Clinical trial results:
Aprepitant in histamine-refractory chronic pruritus: a multicenter, randomized, double-blind, placebo-controlled, cross-over, phase II trial

Summary

EudraCT number	2013-001601-85
Trial protocol	DE
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	08 January 2017
First version publication date	08 January 2017
Summary attachment (see zip file)	APREPRU (ct_result_2013-001601-85(4).pdf)

Trial information

Trial identification

Sponsor protocol code	UKM10_0037

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1140-6701

Notes:

Sponsors

Sponsor organisation name	University Hospital Münster
Sponsor organisation address	Von-Esmach-Str. 58, Münster, Germany, 48149
Public contact	Competence Center Chronic Pruritus, University Hospital Münster, Department of Dermatology, sonja.staender@ukmuenster.de
Scientific contact	Competence Center Chronic Pruritus, University Hospital Münster, Department of Dermatology, sonja.staender@ukmuenster.de

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	08 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of aprepitant relative to placebo in reducing chronic pruritus according to the Patient Global Assessment (PGA) as measured by the Visual Ana-logue Scale (VAS, average itch, visit-obtained)

Protection of trial subjects:

None

Background therapy:

Patients were allowed to use emollients including urea which is known to have antipruritic properties in addition to the trial medication. Any other medication taken for any medical condition had to be documented in the patient`s file. If patients needed systemic rescue medication, cetirizine had to be used and documented in the patient´s file. This was not a drop-out criterion but was analyzed as secondary endpoint.

Evidence for comparator:

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Actual start date of recruitment	30 June 2014
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	Germany: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	46

From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

58 patients were recruited at 5 centers within Germay (Muenster, Gera, Mainz, Berlin, Hannover).

Pre-assignment

Screening details:

67 patients were screened, of which 58 were enrolled.

Period 1

Period 1 title	Baseline
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?	Yes
Arm title	Aprepitant in first period, placebo in second period

Arm description:

The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm A
Investigational medicinal product name	Aprepitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

80mg , once daily

Arm title	Placebo in first period, aprepitant in second period

Arm description:

The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepitant in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm B
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

One capsula daily

Number of subjects in period 1	Aprepitant in first period, placebo in second period	Placebo in first period, aprepitant in second period
Started	30	28
Completed	30	28

Period 2	
Period 2 title	First treatment-period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Aprepritant in first period, placebo in second period

Arm description:

The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm A

No investigational medicinal product assigned in this arm

Arm title	Placebo in first period, aprepritant in second period

Arm description:

The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepritant in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm B

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Aprepritant in first period, placebo in second period	Placebo in first period, aprepritant in second period
Started	30	28
Completed	28	25
Not completed	2	3
Consent withdrawn by subject	2	3

Period 3

Period 3 title	Second treatment-period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Aprepritant in first period, placebo in second period

Arm description:

The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm A

No investigational medicinal product assigned in this arm

Arm title	Placebo in first period, aprepritant in second period

Arm description:

The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepritant in the second treatment-period (daily, 4 weeks).

Arm type	Cross-over arm B

No investigational medicinal product assigned in this arm

Number of subjects in period 3[1]	Aprepritant in first period, placebo in second period	Placebo in first period, aprepritant in second period
Started	28	22
Completed	28	22

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: After the end of treatment-period 1, a two-week wash-out period started. Some patients dropped out during the wash-out period.

Baseline characteristics

Reporting groups	
Reporting group title	Aprepitant in first period, placebo in second period
Reporting group description:	
The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).	
Reporting group title	Placebo in first period, aprepitant in second period
Reporting group description:	
The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepitant in the second treatment-period (daily, 4 weeks).	

Reporting group values	Aprepitant in first period, placebo in second period	Placebo in first period, aprepitant in second period	Total
Number of subjects	30	28	58
Age categorical 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
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	24	46
From 65-84 years	8	4	12
85 years and over	0	0	0
Age continuous Units: years			
median	58.5	58	
inter-quartile range (Q1-Q3)	52 to 65	46 to 61.5	-
Gender categorical Units: Subjects			
Female	12	15	27
Male	18	13	31

End points

End points reporting groups

Reporting group title	Aprepitant in first period, placebo in second period
Reporting group description:	
The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).	
Reporting group title	Placebo in first period, aprepitant in second period
Reporting group description:	
The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepitant in the second treatment-period (daily, 4 weeks).	
Reporting group title	Aprepritant in first period, placebo in second period
Reporting group description:	
The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).	
Reporting group title	Placebo in first period, aprepritant in second period
Reporting group description:	
The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepritant in the second treatment-period (daily, 4 weeks).	
Reporting group title	Aprepritant in first period, placebo in second period
Reporting group description:	
The patients in this arm received aprepitant in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received placebo in the second treatment-period (daily, 4 weeks).	
Reporting group title	Placebo in first period, aprepritant in second period
Reporting group description:	
The patients in this arm received placebo in the first treatment-period (daily, 4 weeks). After a wash-out period (2 weeks), the patients received aprepritant in the second treatment-period (daily, 4 weeks).	

Primary: Primary efficacy endpoint of treatment-period 1 (PE1)

End point title	Primary efficacy endpoint of treatment-period 1 (PE1)[1]
End point description:	
The PE1 was the intra-individual difference of the reported VAS (average itch during the past 24h, ranging from 0= "no itch" to 100="worst imaginable itch") at the beginning and at the end of the treatment-period 1. A negative PE1 therefore means an itch relief during treatment-period 1.	
End point type	Primary
End point timeframe:	
The primary efficacy endpoint PE1 was measured in treatment-period 1.	

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: The primary efficacy analysis was conducted considering CROS(PE)=PE1-PE2.

End point values	Aprepritant in first period, placebo in second period	Placebo in first period, aprepritant in second period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: VAS				
median (inter-quartile range (Q1-Q3))	-19.5 (-26.5 to 1.5)	-21 (-33 to -1)		

Statistical analyses

No statistical analyses for this end point

Primary: Primary efficacy endpoint of treatment-period 2 (PE2)

End point title	Primary efficacy endpoint of treatment-period 2 (PE2)[2]

End point description:

The PE2 was the intra-individual difference of the reported VAS (average itch during the past 24h, ranging from 0= "no itch" to 100="worst imaginable itch") at the beginning and at the end of the treatment-period 2. A negative PE2 therefore means an itch relief during treatment-period 2.

End point type	Primary

End point timeframe:

The primary efficacy endpoint PE2 was measured in treatment-period 2.

Notes:

[2] - 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: The primary efficacy analysis was conducted considering CROS(PE)=PE1-PE2.

End point values	Aprepritant in first period, placebo in second period	Placebo in first period, aprepritant in second period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	22		
Units: VAS				
median (inter-quartile range (Q1-Q3))	-2 (-13.5 to 6)	1.5 (-23 to 20)		

Statistical analyses

No statistical analyses for this end point

Primary: CROS(PE)=PE1-PE2

End point title	CROS(PE)=PE1-PE2

End point description:

The primary efficacy analysis was conducted considering the intra-individual difference of PE1 and PE2, denoted as CROS (PE)= PE1 – PE2.

End point type	Primary

End point timeframe:

CROS(PE) is the difference of PE1 and PE2, which were measured during treatment-period 1 and 2.

End point values	Aprepritant in first period, placebo in second period	Placebo in first period, aprepritant in second period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	22		
Units: VAS				
median (inter-quartile range (Q1-Q3))	-10.5 (-35.5 to 9)	-23.5 (-38 to 14)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis (Intention-to-Treat)

Statistical analysis description:

For each patient, the intra-individual difference CROS(PE) = PE1 – PE2 was calculated. The two arms A (aprepitant in treatment-period 1, placebo in treatment-period 2) and B (placebo in treatment-period 1, aprepitant in treatment-period 2) were compared regarding CROS(PE) by a stratified Wilcoxon-Mann-Whitney test (van Elteren-test) on a two-sided significance level of 5% with strata defined by the patients' atopic/non-atopic predisposition.

Comparison groups	Aprepritant in first period, placebo in second period v Placebo in first period, aprepritant in second period
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.742
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - This was an intention-to-treat analysis that was conducted considering all patients who were randomized (full-analysis set).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first Patient in until last Patient out.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Under aprepitant

Reporting group description:

This reporting group includes all adverse events that occurred in patients in arm A during treatment-period 1 (under aprepitant) and during the wash-out period, and all adverse events that occurred in patients in arm B during and after treatment-period 2 (under aprepitant).

Reporting group title	Under placebo

Reporting group description:

This reporting group includes all adverse events that occurred in patients in arm B during treatment-period 1 (under placebo) and during the wash-out period, and all adverse events that occurred in patients in arm A during and after treatment-period 2 (under placebo).

Serious adverse events	Under aprepitant	Under placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	2 / 54 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Neurodermatitis	Additional description: Exacerbation prurigo nodularis		
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis	Additional description: Chronic tonsillitis		
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	
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: 0.05 %

Non-serious adverse events	Under aprepitant	Under placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 54 (20.37%)	13 / 54 (24.07%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 54 (3.70%)	3 / 54 (5.56%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 54 (5.56%)	1 / 54 (1.85%)	
occurrences (all)	3	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 54 (11.11%)	9 / 54 (16.67%)	
occurrences (all)	6	9	

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