



Clinical trial results:

A multicenter, open label, single-arm pilot study to evaluate the efficacy and safety of oral apremilast in patients with moderate to severe palmoplantar pustulosis (PPP) (APLANTUS)

Summary

EudraCT number	2016-005122-11
Trial protocol	DE
Global end of trial date	29 August 2019

Results information

Result version number	v1 (current)
This version publication date	04 July 2021
First version publication date	04 July 2021

Trial information

Trial identification

Sponsor protocol code	069-008
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Prof. Dr. Kristian Reich
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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	29 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2019
Global end of trial reached?	Yes
Global end of trial date	29 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate a significant improvement of Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at week 20 compared with baseline in moderate to severe chronic palmoplantar pustulosis under apremilast therapy.

Protection of trial subjects:

Patients were free to discontinue their participation in the study at any time. Withdrawal from the study did not affect or prejudice the patient's further treatment. Patients could be withdrawn from study treatment and assessments at any time, if deemed necessary by the Investigator.

Moreover, to mitigate potential gastrointestinal side effects (primarily mild-to-moderate nausea and diarrhoea), dose titration was implemented in this study in accordance with the Summary of Product Characteristics (SmPC).

Background therapy:

Not applicable.

Evidence for comparator:

The wide spectrum of antiinflammatory actions of apremilast might be important in the therapy of PPP. PPP is characterized by a strong inflammation in lesional skin, in which both the innate and adaptive immune systems are represented. While PPP has great similarities in the cytokine profiles compared to plaque-type psoriasis, including overexpression of IL-17 and TNF- α , neutrophils are more prominent both clinically (pustules) and in histopathology in PPP compared to plaque-type psoriasis.

Apremilast has already proven to be effective in the treatment of plaque-type psoriasis and psoriatic arthritis, and in a sub-analysis also in palmoplantar involvement of plaque-psoriasis. Given the wide overlap of clinical, immunological and histological features of PPP and plaque-type psoriasis in conjunction with the observation that apremilast also effectively targets the innate immune system (e.g. neutrophils) it might be speculated that apremilast could successfully be used in the treatment of PPP.

Actual start date of recruitment	29 November 2018
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	Germany: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	15
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a national study with all patients being included at 5 German sites. Twenty-four patients signed the ICF and were assessed for eligibility, of whom 3 were screening failures. The remaining 21 patients received apremilast treatment. A patient did not complete 20 weeks of treatment and prematurely discontinued the study due to an AE (nausea)

Pre-assignment

Screening details:

Adults with chronic PPP (disease history of at least 6 months of diagnosis), who were eligible for treatment with systemic therapy defined as having PPP inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy, and with chronic moderate to severe PPP defined as patients with a PPPASI ≥ 12 .

Period 1

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

Blinding implementation details:

Not applicable. This was an open-label, single-arm study.

Arms

Arm title	Full analysis set (FAS)
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Arm description:

The full analysis set (FAS) consisted of all patients who received at least one dose of study drug.

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

Dosage and administration details:

Apremilast was taken orally twice daily (except Day 1). Patients received tablets in blister/bottles sufficient for one month. To mitigate potential gastrointestinal side effects (primarily mild-to-moderate nausea and diarrhoea), dose titration was implemented in this study in accordance with the Summary of Product Characteristics (SmPC). A titration pack included tablets of 10, 20 and 30 mg for a period of one month.

During the first 5 days, the dosage was up-titrated. The initial dose on day 1 was 10 mg in the morning; this was increased to 10 mg in the morning and evening on day 2. The evening dose was further increased by 10 mg (to 20 mg) on day 3. On day 4, the morning dose was increased to 20 mg, so that 20 mg was taken twice daily, and on day 5 the evening dose was increased to 30 mg. From Day 6 onwards, patients received the 30 mg dose twice a day. Subsequent packs included only tablets of 30 mg strength.

Number of subjects in period 1	Full analysis set (FAS)
Started	21
Completed	20
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	21	21	
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	6	6	
Age continuous			
Units: years			
arithmetic mean	59.76		
standard deviation	± 9.26	-	
Gender categorical			
Units: Subjects			
Female	16	16	
Male	5	5	
Race			
Units: Subjects			
White	20	20	
Other (Sinti)	1	1	
Highest educational status			
Units: Subjects			
University degree	2	2	
Professional School	5	5	
Secondary school leaving certificate	14	14	
Is the Patient a smoker?			
Units: Subjects			
Non-smoker	2	2	
Ex-smoker	4	4	
Current smoker	15	15	
Current Involvement of scalp			
Units: Subjects			
No	20	20	
Yes	1	1	
Current Involvement of nails			
Units: Subjects			
No	11	11	
Yes	9	9	
Unknown	1	1	
Psoriatic arthritis			
Three patients (14.3%) were previously diagnosed with psoriatic arthritis, although one of these diagnoses was not verified by a rheumatologist.			
Units: Subjects			
No	18	18	
Yes	3	3	

Psoriasis erythrodermica Units: Subjects			
No	21	21	
Yes	0	0	
Psoriasis inversa Units: Subjects			
No	19	19	
Yes	2	2	
Psoriasis pustulosa generalisata Units: Subjects			
No	21	21	
Yes	0	0	
Plaque Psoriasis Units: Subjects			
No	15	15	
Yes	6	6	
Do you suffer from P. vulgaris? Units: Subjects			
No	15	15	
Yes	6	6	
Age at initial diagnosis of PPP Units: years arithmetic mean standard deviation	52.10 ± 13.58	-	
Number of involved Fingernails Units: nails arithmetic mean full range (min-max)	1.22 0.0 to 5.0	-	
Number of involved Toenails Units: nails arithmetic mean full range (min-max)	3.33 0.0 to 9.0	-	

Subject analysis sets

Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description: The per protocol set (PPS) consisted of all patients who received at least one dose of study drug who completed the study with no major protocol violations	
Subject analysis set title	Full Analysis Set - LOCF
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) consisted of all patients who received at least one dose of study drug. Missing values were imputed by the Last Observation Carried Forward (LOCF) method.	

Reporting group values	Per protocol set (PPS)	Full Analysis Set - LOCF	
Number of subjects	20	21	
Age categorical Units: Subjects			
Adults (18-64 years)	14		

From 65-84 years	6		
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Age continuous Units: years arithmetic mean standard deviation	60.15 ± 9.33	±	
Gender categorical Units: Subjects			
Female	15		
Male	5		
Race Units: Subjects			
White	19		
Other (Sinti)	1		
Highest educational status Units: Subjects			
University degree	2		
Professional School	5		
Secondary school leaving certificate	13		
Is the Patient a smoker? Units: Subjects			
Non-smoker	2		
Ex-smoker	4		
Current smoker	14		
Current Involvement of scalp Units: Subjects			
No			
Yes			
Current Involvement of nails Units: Subjects			
No			
Yes			
Unknown			
Psoriatic arthritis			
Three patients (14.3%) were previously diagnosed with psoriatic arthritis, although one of these diagnoses was not verified by a rheumatologist.			
Units: Subjects			
No			
Yes			
Psoriasis erythrodermica Units: Subjects			
No			
Yes			
Psoriasis inversa Units: Subjects			
No			
Yes			
Psoriasis pustulosa generalisata Units: Subjects			
No			

Yes			
Plaque Psoriasis Units: Subjects			
No Yes			
Do you suffer from P. vulgaris? Units: Subjects			
No Yes			
Age at initial diagnosis of PPP Units: years arithmetic mean standard deviation	$\pm$	$\pm$	
Number of involved Fingernails Units: nails arithmetic mean full range (min-max)			
Number of involved Toenails Units: nails arithmetic mean full range (min-max)			

End points

End points reporting groups

Reporting group title	Full analysis set (FAS)
Reporting group description: The full analysis set (FAS) consisted of all patients who received at least one dose of study drug.	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description: The per protocol set (PPS) consisted of all patients who received at least one dose of study drug who completed the study with no major protocol violations	
Subject analysis set title	Full Analysis Set - LOCF
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) consisted of all patients who received at least one dose of study drug. Missing values were imputed by the Last Observation Carried Forward (LOCF) method.	

Primary: PPPASI at week 20

End point title	PPPASI at week 20
End point description: PPPASI score range from 0–72, with higher scores indicating more severe disease.	
End point type	Primary
End point timeframe: PPPASI Score at Baseline and Week 20	

End point values	Full analysis set (FAS)	Per protocol set (PPS)	Full Analysis Set - LOCF	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	20	21 ^[1]	
Units: PPPASI Score				
median (inter-quartile range (Q1-Q3))				
Visit 2 – Baseline	16.50 (14.00 to 19.50)	15.85 (13.95 to 19.85)	16.50 (14.00 to 19.50)	
Visit 5 - End of Study - Week 20	7.65 (4.45 to 10.6)	7.65 (4.45 to 10.60)	8.10 (4.50 to 11.20)	

Notes:

[1] - Missing values were imputed by the Last Observation Carried Forward (LOCF) method

Statistical analyses

Statistical analysis title	Wilcoxon Signed-rank test
Comparison groups	Full analysis set (FAS) v Per protocol set (PPS)
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.0001
Method	Wilcoxon Signed-rank test

Notes:

[2] - At Week 20, there was a significant median percentage reduction from baseline of -57.1% ($p < 0.0001$) in the PPPASI Score

Secondary: PPPASI 50 response

End point title	PPPASI 50 response
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End point description:

Patients achieving a PPPASI 50 response

End point type	Secondary
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End point timeframe:

At Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (Week 20).

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	20		
Units: Subjects				
Visit 3 - Week 4	7	7		
Visit 4 - Week 12	12	12		
Visit 5 - End of Study - Week 20	13	13		

Attachments (see zip file)	Bar chart PPPASI 50 over time (FAS population)/PPPASI 50.png
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Statistical analyses

No statistical analyses for this end point

Secondary: PPPASI 75 response

End point title	PPPASI 75 response
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End point description:

Patients achieving a PPPASI 75 response.

End point type	Secondary
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End point timeframe:

At Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (Week 20).

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	20		
Units: Subjects				
Visit 3 - Week 4	2	2		
Visit 4 - Week 12	6	6		
Visit 5 - End of Study - Week 20	3	3		

Attachments (see zip file)	Bar chart PPPASI 75 over time (FAS population)/PPPASI 75.png
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Statistical analyses

No statistical analyses for this end point

Secondary: DLQI bands (Visit 2 - Baseline)

End point title	DLQI bands (Visit 2 - Baseline)
End point description:	
The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of a disease on the patient's daily life which is also validated for PPP (15). It is a 10-item questionnaire and can be used to assess 6 different aspects: symptoms and feelings, leisure, daily activities, work or school performance, personal relationship and treatment. The DLQI was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. Meaning of DLQI Scores • 0 to 1 = No effect at all on patient's life • 2 to 5 = Small effect on patient's life • 6 to 10 = Moderate effect on patient's life • 11 to 20 = Very large effect on patient's life • 21 to 30 = Extremely large effect on patient's life	
End point type	Secondary
End point timeframe:	
At Visit 2 (Baseline).	

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	19		
Units: Subjects				
0-1 no effect at all patient's life	2	2		
2-5 small effect on patient's life	5	5		
6-10 moderate effect on patient's life	4	4		
11-20 very large effect on patient's life	8	7		
21-30 extremely large effect on patient's life	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: DLQI bands (Visit 4 - Week 12)

End point title	DLQI bands (Visit 4 - Week 12)
End point description:	
The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of a disease on the patient's daily life which is also validated for PPP (15). It is a 10-item questionnaire and can be used to assess 6 different aspects: symptoms and feelings, leisure, daily activities, work or school performance, personal relationship and treatment. The DLQI was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. Meaning of DLQI Scores • 0 to 1 = No effect at all on patient's life • 2 to 5 = Small effect on patient's life • 6 to 10 = Moderate effect on patient's life • 11 to 20 = Very large effect on patient's life • 21 to 30 = Extremely large effect on patient's life	
End point type	Secondary
End point timeframe:	
At Visit 4 (Week 12).	

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Subjects				
0-1 no effect at all patient's life	7	7		
2-5 small effect on patient's life	5	5		
6-10 moderate effect on patient's life	3	3		
11-20 very large effect on patient's life	5	5		
21-30 extremely large effect on patient's life	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: DLQI bands (Visit 5 - End of Study - Week 20)

End point title	DLQI bands (Visit 5 - End of Study - Week 20)
End point description:	
The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of a disease on the patient's daily life which is also validated for PPP (15). It is a 10-item questionnaire and can be used to assess 6 different aspects: symptoms and feelings, leisure, daily activities, work or school performance, personal relationship and treatment. The DLQI was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. Meaning of DLQI Scores • 0 to 1 = No effect at all on patient's life • 2 to 5 = Small effect on patient's life • 6 to 10 = Moderate effect on patient's life • 11 to 20 = Very large effect on patient's life • 21 to 30 = Extremely large effect on patient's life	
End point type	Secondary

End point timeframe:

At Visit 5 (End of Study - Week 20).

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Subjects				
0-1 no effect at all patient's life	8	8		
2-5 small effect on patient's life	4	4		
6-10 moderate effect on patient's life	1	1		
11-20 very large effect on patient's life	6	6		
21-30 extremely large effect on patient's life	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute DLQI

End point title	Absolute DLQI
End point description: Absolute DLQI score by visit.	
End point type	Secondary
End point timeframe: At Visit 2 (Baseline), Visit 4 (Week 12) and Visit 5 (End of Study-Week 20).	

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21 ^[3]	20 ^[4]		
Units: DLQI Score				
median (inter-quartile range (Q1-Q3))				
Visit 2 – Baseline	8.50 (5.00 to 15.50)	8.00 (5.00 to 16.00)		
Visit 4 - Week 12	2.50 (1.00 to 10.50)	2.50 (1.00 to 10.50)		
Visit 5 - End of Study - Week 20	2.00 (1.00 to 13.00)	2.00 (1.00 to 13.00)		

Notes:

[3] - Visit 2 (n=20), Visit 4 (n=20) and Visit 5 (n=19)

[4] - Visit 2 (n=19), Visit 4 (n=20) and Visit 5 (n=19)

Attachments (see zip file)	Box plot of absolute DLQI values over time (FAS)/DLQI Box
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Hand and Feet Physician Global Assessment (H&F PGA)

End point title	Hand and Feet Physician Global Assessment (H&F PGA)
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End point description:

The H&F PGA describes the severity of psoriasis on the hands and/or feet using five categories ranging from 0 (clear) to 4 (severe).

End point type	Other pre-specified
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End point timeframe:

At Visit 2 (Baseline), Visit 3 (Week 4) , Visit 4 (Week 12) and Visit 5 (Week 20)

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20 ^[5]	20		
Units: Subjects				
Visit 2 - 0 clear	0	0		
Visit 2 - 1 almost clear	0	0		
Visit 2 - 2 mild	2	2		
Visit 2 - 3 moderate	19	18		
Visit 2 - 4 severe	0	0		
Visit 3 - 0 clear	0	0		
Visit 3 - 1 almost clear	1	1		
Visit 3 - 2 mild	10	10		
Visit 3 - 3 moderate	9	9		
Visit 3 - 4 severe	0	0		
Visit 4 - 0 clear	0	0		
Visit 4 - 1 almost clear	3	3		
Visit 4 - 2 mild	9	9		
Visit 4 - 3 moderate	8	8		
Visit 4 - 4 severe	0	0		
Visit 5 - 0 clear	1	1		
Visit 5 - 1 almost clear	1	1		
Visit 5 - 2 mild	10	10		
Visit 5 - 3 moderate	8	8		
Visit 5 - 4 severe	0	0		

Notes:

[5] - Except at Visit 2 (n=21)

Attachments (see zip file)

H&F PGA at all assessment times (n=20)/Hand&Feet PGA.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pustules count percent change from baseline

End point title	Pustules count percent change from baseline
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End point description:	
Percentage change from baseline in Pustules count after 20 weeks of treatment with Apremilast	
End point type	Other pre-specified
End point timeframe:	
At Visit 2 (Baseline) and Visit 5 (End of Study - Week 20)	

End point values	Per protocol set (PPS)	Full Analysis Set - LOCF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	21 ^[6]		
Units: percent				
median (inter-quartile range (Q1-Q3))	-79.82 (-100 to -57.33)	-76.3 (-100 to -53.4)		

Notes:

[6] - Missing values were imputed by the Last Observation Carried Forward (LOCF) method

Attachments (see zip file)	Box plot of Pustules count on each visit/Pustules count.PNG
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Statistical analyses

Statistical analysis title	Wilcoxon Signed-rank test
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Statistical analysis description:

Statistical comparison between treatment and baseline values was done based on the Wilcoxon signed-rank test with two-sided p-values <0.05 indicating significance.

Comparison groups	Full Analysis Set - LOCF v Per protocol set (PPS)
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	< 0.001
Method	Wilcoxon Signed-rank test

Notes:

[7] - At Week 20, there was a significant median percentage reduction (Q1, Q3) from baseline in the FAS Population (LOCF) of 76.3% (53.4%, 100%; p<0.001) in the pustules count.

Other pre-specified: Pustules count 50 and 75 response

End point title	Pustules count 50 and 75 response
End point description:	
Patients experiencing a 50% and 75% decrease in Pustules count from baseline	
End point type	Other pre-specified
End point timeframe:	
At Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (End of Study-Week 20).	

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	20		
Units: Subjects				
Pustules count 50: Visit 3 - Week 4	13	14		
Pustules count 50: Visit 4 - Week 12	18	17		
Pustules count 50: Visit 5-End of Study-Week 20	16	16		
Pustules count 75: Visit 3 - Week 4	8	9		
Pustules count 75: Visit 4 - Week 12	14	14		
Pustules count 75: Visit 5-End of Study-Week 20	12	12		

Attachments (see zip file)	Pustules count reaching 50 and 75 response/Pustules count 50
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: VAS discomfort/pain

End point title	VAS discomfort/pain
End point description:	
Visual Analogue Scale (VAS) was used to assess discomfort/pain. The patient was asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represented no discomfort/pain, and the right-hand boundary represented discomfort/pain as severe as can be imagined. The distance from the mark to the left-hand boundary was recorded.	
End point type	Other pre-specified
End point timeframe:	
At Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (End of Study - Week 20).	

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	20		
Units: VAS discomfort/pain				
median (inter-quartile range (Q1-Q3))				
Visit 2 – Baseline	44.0 (11.0 to 67.0)	37.5 (9.0 to 61.0)		
Visit 3 - Week 4	4.0 (0.0 to 19)	3.0 (0.0 to 19.0)		
Visit 4 - Week 12	2.0 (0.0 to 27.0)	1.5 (0.0 to 21.0)		
Visit 5 - End of Study - Week 20	9.0 (3.0 to 61.0)	7.5 (2.5 to 29.5)		

Attachments (see zip file)	Mean change of pain measured with VAS Scale (PPS)/VAS pain.
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: VAS pruritus/itch

End point title	VAS pruritus/itch
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End point description:

Visual Analogue Scale (VAS) was used to assess pruritus/itch. The patient was asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represented no pruritus/itch, and the right-hand boundary represented pruritus/itch as severe as can be imagined. The distance from the mark to the left-hand boundary was recorded.

End point type	Other pre-specified
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End point timeframe:

At Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (End of Study - Week 20).

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	20		
Units: VAS pruritus/itch				
median (inter-quartile range (Q1-Q3))				
Visit 2 - Baseline	31.0 (16.0 to 55.0)	29.5 (12.5 to 49.0)		
Visit 3 - Week 4	2.0 (2.0 to 48.0)	11.0 (2.0 to 39.75)		
Visit 4 - Week 12	25.0 (4.0 to 44.0)	24.0 (3.5 to 37.25)		
Visit 5 - End of Study - Week 20	12.0 (6.0 to 49.0)	11.5 (5.25 to 30.25)		

Attachments (see zip file)	Mean change of pruritus/itch measured with VAS /VAS
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Psoriasis Area and Severity Index (PASI)

End point title	Psoriasis Area and Severity Index (PASI)
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End point description:

PASI score at all assessment times for 6 patients included in the PPS population. The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

End point type	Other pre-specified
End point timeframe:	
At Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (End of Study - Week 20).	

End point values	Per protocol set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: PASI Score				
median (inter-quartile range (Q1-Q3))				
Visit 2 - Baseline	3.85 (1.93 to 5.18)			
Visit 3 - Week 4	2.27 (0.3 to 3.65)			
Visit 4 - Week 12	0.5 (0.0 to 2.35)			
Visit 5-End of Study-Week 20	0.95 (0.0 to 2.28)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Dynamic H&F PGA

End point title	Dynamic H&F PGA
End point description:	
The dynamic H&F PGA describes the global improvement compared with baseline. It relies on the physician's memory of the baseline severity to evaluate the level of alteration. The categories vary between 0 (cleared) and 6 (worse).	
End point type	Other pre-specified
End point timeframe:	
At Visit 3 (Week 4), Visit 4 (Week 12) and Visit 5 (End of Study - Week 20).	

End point values	Per protocol set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects				
Visit 3 - 0 cleared	0			
Visit 3 - 1 excellent	2			
Visit 3 - 2 good	4			
Visit 3 - 3 slight	3			
Visit 3 - 4 unchanged	4			
Visit 3 - 5 fair	7			
Visit 3 - 6 worse	0			
Visit 4 - 0 cleared	0			

Visit 4 - 1 excellent	5			
Visit 4 - 2 good	5			
Visit 4 - 3 slight	2			
Visit 4 - 4 unchanged	2			
Visit 4 - 5 fair	6			
Visit 4 - 6 worse	0			
Visit 5 - 0 cleared	0			
Visit 5 - 1 excellent	5			
Visit 5 - 2 good	7			
Visit 5 - 3 slight	2			
Visit 5 - 4 unchanged	2			
Visit 5 - 5 fair	4			
Visit 5 - 6 worse	0			

Attachments (see zip file)	Dynamic H&F PGA per visit/Dynamic H&F PGA.png
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs from baseline (V2) until the patient's last study visit and all SAEs upon ICF signature (V1) until 30 days after the patient had stopped study participation as well as those SAEs suspected of being related to the IMP at any time thereafter.

Adverse event reporting additional description:

The date of onset, intensity, relationship of the AE to study drug, action(s) taken, seriousness, time course, duration and outcome were recorded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	FAS population
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Reporting group description:

Since the FAS consisted of all patients who received at least one dose of study drug, the FAS additionally served as safety analysis set and was used for analysis of safety endpoints.

Serious adverse events	FAS population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	FAS population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Post procedural swelling			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Ligament sprain	Additional description: No treatment-emergent		

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Surgical and medical procedures			
Artificial crown procedure			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Endodontic procedure			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	7		
Nerve compression			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Tension headache	Additional description: No treatment-emergent		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Abdominal pain			

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Epulis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasal dryness			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Hyperkeratosis			

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Psychiatric disorders Anxiety disorder subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Exostosis subjects affected / exposed occurrences (all) Intervertebral disc disorder subjects affected / exposed occurrences (all) Limb discomfort subjects affected / exposed occurrences (all) Tendonitis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Gastrointestinal infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Respiratory tract infection	Additional description: One event of nasopharyngitis was no treatment-emergent 5 / 21 (23.81%) 6 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1		

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Urinary tract infection	Additional description: No treatment-emergent		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2018	Protocol Final 3.0 (07-Jun-2018) was authorized after the following changes were made: • Change of the sponsor`s address – Prof. Dr. Reich remained being the sponsor as private person although his office address changed • New data manager • New statistician • Correction of the packaging of the study drug (30 mg) • The ICF was updated according to the new General Data Protection Regulation (GDPR). There were no changes in the planned statistical analyses once the Statistical Analysis Plan was finalized and the database was locked.

Notes:

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.

The interpretation of APLANTUS study is limited by the short-term 20-week treatment period and the size of the population.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34077577>