non-serious adverse events                            | rhC1INH          | Placebo (Saline) |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 18 / 56 (32.14%) | 10 / 18 (55.56%) |  |
| Investigations                                        |                  |                  |  |

|                                                                                                                         |                     |                     |  |
|-------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| Fibrin D-dimer increased<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 56 (1.79%)<br>1 | 1 / 18 (5.56%)<br>1 |  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Blood pressure diastolic increased<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Injury, poisoning and procedural complications<br>Sunburn<br>subjects affected / exposed<br>occurrences (all)           | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| General disorders and administration site conditions<br>Spinal pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Gastrointestinal disorders<br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Diarrhea<br>subjects affected / exposed<br>occurrences (all)                                                            | 2 / 56 (3.57%)<br>2 | 1 / 18 (5.56%)<br>1 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                        | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders<br>Sinus congestion<br>subjects affected / exposed<br>occurrences (all) | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Vasomotor rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Renal and urinary disorders                                                                                             |                     |                     |  |

|                                                                             |                     |                     |  |
|-----------------------------------------------------------------------------|---------------------|---------------------|--|
| Hematuria<br>subjects affected / exposed<br>occurrences (all)               | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Infections and infestations                                                 |                     |                     |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 4 / 56 (7.14%)<br>4 | 1 / 18 (5.56%)<br>1 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 56 (7.14%)<br>4 | 0 / 18 (0.00%)<br>0 |  |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)              | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 56 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                          |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 October 2010  | to document the update information and to document the changes made from using a paper CRF to eCRF                                                                 |
| 17 December 2010 | To document the update information                                                                                                                                 |
| 15 July 2011     | Rewriting part disallowed concomitant medication and explain the order of clinical seriousness of attacks                                                          |
| 19 July 2011     | This amendment has been submitted in countries where minors could not be enrolled. Inclusion criteria has been changes: age at least 18 years instead of 13 years. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported