

**Clinical trial results:****A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Period Crossover Study to Evaluate the Efficacy and Safety of Recombinant Human C1 Inhibitor in the Prophylaxis of Angioedema Attacks in Patients with Hereditary Angioedema (HAE)****Summary**

EudraCT number	2014-002839-33
Trial protocol	CZ IT
Global end of trial date	03 May 2016

Results information

Result version number	v1 (current)
This version publication date	24 August 2017
First version publication date	24 August 2017

Trial information**Trial identification**

Sponsor protocol code	C1-3201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02247739
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharming Group N.V.
Sponsor organisation address	Darwinweg 24, Leiden, Netherlands, 2333 CR
Public contact	Anurag Relan, MD, Pharming Group NV, +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	03 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2016
Global end of trial reached?	Yes
Global end of trial date	03 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is:

To evaluate the efficacy of rhC1INH in the prophylaxis of angioedema attacks in patients with HAE.

Protection of trial subjects:

During all treatment periods, patients may receive acute treatment for angioedema attacks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 December 2014
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	Romania: 6
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 8
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	32
EEA total number of subjects	9

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)	28
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject with documented Hereditary Angioedema diagnosis to be included

Pre-assignment

Screening details:

35 subjects were screened, 32 subjects were eligible

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	rhC1INH twice weekly

Arm description:

Subjects administered rhC1INH twice weekly

Arm type	Active comparator
Investigational medicinal product name	rhC1INH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50 U/kg with a maximum of 4200 U to be administered by slow IV injection

Arm title	rhC1INH once weekly
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Arm description:

subjects administered with rhC1INH once and saline once weekly

Arm type	Active comparator
Investigational medicinal product name	rhC1INH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 U/kg with a maximum of 4200 U to be administered by slow IV injection

Arm title	Placebo
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Arm description:

Subjects administered with saline twice weekly

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
dosing equivalent to active

Number of subjects in period 1	rhC1INH twice weekly	rhC1INH once weekly	Placebo
Started	32	32	32
Completed	29	29	28
Not completed	3	3	4
Consent withdrawn by subject	3	3	3
Pregnancy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	rhC1INH twice weekly
Reporting group description: Subjects administered rhC1INH twice weekly	
Reporting group title	rhC1INH once weekly
Reporting group description: subjects administered with rhC1INH once and saline once weekly	
Reporting group title	Placebo
Reporting group description: Subjects administered with saline twice weekly	

Reporting group values	rhC1INH twice weekly	rhC1INH once weekly	Placebo
Number of subjects	32	32	32
Age categorical			
participants aged below 18 participants aged 18-65 participants above 65			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
below 18	1	1	1
age 18-65	28	28	28
above 65	3	3	3
Gender categorical			
Units: Subjects			
Female	26	26	26
Male	6	6	6

Reporting group values	Total		
Number of subjects	32		
Age categorical			
participants aged below 18 participants aged 18-65 participants above 65			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
below 18	1		
age 18-65	28		
above 65	3		
Gender categorical			
Units: Subjects			
Female	26		
Male	6		

Subject analysis sets

Subject analysis set title	rhC1INH twice weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects administered with rhC1INH twice weekly for a 4 week period	
Subject analysis set title	rhC1INH once weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects administered with rhC1INH once weekly and saline once weekly	
Subject analysis set title	Saline twice weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subject administered with Saline twice weekly	

Reporting group values	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly
Number of subjects	29	29	28
Age categorical			
participants aged below 18			
participants aged 18-65			
participants above 65			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
below 18	1	1	1
age 18-65	25	28	25
above 65	3	3	2
Gender categorical			
Units: Subjects			
Female	23	23	22
Male	6	6	6

End points

End points reporting groups

Reporting group title	rhC1INH twice weekly
Reporting group description: Subjects administered rhC1INH twice weekly	
Reporting group title	rhC1INH once weekly
Reporting group description: subjects administered with rhC1INH once and saline once weekly	
Reporting group title	Placebo
Reporting group description: Subjects administered with saline twice weekly	
Subject analysis set title	rhC1INH twice weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects administered with rhC1INH twice weekly for a 4 week period	
Subject analysis set title	rhC1INH once weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects administered with rhC1INH once weekly and saline once weekly	
Subject analysis set title	Saline twice weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subject administered with Saline twice weekly	

Primary: Average number of HAE attacks

End point title	Average number of HAE attacks
End point description: Average number of HAE attacks normalized to a 28 day period	
End point type	Primary
End point timeframe: 28 days	

End point values	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	29	28	
Units: attacks				
number (confidence interval 95%)	2.74 (1.8 to 3.7)	4.36 (3.1 to 5.6)	7.18 (5.8 to 8.6)	

Statistical analyses

Statistical analysis title	number of HAE attacks per 28-day period
Statistical analysis description: The primary efficacy variable was the number of HAE attacks per 28-day period. Attacks that occurred	

during a washout period or during the follow-up period were not included in the analysis. The primary variable was analysed using the Generalized Estimation Equation (GEE). A sensitivity analysis of the primary endpoint was performed in which the data for patients who terminate the study early are imputed.

Comparison groups	rhC1INH twice weekly v rhC1INH once weekly v Saline twice weekly
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	GEE

Notes:

[1] - The null hypothesis to be tested for the primary and other efficacy endpoints is that there are no differences between rhC1INH and saline. The alternative hypothesis is that there are differences between rhC1INH and saline.

Secondary: Adverse events

End point title	Adverse events
End point description:	Treatment Emergent Adverse Events observed in safety population
End point type	Secondary
End point timeframe:	28 days

End point values	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	29	28	
Units: adverse events	10	13	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate

End point title	Response rate
End point description:	Responders are defined as achieving at least 50% reduction in the number of attacks normalized to a 28-day period as compared to the placebo treatment period.
End point type	Secondary
End point timeframe:	28 days

End point values	rhC1INH twice weekly	rhC1INH once weekly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 ^[2]	32 ^[3]		
Units: number of responders	23	13		

Notes:

[2] - 74.2% of subjects achieved reduction of >50% in the number of HAE attacks as compared to placebo

[3] - 41.9% of subjects achieved reduction of >50% in the number of HAE attacks as compared to placebo

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunogenicity

End point title	Immunogenicity
End point description:	Neutralizing antibodies analyzed for patients with confirmed anti-C1INH and anti rhC1INH IgM or IgG antibodies
End point type	Other pre-specified
End point timeframe:	20 weeks

End point values	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	5	2	
Units: number of subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

20 weeks

Adverse event reporting additional description:

Treatment Emergent Adverse Events observed in safety population

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	rhC1INH twice weekly
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Reporting group description:

Subjects administered with rhC1INH twice weekly

Reporting group title	rhC1INH once weekly
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Reporting group description: -

Reporting group title	Saline twice weekly
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Reporting group description: -

Serious adverse events	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	rhC1INH twice weekly	rhC1INH once weekly	Saline twice weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 29 (34.48%)	13 / 29 (44.83%)	8 / 28 (28.57%)
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 5	2 / 29 (6.90%) 2	0 / 28 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 29 (6.90%) 2	0 / 28 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	3 / 29 (10.34%) 3	2 / 28 (7.14%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported