Clinical trial results:
An open-label exploratory Phase II study of the safety and prophylactic effect of a weekly 50 U/kg rC1INH treatment in asymptomatic patients with hereditary C1INH deficiency (HAE)

Summary

EudraCT number	2009-010736-18
Trial protocol	HU
Global end of trial date	19 April 2010

Results information

Result version number	v1 (current)
This version publication date	26 September 2018
First version publication date	26 September 2018

Trial information

Trial identification

Sponsor protocol code	C1 1207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00851409
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, MD, Pharming Technologies BV, +31 715247400, medical-information@pharming.com
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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	19 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2010
Global end of trial reached?	Yes
Global end of trial date	19 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the occurrence of HAE attacks under prophylactic administration of rhC1INH (50 U/kg, once a week)

Protection of trial subjects:

Breakthrough angioedema acute attacks were allowed to be treated with rhC1INH at 50 U/kg with the provision of a second 50 U/kg dose. The maximum allowed total number of rhC1INH administrations within this study was 15 per patient.
For the purpose of this study, patients were recruited in 3 Phases. The study commenced with the simultaneous recruitment of 4 patients (Phase 1). Safety Laboratory Data from the 4th treatment visit was analyzed for clinically significant abnormalities. If no safety problems were identified in the Phase 1 patients, the next 4 patients (Phase 2) started.
Safety Laboratory Data from the last treatment visit from the Phase 1 patients along with Safety Laboratory Data from the 4th treatment visit from Phase 2 patients were analyzed for clinically significant abnormalities. If no safety problems were identified in the Phase 1 and Phase 2 patients, then the last 17 patients (Phase 3) were able to start.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Poland: 8
Worldwide total number of subjects	25
EEA total number of subjects	18

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-five patients from five countries (Italy, Hungary, Romania, Poland and Israel) with a confirmed HAE diagnosis, of at least 18 years old (men and women) were planned to be included in the study.

Pre-assignment

Screening details:

Confirmed diagnosis of HAE with baseline plasma level of functional C1 INH activity of less than 50% of normal, and/or proven HAE mutation in C1INH gene and occurrence of HAE attacks at least fortnight. In total: 25 screened, 25 eligible, 25 treated and 24 completed patients, from Israel, Romania and Poland.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment period
Arm description: -	
Arm type	Experimental
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:

rhC1INH at 50 U/kg

Number of subjects in period 1	Treatment period
Started	25
Completed	25

Period 2

Period 2 title	Follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Follow up

Arm description:

After the last treatment patients were followed up for 42 days. One study visit took place 7 days after the last study treatment and one visit 42 days after last study treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Follow up
Started	25
Completed	24
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	25	25	
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)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	37.9		
standard deviation	± 13.4	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	5	5	

End points

End points reporting groups

Reporting group title	Treatment period
Reporting group description: -	
Reporting group title	Follow up

Reporting group description:

After the last treatment patients were followed up for 42 days. One study visit took place 7 days after the last study treatment and one visit 42 days after last study treatment.

Primary: Incidence of documented HAE attacks during treatment period

End point title	Incidence of documented HAE attacks during treatment

End point description:

End point type	Primary

End point timeframe:

8 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this was an open-label single arm study, no statistical analyses could be provided. The pre defined endpoint was the number of HAE attacks during the treatment period. No comparison has been against a control or placebo group, so therefore no statistical analyses could be presented.

End point values	Treatment period			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Amount of attacks				
arithmetic mean (standard deviation)	3.3 (± 2.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment emergent adverse events have been listed, including any events that happened in the follow up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	Treatment phase

Reporting group description:

Administrations of rhC1INH were given once weekly over an 8-week period.

Serious adverse events	Treatment phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Respiratory, thoracic and mediastinal disorders			
Laryncheal edema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Treatment phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)		
Investigations			

White blood cell count increased subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Reproductive system and breast disorders Cervical polyp subjects affected / exposed occurrences (all) Vaginal haemorrhage	1 / 25 (4.00%) 1		

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Appendicitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Cervicitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tooth abscess			

subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2009	This amendment is written to make the protocol more clear and to rectify any discrepancies in the text body or between the text body and appendix. Also to reflect changes that occurred in the time between the first final protocol and this amendment 1.
10 December 2009	This amendment was written to clarify the methodology for immunology testing. To avoid inconsistencies, the body text needed adaptation in some points.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported