



## 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
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#### 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:

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**Subjects enrolled per age group**

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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

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## 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
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<b>Arm title</b>	rhC1INH
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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)
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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
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Reporting group description: -

<b>Reporting group values</b>	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: 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: 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

<b>Statistical analysis title</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15
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### Reporting groups

Reporting group title	rhC1INH
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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)
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Reporting group description:

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

<b>Serious adverse events</b>	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 %

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

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