Clinical trial results:
A randomized, placebo-controlled, double-blind Phase III study of the efficacy and safety of recombinant human C1 inhibitor for the treatment of acute attacks in patients with hereditary angioedema

Summary

EudraCT number	2005-000206-31
Trial protocol	IT GB ES
Global end of trial date	13 November 2007

Results information

Result version number	v1 (current)
This version publication date	06 December 2018
First version publication date	06 December 2018

Trial information

Trial identification

Sponsor protocol code	C1 1304-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00262301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharming Technologies BV
Sponsor organisation address	Darwinweg 24, Leiden, Netherlands,
Public contact	Anurag Relan, MD, Pharming Technologies BV, +31 715247400, medical-information@pharming.com
Scientific contact	Anurag Relan, MD, Pharming Technologies BV, +31 715347400, 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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2007
Global end of trial reached?	Yes
Global end of trial date	13 November 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of rhC1INH in the treatment of acute angioedema attacks in patients with HAE.

Protection of trial subjects:

Patients developing a life-threatening attack after randomization or after the administration of study medication were to be treated with any treatment procedure as deemed necessary by the investigator, in the patients best interests.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Romania: 2
Worldwide total number of subjects	32
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	27

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with a clinically confirmed diagnosis of HAE were recruited for the study. Patients who presented to the clinic with an acute angioedema attack with 5 hours of onset were to be randomized.

Pre-assignment

Screening details:

In total: 177 screened patients, 159 eligible, 34 randomized, 32 treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rhC1INH RCT-phase

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:

rhC11NH at 100 U/kg dosage

Arm title	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:

Saline at 100 U/kg dosage

Number of subjects in period 1	rhC1INH RCT-phase	Saline
Started	16	16
Completed	16	16

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Phase

Reporting group description: -

Reporting group values	Double-blind Phase	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	27	27	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
median	40.5		
full range (min-max)	17 to 71	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	15	15	

End points

End points reporting groups

Reporting group title	rhC1INH RCT-phase
Reporting group description: -	
Reporting group title	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:

The primary efficacy variable was time to beginning of relief of symptoms assessed using the overall severity VAS score. For the primary endpoint, the time of beginning of relief of symptoms was the first timepoint at which the overall severity VAS score decreased by at least 20 mm with respect to baseline, at any eligible location.

End point type	Primary

End point timeframe:

up to 48 hours after study drug administration in RCT-phase

End point values	rhC1INH RCT-phase	Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Minutes				
median (confidence interval 95%)	61.5 (40 to 75)	508 (70 to 720)		

Statistical analyses

Statistical analysis title	Time to beginning of relief
Comparison groups	rhC1INH RCT-phase v Saline
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0294
Method	Logrank

Secondary: Time to Minimal Symptoms in RCT-phase

End point title	Time to Minimal Symptoms in RCT-phase

End point description:

Time to minimal symptoms, where ‘minimal symptoms’ was defined as an overall severity VAS score of <20 mm in severity of symptoms for all anatomical locations of an attack.

End point type	Secondary

End point timeframe:

Up to 48 hours after study drug administration

End point values	rhC1INH RCT-phase	Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Minutes				
median (confidence interval 95%)	480 (243 to 723)	1440 (720 to 2885)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events for each arm with onset dates within 7 days of study drug administration have been listed

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	rhC1INH in RCT-phase
Reporting group description: -	
Reporting group title	Saline

Reporting group description: -

Serious adverse events	rhC1INH in RCT-phase	Saline	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	3 / 16 (18.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Prostate examination			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ureteric calculus removal			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	rhC1INH in RCT-phase	Saline	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	8 / 16 (50.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Ureteric calculus removal			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Scrotal swelling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			
Prostate examination			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal and urinary disorders			
calculus ureteric			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Infections and infestations			
Herpes simplex			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2004	Amendment 1 included the following changes to the original protocol: • Changes were made to the inclusion criteria • A description of the differential diagnosis was added • The randomization method was changed • The type of blood sampling tubes for the diagnostic purpose and immunogenicity analyses were changed • The cleaved C1INH, C4b/c and PAP complex assays were removed • Amylase was added to the routine biochemistry measurements • The Time 20 minutes time point on Day 1 was changed to 45 minutes • The schedule of assessments was updated • An independent data monitoring committee was formed • The last question in the VAS was updated • Additional minor corrections and clarifications.
23 October 2006	• Changes were made to the method of preparation and administration of the study drug • Additional Investigator sites were added • The follow up window was made larger • The AE section was updated to include text that conformed to European regulations • In addition some administrative changes were made.
16 November 2006	• The discharge criteria were changed to allow patients to be discharged between 4 and 12 hours after treatment if they had no or minimal symptoms • An OLE to the study was added to allow patients who had been treated for a previous attack to be treated again • Day 7 was removed from the study • Treatment with plasma-derived C11NH or fresh frozen plasma was changed so that it was only not allowed within 7 days prior to treatment with rhC1INH compared to the 2 weeks in the original protocol.
10 May 2007	An interim analysis was added. The interim analysis was to be conducted once 26 patients had been treated.
03 August 2007	The IDMC concluded that "continuation of the trial in view of the current interim analysis is not appropriate and we would support a decision of Pharming to discontinue the trial". Therefore the Sponsor stopped the randomized, Saline-controlled arm of the trial. The open label-treatment extension of the study was continued for all eligible patients to collect additional safety data. Open-label treatment was extended to all of the screened patients meeting inclusion and exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported