

**Clinical trial results:**

A multi centre, double blind, randomised, placebo controlled crossover study to evaluate the efficacy and tolerability of picotamide in the prophylaxis of migraine in patients presenting with migraine with aura
Summary

EudraCT number	2011-006207-36
Trial protocol	HU
Global end of trial date	12 October 2016

Results information

Result version number	v1 (current)
This version publication date	21 November 2018
First version publication date	21 November 2018
Summary attachment (see zip file)	Clinical study report summary (1. CLINICAL_STUDY_REPORT_PICOTAMIDE_AURA_FINAL_VERSION_1_0_2018_06_07_signed summary.pdf)

Trial information**Trial identification**

Sponsor protocol code	19122011
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Proreo Pharma Innovation AG
Sponsor organisation address	Weierweg 7, Liestal, Switzerland, CH-4410
Public contact	Prof. Klaus Kutz, Proreo Pharma Innovation AG, 41 795432152, klaus.kutz@bluewin.ch
Scientific contact	Prof. Klaus Kutz, Proreo Pharma Innovation AG, 41 795432152, klaus.kutz@bluewin.ch

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	06 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2016
Global end of trial reached?	Yes
Global end of trial date	12 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of picotamide compared to placebo in the reduction of the number of auras in patients with migraine with aura.

Protection of trial subjects:

Patients were permitted to use their usual symptomatic or acute treatment as rescue medication throughout the trial.

Background therapy: -

Evidence for comparator:

A cross-over design with treatment periods of picotamide and placebo substantially improves the power to detect a difference between treatment regimens with a small number of patients compared to a parallel group design and thus a smaller number of patients are needed.

Actual start date of recruitment	11 July 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	Denmark: 27
Country: Number of subjects enrolled	Hungary: 35
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	0
Adults (18-64 years)	62
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 11/July/2012 in Denmark, and on 06/Mar/2013 in Hungary. Last patient last visit took place on 12/Oct/2016.

Pre-assignment

Screening details:

Screening and randomisation could be performed at once. Patients with an established medical history of migraine with aura were considered for the study. During the screening a laboratory test was performed to exclude renal and hepatic dysfunction.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Picotamide

Arm description:

Picotamide 300 mg

Arm type	Experimental
Investigational medicinal product name	picotamide
Investigational medicinal product code	
Other name	Plactidil
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet of 300 mg picotamide two times daily for 12 weeks orally.

Arm title	Placebo
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Arm description:

Placebo 300 mg

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg twice daily

Number of subjects in period 1 ^[1]	Picotamide	Placebo
Started	32	30
Completed	54	53
Not completed	2	8
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	4
Lost to follow-up	-	1
Protocol deviation	-	1
Joined	24	31
Transferred in from other group/arm	24	31

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Crossover design.

Period 2

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

Arms

Arm title	Washout
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Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg twice daily

Number of subjects in period 2	Washout
Started	55
Completed	55

Period 3	
Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst
Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo
Arm description: Placebo 300 mg twice daily	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg twice daily	
Arm title	Picotamide
Arm description: Picotamide 300 mg twice daily	
Arm type	Experimental
Investigational medicinal product name	picotamide
Investigational medicinal product code	
Other name	Plactidil
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet of 300 mg picotamide two times daily for 12 weeks orally.	

Number of subjects in period 3	Placebo	Picotamide
Started	31	24
Completed	29	23
Not completed	2	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups^[1]

Reporting group title	Period 1
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Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Crossover design.

Reporting group values	Period 1	Total	
Number of subjects	62	62	
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)	62	62	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	41.9		
standard deviation	± 13.12	-	
Gender categorical			
Units: Subjects			
Female	55	55	
Male	7	7	
Migraine			
The estimated number of migraine attacks over the last three months before entering the study			
Units: events			
arithmetic mean	14.7		
standard deviation	± 15.1	-	
Headache			
the estimated number of migraine headache over the last three months before entering the study			
Units: events			
arithmetic mean	17.8		
standard deviation	± 16.2	-	
Aura			
the estimated number of auras over the last three months before entering the study			
Units: events			
arithmetic mean	15.7		
standard deviation	± 18.8	-	

End points

End points reporting groups

Reporting group title	Picotamide
Reporting group description:	
Picotamide 300 mg	
Reporting group title	Placebo
Reporting group description:	
Placebo 300 mg	
Reporting group title	Washout
Reporting group description:	
Placebo	
Reporting group title	Placebo
Reporting group description:	
Placebo 300 mg twice daily	
Reporting group title	Picotamide
Reporting group description:	
Picotamide 300 mg twice daily	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This population consists of all patients who are randomized.	
Subject analysis set title	ITT2
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The intention to treat population 2 (ITT2) consists of all patients in ITT, who received at least one dose of study medication during period 1 and period 2 and documented at least one day in the diary during period 1 and period 2.	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients were included into the safety population if they had received at least one drug administration (picotamide or placebo).	
Subject analysis set title	PPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients were included in the per-protocol population (PPP) if they	
<ul style="list-style-type: none">• had met all inclusion criteria;• did not fulfill any exclusion criteria;• had met all inclusion criteria during the study;• did not fulfill any exclusion criteria during the study;• had completed the study in accordance with the protocol.	

Primary: Days with Aura

End point title	Days with Aura
End point description:	
A possible effect of active treatment was evaluated by a comparison between the mean number of auras in sequence A (period 1-2) and sequence B (period 1-2).	
End point type	Primary
End point timeframe:	
During each treatment period	

End point values	Picotamide	Placebo	ITT2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56 ^[1]	60 ^[2]	47	
Units: days				
arithmetic mean (standard deviation)	8.2 (± 9.29)	7.8 (± 8.98)	4.6 (± 5.29)	

Notes:

[1] - Combined with treatment period 2.

[2] - Combined with treatment period 2.

Statistical analyses

Statistical analysis title	Statistical analysis of Days with Aura
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Statistical analysis description:

The statistical analysis of days with aura in the ITT2 showed no treatment effect and no carry-over effect. However, there was a very strong period effect indicating that in the second treatment period the days with aura were significantly lower.

Comparison groups	Picotamide v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA

Secondary: Days with Migraine Headache

End point title	Days with Migraine Headache
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End point description:

A migraine headache day is a calendar day at which a migraine headache started and/or ended. Mean number of migraine headache days in each treatment period.

End point type	Secondary
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End point timeframe:

Per treatment (12 weeks)

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[3]	60 ^[4]		
Units: days				
arithmetic mean (standard deviation)	9.7 (± 8.79)	9.6 (± 10.08)		

Notes:

[3] - Including patients in Treatment period 2.

[4] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Migraine Headache

End point title	Number of Migraine Headache
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End point description:

Mean number of migraine headache attacks in each treatment period.

End point type	Secondary
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End point timeframe:

Treatment period (12 weeks)

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[5]	60 ^[6]		
Units: episodes				
arithmetic mean (standard deviation)	8.3 (± 7.16)	8.2 (± 8.88)		

Notes:

[5] - Including patients in Treatment period 2.

[6] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Days with Headache

End point title	Days with Headache
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End point description:

Mean number of any headache (migraine or not) days in each treatment period

End point type	Secondary
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End point timeframe:

Treatment period (12 weeks)

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[7]	60 ^[8]		
Units: days				
arithmetic mean (standard deviation)	12.7 (± 11.28)	13.0 (± 12.61)		

Notes:

[7] - Including patients in Treatment period 2.

[8] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Auras followed by Headache

End point title	Number of Auras followed by Headache
End point description: Mean number of auras followed by headache in each treatment period.	
End point type	Secondary
End point timeframe: Treatment period (12 weeks)	

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[9]	60 ^[10]		
Units: Episodes				
arithmetic mean (standard deviation)	5.1 (± 5.84)	5.0 (± 6.70)		

Notes:

[9] - Including patients in Treatment period 2.

[10] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Days with Aura and / or Migraine Headache

End point title	Days with Aura and / or Migraine Headache
End point description: Mean number of auras and/or migraine headache during each treatment period.	
End point type	Secondary
End point timeframe: Treatment period(12 weeks)	

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[11]	60 ^[12]		
Units: days				
arithmetic mean (standard deviation)	12.3 (± 10.97)	12.1 (± 11.39)		

Notes:

[11] - Including patients in Treatment period 2.

[12] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Migraine Headache Attacks

End point title	Number of Migraine Headache Attacks
End point description: Mean number of migraine headache attacks in each treatment period.	
End point type	Secondary

End point timeframe:
Treatment period (12 weeks)

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[13]	60 ^[14]		
Units: episodes				
arithmetic mean (standard deviation)	7.4 (± 6.99)	7.3 (± 8.34)		

Notes:

[13] - Including patients in Treatment period 2.

[14] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Days with Consumption of Rescue Medication

End point title	Days with Consumption of Rescue Medication
End point description:	Mean monthly consumption of rescue medication during the last month and the whole of each treatment period from the baseline period to Month 3.
End point type	Secondary
End point timeframe:	Treatment period (12 weeks)

End point values	Picotamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[15]	60 ^[16]		
Units: days				
arithmetic mean (standard deviation)	6.9 (± 7.62)	6.2 (± 7.47)		

Notes:

[15] - Including patients in Treatment period 2.

[16] - Including patients in Treatment period 2.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the period of observation in the study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Safety analysis
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Reporting group description:

Patients receiving at least one dose of IMP were included in the safety analysis

Reporting group title	Picotamide
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Reporting group description:

Patients on picotamide treatment

Reporting group title	Placebo
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Reporting group description:

Patients receiving placebo treatment

Serious adverse events	Safety analysis	Picotamide	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)	1 / 56 (1.79%)	1 / 60 (1.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Inguinal hernia repair			
subjects affected / exposed	1 / 62 (1.61%)	0 / 56 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy	Additional description: Laparoscopic cholecystectomy for cholelithiasis		
subjects affected / exposed	1 / 62 (1.61%)	1 / 56 (1.79%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	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	Safety analysis	Picotamide	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 62 (62.90%)	22 / 56 (39.29%)	17 / 60 (28.33%)
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	7 / 62 (11.29%)	3 / 56 (5.36%)	4 / 60 (6.67%)
occurrences (all)	7	3	4
gastrointestinal reflux disease			
subjects affected / exposed	6 / 62 (9.68%)	4 / 56 (7.14%)	2 / 60 (3.33%)
occurrences (all)	6	4	2
Nausea			
subjects affected / exposed	4 / 62 (6.45%)	4 / 56 (7.14%)	0 / 60 (0.00%)
occurrences (all)	4	4	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 62 (4.84%)	3 / 56 (5.36%)	0 / 60 (0.00%)
occurrences (all)	3	3	0
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 62 (8.06%)	3 / 56 (5.36%)	2 / 60 (3.33%)
occurrences (all)	5	3	2
Pneumonia			
subjects affected / exposed	3 / 62 (4.84%)	2 / 56 (3.57%)	1 / 60 (1.67%)
occurrences (all)	3	2	1

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