Clinical trial results:
Open-label, phase II, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in pediatric patients with hereditary angioedema, from 2 up to and including 13 years of age

Summary

EudraCT number	2011-000987-92
Trial protocol	DE IT CZ SK HU
Global end of trial date	17 July 2017

Results information

Result version number	v1 (current)
This version publication date	08 March 2018
First version publication date	08 March 2018

Trial information

Trial identification

Sponsor protocol code	C1 1209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01359969
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharming Technologies BV
Sponsor organisation address	Darwinweg 24, Leiden, Netherlands, 2333 CR
Public contact	Anurag Relan, MD, Pharming Technologies B.V., +31 715247400, a.relan@pharming.com
Scientific contact	Anurag Relan, MD, Pharming Technologies B.V., +31 715247400, a.relan@pharming.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000367-PIP01-08
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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2017
Global end of trial reached?	Yes
Global end of trial date	17 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical safety, immunogenicity and tolerability of Ruconest in the treatment of acute angioedema attacks in 2-13 year old HAE patients.

Protection of trial subjects:

All study-related procedures were to be hosted in a familiar environment in facilities selected for childcare: the staff were to be trained in communicating to and looking after (young) children and their legal representatives. All study-related procedures (e.g. blood samplings) were to be optimized and modeled in order to minimize risk and distress. Age appropriate information was to be given to the child and his/her representatives prior to any investigations or procedures. Eventual changes in the procedures were to be announced to them well in advance.

For blood sampling it was recommended, for the sake of patient's comfort, to use butterfly needles and to place a catheter during the time of hospitalization for easy blood collection. Also, applying a topical anesthetic before catheter placement was to be considered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2012
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	United States: 1
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 1
Worldwide total number of subjects	20
EEA total number of subjects	8

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)	17
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female patients, from 2 up to and including 13 years of age with a clinically suspected and/or confirmed diagnosis of HAE will be recruited for this study. Patients will be identified and invited to participate by the investigators at the respective study centers.

Pre-assignment

Screening details:

Pts with a med hist of HAE (age 2-13 yrs) were invited for a screening visit. At screening the diagnosis HAE was confirmed via Central lab testing. If the diagnosis was confirmed, pts were eligible for treatment if an acute attack would occur and they presented to study center within 5 hrs of onset of attack. Total: 63 scr, 57 eligible, 20 treated

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment of HAE attack

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:

50 U/kg body weight (with a maximum of 4200 U)

Number of subjects in period 1	Treatment of HAE attack
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Out of the 57 eligible subjects, 20 developed one or more treatments during the recruitment period and were treated. The number of treatments varied due to the number of HAE attacks occurring during this period.

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Age at presentation of first attack			
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)	17	17	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age at presentation of first attack			
Units: years			
median	8.2		
full range (min-max)	5 to 14	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	11	11	

Subject analysis sets

Subject analysis set title	Intention to treat analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The set of patients who received at least one dose of the study medication, and for whom any efficacy data is available.

Reporting group values	Intention to treat analysis set		
Number of subjects	20		
Age categorical			
Age at presentation of first attack			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	 17 3 		
Age continuous			
Age at presentation of first attack			
Units: years median full range (min-max)	 8.2 5 to 14		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Treatment of HAE attack
Reporting group description: -	
Subject analysis set title	Intention to treat analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The set of patients who received at least one dose of the study medication, and for whom any efficacy data is available.

Primary: Time to beginning of relief

End point title	Time to beginning of relief[1]

End point description:

Time to beginning of relief for all attacks is presented.

End point type	Primary

End point timeframe:

Time to beginning of relief of symptoms that showed the response to treatment based on the overall VAS score decrease of ≥ 20 mm from baseline.

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 to show relief of symptoms, which was defined as a reduction of ≥ 20 mm on VAS compared the baseline VAS score. In the result section the median time to beginning of relief in minutes is presented with the 95% CI. No comparison has been against a control or placebo group, so therefore no statistical analyses could be presented.

End point values	Treatment of HAE attack			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Minutes				
median (confidence interval 95%)	60 (60 to 65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to minimal symptoms

End point title	Time to minimal symptoms

End point description:

Time to minimal symptoms for all attacks is presented.

End point type	Secondary

End point timeframe:

Time to minimal symptoms was defined as the time at which the Overall VAS score fell below 20 mm for all locations where VAS Scores were recorded.

End point values	Treatment of HAE attack			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Minutes				
median (confidence interval 95%)	122.5 (120 to 126)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected for eligible patients (n=57), commencing with the signing of the ICF through the last follow-up visit, regardless if treatment was given.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	All treated patients

Reporting group description:

The reported values are based on the treatment-emergent adverse events (TEAE), which are the AEs with an onset at any time between the start of treatment and 97 days after treatment for any treated attack.

Serious adverse events	All treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngeal oedema			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)		
Investigations			
Lymphocyte morphology abnormal			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

Body temperature increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Vascular disorders Pallor subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
General disorders and administration site conditions Feeling cold subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Ear and labyrinth disorders Middle ear effusion subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Eye disorders Eye swelling subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders			

Catarrh subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Pharyngeal oedema subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Pharyngitis streptococcal subjects affected / exposed occurrences (all) Pharyngotonsillitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) tonsilitis	 3 / 20 (15.00%) 3 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 		

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2011	This amendment was implemented in order to ensure consistent evaluation of the VAS and TEQ efficacy parameters, as it was agreed with the FDA for a concurrent study. Furthermore, in order to obtain consistent immungenicity safety data, anti-rabbit IgE antibody testing is added to the immunology test-panel at Day 28. Also, following remarks from Ethics Committees and Competent Authorities, various corrections are implemented.
27 October 2011	This amendment corrects the investigator's score to reflect the more refined analysis of attack locations. It also specifies the analysis of anti-rabbit epithelium IgE, which assessment was added previously.
09 November 2012	This amendment updates the section about sponsor personnel and stipulates that pregnancies have to be reported as SAE; this has been added to the safety section. Also, some (minor) textual corrections have been made.
10 June 2014	The amendment describes administrative changes. The Pharming Project Manager has been changes as well as the Pharmacovigilance contact details.
15 August 2014	This amendment is prepared upon request of the Czech Republic Competent Authorities (SUKL) and includes country specific updates in the sections of blood sampling procedures to ensure compliance with the guidelines, extension of the reasons for withdrawal and the usage of contraception is removed because sexual intercourse at persons until the age of 15 is illegal in the Czech Republic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported