Clinical trial results:
Apremilast as anti-pruritic treatment in patients with prurigo nodularis

Summary

EudraCT number	2016-003018-29
Trial protocol	DK
Global end of trial date	27 February 2019

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020

Trial information

Trial identification

Sponsor protocol code	2016-003018-29

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dept of Dermatology and Allergy, Herlev and Gentofte Hospital
Sponsor organisation address	Gentofte Hospitalsvej 15, Hellerup, Denmark, 2900
Public contact	Dept of Dermatology and Allergy, Herlev and Gentofte Hospital, 0045 38673203, claus.zachariae@regionh.dk
Scientific contact	Dept of Dermatology and Allergy, Herlev and Gentofte Hospital, 0045 38673203, claus.zachariae@regionh.dk

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	01 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2019
Global end of trial reached?	Yes
Global end of trial date	27 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the anti-pruritic effect of apremilast in patients with known PN.
1) Reduction in mean absolute VAS-pruritus score after 12 weeks treatment with apremilast compared to mean VAS-pruritus score before treatment with apremilast

Protection of trial subjects:

This study was established as a pilot study with no placebo controlled group as patients with prurigo nodularis (PN) suffer from severe pruritus. There fore it would be unethical to placebo treat these patients.

Patients were provided with written and oral information of this study and were enrolled when given their written informed consent. The study was designed in accordance to the Helsinki-declaration. Herlev and Gentofte Hospital will ensure that collection and processing of personal data are in compliance with national legislation on data protection and privacy.
Patients were treated with apremilast, which is an approved drug for psoriasis and PsA. The drug is demonstrated to be safe and well tolerated and with low side-effects and is used for patients with psoriasis in the daily clinic at the Department of Dermatology and Allergy, Herlev and Gentofte Hospital.

Background therapy: -

Evidence for comparator:

Single arm. No comparators were used

Actual start date of recruitment	30 June 2017
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	Denmark: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient with moderate to severe PN were recruited from the department of Dermatology and Allergy
Main criteria for inclusion
- > 18 years of age
- PN verified diagnosis by characteristic clinical features
- Moderate to severe PN
- Failure of local steroid and light treatment to control disease and symptoms.

Pre-assignment

Screening details:

Failure to topical therapy and UV therapy
Blood samples, chest x-ray, urin test for pregnancy/infection

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

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

Blinding implementation details:

Not blinded. All participants received the same treatment

Arms

Are arms mutually exclusive?	No
Arm title	Apremilast treatment

Arm description:

apremilast 30 mg x 2 daily, initially a titration period of 6 days. Total treatment period is 12 weeks

Arm type	Single arm
Investigational medicinal product name	apremilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Apremilast was titrated from 10 mg x 1 (day 1), 10 mg x 2 (day 2), 10 + 20 mg (day 3), 20 x 2 mg (day 4), 20 + 30 mg (day 5) to 30 mg x 2 (day 6) corresponding to recommended daily dose for psoriasis treatment. Total treatment period was 12 weeks, with patients administering the medication at home.

Arm title	Baseline pre-treatment

Arm description:

Pre-treatment as advised in guidance dated - EudraCT FAQ v1.4 May 2019: Currently the system cannot accommodate this specific scenario. Hence, you can proceed with a workaround whereby the baseline is considered one group and the end data another group. By doing that you will be able to use the statistical analysis set to report analysis for a single arm.

Arm type	baseline

Investigational medicinal product name	No investigational medicinal product assigned in this arm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Unknown use

Dosage and administration details:

No investigational medicinal product assigned in this arm

Investigational medicinal product name	apremilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Apremilast was titrated from 10 mg x 1 (day 1), 10 mg x 2 (day 2), 10 + 20 mg (day 3), 20 x 2 mg (day 4), 20 + 30 mg (day 5) to 30 mg x 2 (day 6) corresponding to recommended daily dose for psoriasis treatment. Total treatment period was 12 weeks, with patients administering the medication at home.

Number of subjects in period 1	Apremilast treatment	Baseline pre-treatment
Started	10	10
Completed	7	7
Not completed	3	3
Lack of efficacy	3	3

Baseline characteristics

Reporting groups

Reporting group title	overall period

Reporting group description: -

Reporting group values	overall period	Total	
Number of subjects	10	10	
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)	5	5	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	61.7		
standard deviation	± 10.0	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	5	5	

Subject analysis sets

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

Subject analysis set description:
Intervention, apremilast

Reporting group values	Intervention		
Number of subjects	10		
Age categorical 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)	5		

From 65-84 years 85 years and over	5		

Age continuous Units: years			
arithmetic mean	61.7		
standard deviation	± 10.0		
Gender categorical Units: Subjects			
Female	5		
Male	5		

End points

End points reporting groups

Reporting group title	Apremilast treatment
Reporting group description:	
apremilast 30 mg x 2 daily, initially a titration period of 6 days. Total treatment period is 12 weeks	
Reporting group title	Baseline pre-treatment
Reporting group description:	
Pre-treatment as advised in guidance dated - EudraCT FAQ v1.4 May 2019: Currently the system cannot accommodate this specific scenario. Hence, you can proceed with a workaround whereby the baseline is considered one group and the end data another group. By doing that you will be able to use the statistical analysis set to report analysis for a single arm.	
Subject analysis set title	Intervention
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intervention, apremilast	

Primary: VAS-pruritus

End point title	VAS-pruritus
End point description:	
Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in VAS pruritus ≥ 3 points	
End point type	Primary
End point timeframe:	
16 weeks	

End point values	Apremilast treatment	Baseline pre-treatment	Intervention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: VAS-pruritus	10	10	10	

Attachments (see zip file)	Change in VAS pruritus/Fig 2.pptx

Statistical analyses

Statistical analysis title	Descriptive
Statistical analysis description:	
Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in VAS pruritus ≥ 3 points	
Comparison groups	Apremilast treatment v Baseline pre-treatment

Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	= 99999 [2]
Method	N/A

Notes:

[1] - Descriptive

[2] - 99999 = N/A

Secondary: Change in PGA

End point title	Change in PGA

End point description:

Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in in PGA ≥ 2 points

End point type	Secondary

End point timeframe:

16 weeks

End point values	Apremilast treatment	Baseline pre-treatment	Intervention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: 0-4				
number (not applicable)	10	10	10	

Attachments (see zip file)	Change in PGA/Fig 2.pptx

Statistical analyses

Statistical analysis title	descriptive

Statistical analysis description:

descriptive

Comparison groups	Baseline pre-treatment v Apremilast treatment
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	other[3]
P-value	= 99999 [4]
Method	N/A

Notes:

[3] - Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in in PGA ≥ 2 points

[4] - 99999 = N/A

Secondary: PaGA

End point title	PaGA

End point description:

Responders were considered as those receiving the minimally important difference/minimally clinically

important difference at week 12 compared to baseline defined as a difference in PaGA ≥ 2 points.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Apremilast treatment	Baseline pre-treatment	Intervention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: 0-5				
number (not applicable)	10	10	10	

Attachments (see zip file)	Change in PaGA/Fig 2.pptx

Statistical analyses

Statistical analysis title	Descriptive

Statistical analysis description:

Descriptive

Comparison groups	Apremilast treatment v Baseline pre-treatment
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	other[5]
P-value	= 99999 [6]
Method	N/A

Notes:

[5] - Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in PaGA ≥ 2 points.
[6] - 99999 = N/A

Secondary: DLQI

End point title	DLQI

End point description:

Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in DLQI ≥ 4 points

End point type	Secondary

End point timeframe:

16 weeks

End point values	Apremilast treatment	Baseline pre-treatment	Intervention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: 0-30				
number (not applicable)	10	10	10	

Attachments (see zip file)	Change in DLQI/Fig 2.pptx

Statistical analyses

Statistical analysis title	Descriptive

Statistical analysis description:

Descriptive

Comparison groups	Apremilast treatment v Intervention
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	other[7]
P-value	= 99999 [8]
Method	N/A

Notes:

[7] - Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in DLQI ≥ 4 points

[8] - 99999 = N/A

Secondary: PSQI

End point title	PSQI

End point description:

Responders were considered as those receiving the minimally important difference/minimally clinically important difference at week 12 compared to baseline defined as a difference in PSQI ≥ 3 points

End point type	Secondary

End point timeframe:

16 weeks

End point values	Apremilast treatment	Baseline pre-treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: 0-21				
number (not applicable)	10	10		

Statistical analyses

Statistical analysis title	Descriptive

Statistical analysis description:

Descriptive

Comparison groups	Apremilast treatment v Baseline pre-treatment
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	other
P-value	= 9999999 [9]
Method	N/A

Notes:

[9] - 99999 = N/A

Secondary: Cytokine expression

End point title	Cytokine expression

End point description:

Additionally, a secondary endpoint was to evaluate changes in cytokine and chemokine expression detected by real-time quantitative polymerase chain reaction (RT qPCR) analyses.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Apremilast treatment	Baseline pre-treatment	Intervention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	7	7	
Units: various	7	7	7	

Attachments (see zip file)	Change in IL-31/Fig 3.pptx

Statistical analyses

Statistical analysis title	wilcoxon/mann-whitney

Statistical analysis description:

Cytokine and chemokine concentrations at week 4 and week 12 were compared with baseline concentrations by use of Wilcoxon signed rank-test. Concentration of IL-31 at week 4 and week 12 was compared with baseline concentration by use of Mann-Whitney test due to missing data for IL-31. Values of P < 0.05 were considered significant.

Comparison groups	Apremilast treatment v Baseline pre-treatment
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Values of P < 0.05 were considered significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

15-06-2017 to 27-02-2019, baseline, week 2, 4, 12, 16.

Adverse event reporting additional description:

Adverse event information including dates of event (including onset and resolution), event diagnosis and description, severity, assessment of relatedness to apremilast and action taken was collected at visit 2 (baseline) and at each study visit thereafter.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Apremilast

Reporting group description:

Apremilast intervention group. This is a single arm study.

Serious adverse events	Apremilast		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Apremilast		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)		
Cardiac disorders			
Chest pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	5		
General disorders and administration site conditions			

Fever	Additional description: Fever		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	10		
Nausea	Additional description: Nausea		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Restless legs syndrome			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Baseline pre-treatment is provided due to system workaround in single-armed studies (reference: EudraCT FAQ v1.4 May 2019 Item no. 61) 99999 = N/A

Notes: