Clinical trial results:
A Randomized, Double Blind, Placebo-controlled, Multi-center, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Prurigo Nodularis who are Inadequately Controlled on Topical Prescription Therapies or When those Therapies are not Advisable

Summary

EudraCT number	2019-003801-90
Trial protocol	FR GB PT HU ES IT
Global end of trial date	22 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	EFC16460

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04202679
WHO universal trial number (UTN)	U1111-1241-8174
Other trial identifiers	STUDY NAME: LIBERTY-PN PRIME2

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

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	20 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of dupilumab on itch response in subjects with prurigo nodularis (PN), inadequately controlled on topical prescription therapies or when those therapies were not advisable.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects continued the background therapy dose regimen as maintained in the parent study or as modified based on Investigator's judgment throughout the study i.e. stable regimen of low to medium potency topical corticosteroids/topical calcineurin inhibitors (TCS/TCI).

Evidence for comparator: -

Actual start date of recruitment	16 January 2020
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	France: 21
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	160
EEA total number of subjects	74

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)	132
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 57 sites in 11 countries. A total of 221 subjects were screened from 16 January 2020 to 24 February 2021, out of which 61 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 160 subjects were randomised in 1:1 ratio to receive study interventions (placebo or dupilumab) by interactive response technology (IRT).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to dupilumab 600 milligrams (mg) (loading dose), subcutaneously (SC) on Day 1 followed by placebo matched to dupilumab 300 mg once every 2 weeks (q2w) for 24 weeks added to background therapy of TCS/TCI at stable dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to dupilumab 300 mg q2w for 24 weeks on top of moisturisers and if applicable low to medium potent TCS/TCI at stable dose.

Arm title	Dupilumab 300 mg Q2W

Arm description:

Subjects received dupilumab at a loading dose of 600 mg, SC on Day 1 followed by dupilumab 300 mg q2w for 24 weeks added to background therapy of TCS/TCI at stable dose.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	SAR231893
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dupilumab 600 mg loading dose SC injection on Day 1 of Week 0 and 300 mg q2w up to Week 24 on top of moisturisers and if applicable low to medium potent TCS/TCI at stable dose.

Number of subjects in period 1	Placebo	Dupilumab 300 mg Q2W
Started	82	78
Treated	82	77
Completed	56	72
Not completed	26	6
Consent withdrawn by subject	23	6
Adverse event, non-fatal	2	-
Poor compliance to protocol	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to dupilumab 600 milligrams (mg) (loading dose), subcutaneously (SC) on Day 1 followed by placebo matched to dupilumab 300 mg once every 2 weeks (q2w) for 24 weeks added to background therapy of TCS/TCI at stable dose.	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received dupilumab at a loading dose of 600 mg, SC on Day 1 followed by dupilumab 300 mg q2w for 24 weeks added to background therapy of TCS/TCI at stable dose.	

Reporting group values	Placebo	Dupilumab 300 mg Q2W	Total
Number of subjects	82	78	160
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	46.7	51.0	
standard deviation	± 15.2	± 15.8	-
Gender categorical			
Units: Subjects			
Female	51	52	103
Male	31	26	57
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	27	25	52
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	5	3	8
White	48	48	96
More than one race	0	1	1
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to dupilumab 600 milligrams (mg) (loading dose), subcutaneously (SC) on Day 1 followed by placebo matched to dupilumab 300 mg once every 2 weeks (q2w) for 24 weeks added to background therapy of TCS/TCI at stable dose.	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received dupilumab at a loading dose of 600 mg, SC on Day 1 followed by dupilumab 300 mg q2w for 24 weeks added to background therapy of TCS/TCI at stable dose.	

Primary: Percentage of Subjects With Greater Than or Equal to (>=) 4 Points Improvement (Reduction) From Baseline in Worst-Itch Numeric Rating Scale (WI-NRS) Scores at Week 12

End point title	Percentage of Subjects With Greater Than or Equal to (>=) 4 Points Improvement (Reduction) From Baseline in Worst-Itch Numeric Rating Scale (WI-NRS) Scores at Week 12
End point description:	
WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. Percentage of subjects with >=4 points improvement (reduction) from baseline in WI-NRS scores at Week 12 is reported in this endpoint. Analysis was performed on intent-to-treat (ITT) population which included all subjects with a treatment kit number allocated and recorded in the IRT database analysed according to the treatment group allocated by randomisation regardless of if treatment kit was used or not.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	22.0	37.2		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo
Statistical analysis description:	
A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when primary endpoint was statistically significant at two-sided 0.05.	
Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0216 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	5

Notes:

[1] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects With >=4 Points Improvement (Reduction) From Baseline in WI-NRS Scores at Week 24

End point title	Percentage of Subjects With >=4 Points Improvement (Reduction) From Baseline in WI-NRS Scores at Week 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. Percentage of subjects with >=4 points improvement (reduction) from baseline in WI-NRS scores at Week 24 is reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	19.5	57.7		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.56
upper limit	22.66

Notes:

[2] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects With Investigator's Global Assessment For Prurigo Nodularis-Stage (IGA PN-S) Scores of 0 or 1 at Week 24

End point title	Percentage of Subjects With Investigator's Global Assessment For Prurigo Nodularis-Stage (IGA PN-S) Scores of 0 or 1 at Week 24

End point description:

IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4 where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. Higher scores indicate severe PN. In this endpoint, percentage of subjects with IGA PN-S score of either 0 (clear) or 1 (almost clear) has been reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

At Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	15.9	44.9		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	9.55

Notes:

[3] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects With Both an Improvement (Reduction) in WI-NRS by >=4 Points and an IGA PN-S Score of 0 or 1 From Baseline at Week 24

End point title	Percentage of Subjects With Both an Improvement (Reduction) in WI-NRS by >=4 Points and an IGA PN-S Score of 0 or 1 From Baseline at Week 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch), higher scores indicated more severity. IGA PN-S assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4 where 0 = clear, 1 = almost clear, 2 =mild, 3 = moderate and 4 = severe. Higher scores indicated greater severity. Percentage of subjects with both an improvement (reduction) in WI-NRS by >=4 Points (from Baseline) and an IGA PN-S score of 0 or 1 were reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	8.5	32.1		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.03
upper limit	18.11

Notes:

[4] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects With IGA PN-S Scores of 0 or 1 at Week 12

End point title	Percentage of Subjects With IGA PN-S Scores of 0 or 1 at Week 12

End point description:

IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4 where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. Higher scores indicate severe PN. In this endpoint, percentage of subjects with IGA PN-S score of either 0 (clear) or 1 (almost clear) has been reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	12.2	25.6		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0194 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	7.52

Notes:

[5] - Threshold of significance at 0.05 level.

Secondary: Percent Change From Baseline in WI-NRS Scores at Week 24

End point title	Percent Change From Baseline in WI-NRS Scores at Week 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. Least squares (LS) means and standard error (SE) were obtained from Analysis of covariance (ANCOVA) model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percent change				
least squares mean (standard error)	-36.18 (± 6.21)	-59.34 (± 6.39)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-23.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.81
upper limit	-12.51

Notes:

[6] - Threshold of significance at 0.05 level.

Secondary: Change From Baseline in Health-related Quality of Life (HRQoL) as Measured by Dermatology Life Quality Index (DLQI) at Week 24

End point title	Change From Baseline in Health-related Quality of Life (HRQoL) as Measured by Dermatology Life Quality Index (DLQI) at Week 24

End point description:

DLQI is developed to measure dermatology specific HRQoL in adult subjects. It comprises of set of 10 questions assessing the impact of skin disease on subject' HRQoL over the previous week. Responses to each question were assessed on a 4-point Likert scale ranged from 0 (not at all) to 3 (very much). Scores from all 10 questions added up to give total DLQI scores ranged from 0 (not at all) to 30 (very much), higher scores indicated more impact on quality of life. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: score on a scale				
least squares mean (standard error)	-6.77 (± 1.18)	-13.16 (± 1.21)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-6.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.42
upper limit	-4.36

Notes:

[7] - Threshold of significance at 0.05 level.

Secondary: Change From Baseline in Skin Pain-NRS at Week 24

End point title	Change From Baseline in Skin Pain-NRS at Week 24

End point description:

Skin Pain-NRS was used to measure skin pain intensity. Subjects were asked daily to rate the intensity of their worst skin pain over the past 24 hours, using a 11-point scale ranging from 0 ("No pain") to 10 ("Worst possible pain"). Higher scores indicated more severity. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: score on a scale				
least squares mean (standard error)	-2.74 (± 0.51)	-4.35 (± 0.53)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [8]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	-0.73

Notes:

[8] - Threshold of significance at 0.05 level.

Secondary: Change From Baseline in Sleep-NRS at Week 24

End point title	Change From Baseline in Sleep-NRS at Week 24

End point description:

Sleep-NRS was used to measure sleep intensity. Subjects were asked to rate their sleep quality on their past night upon awakening, using a 11-point NRS ranging from 0 to 10, where 0 = worst possible sleep and 10 = best possible sleep. Higher scores indicated less severity. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: score on a scale				
least squares mean (standard error)	0.76 (± 0.45)	1.30 (± 0.46)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Dupilumab 300 mg Q2W

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1658 [9]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	1.3

Notes:

[9] - Threshold of significance at 0.05 level.

Secondary: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Week 24

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Week 24

End point description:

HADS is a 14-item self-administered questionnaire that consists of 2 scales, one measuring anxiety (HADS-A), and the other measuring depression (HADS-D). Each subscale comprised of 7 items with a scoring range from 0 (less severity of anxiety and depression) to 21 (greater severity of anxiety and depression symptoms) for each subscale. The total HADS score ranges from 0 (less severity) to 42 (more severity), with a high score indicative of a severe anxiety and/or depression level. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	77		
Units: score on a scale				
least squares mean (standard error)	-2.59 (± 1.03)	-5.55 (± 1.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Probability of Subjects With an Improvement (Reduction) in WI-NRS by >=4 From Baseline at Week 24

End point title	Probability of Subjects With an Improvement (Reduction) in WI-NRS by >=4 From Baseline at Week 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst

imaginable itch). Higher scores indicated more severity. Probability of subjects with an improvement (reduction) in WI-NRS at Week 24 was based on Kaplan-Meier estimates and was reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: probability of subjects				
number (confidence interval 95%)	0.353 (0.250 to 0.457)	0.670 (0.552 to 0.764)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WI-NRS Scores at Weeks 12 and 24

End point title	Change From Baseline in WI-NRS Scores at Weeks 12 and 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	77		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=79,77)	-3.04 (± 0.46)	-4.11 (± 0.47)		
Week 24 (n=74,76)	-3.10 (± 0.53)	-5.05 (± 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in WI-NRS Scores at Weeks 2, 4 and 12

End point title	Percent Change From Baseline in WI-NRS Scores at Weeks 2, 4 and 12

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4 and 12

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	77		
Units: percent change				
least squares mean (standard error)				
Week 2 (n=81,77)	-15.61 (± 3.06)	-17.41 (± 3.15)		
Week 4 (n=81,77)	-22.61 (± 4.00)	-30.09 (± 4.12)		
Week 12 (n=79,77)	-35.83 (± 5.42)	-48.86 (± 5.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in WI-NRS Scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24

End point title	Percent Change From Baseline in WI-NRS Scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percent change				
least squares mean (standard error)				
Week 1 (n=82,78)	-9.49 (± 2.12)	-8.66 (± 2.18)		
Week 2 (n=81,77)	-15.61 (± 3.06)	-17.41 (± 3.15)		
Week 3 (n=81,77)	-20.44 (± 3.66)	-25.26 (± 3.77)		
Week 4 (n=81,77)	-22.61 (± 4.00)	-30.09 (± 4.12)		
Week 5 (n=81,77)	-25.21 (± 4.21)	-34.41 (± 4.33)		
Week 6 (n=80,77)	-27.87 (± 4.33)	-36.98 (± 4.46)		
Week 7 (n=78,76)	-28.99 (± 4.69)	-39.30 (± 4.84)		
Week 8 (n=79,77)	-30.45 (± 4.56)	-41.32 (± 4.70)		
Week 9 (n=79,77)	-34.86 (± 4.89)	-47.08 (± 5.04)		
Week 10 (n=78,76)	-32.90 (± 5.04)	-44.65 (± 5.20)		
Week 11 (n=79,77)	-34.64 (± 5.25)	-45.98 (± 5.41)		
Week 12 (n=79,77)	-35.83 (± 5.42)	-48.86 (± 5.59)		
Week 13 (n=79,77)	-34.49 (± 5.69)	-48.32 (± 5.86)		
Week 14 (n=79,77)	-36.60 (± 5.71)	-50.67 (± 5.88)		
Week 15 (n=79,77)	-35.96 (± 5.74)	-51.89 (± 5.91)		
Week 16 (n=77,77)	-37.80 (± 5.74)	-54.36 (± 5.91)		
Week 17 (n=77,77)	-39.15 (± 5.98)	-55.95 (± 6.15)		
Week 18 (n=77,77)	-40.38 (± 6.15)	-56.80 (± 6.32)		
Week 19 (n=76,77)	-40.03 (± 6.05)	-57.75 (± 6.23)		
Week 20 (n=74,77)	-36.12 (± 5.94)	-56.80 (± 6.10)		
Week 21 (n=74,76)	-36.43 (± 6.16)	-56.91 (± 6.34)		
Week 22 (n=74,76)	-37.34 (± 6.19)	-58.78 (± 6.33)		
Week 23 (n=73,75)	-36.87 (± 6.19)	-59.43 (± 6.32)		
Week 24 (n=74,76)	-36.18 (± 6.21)	-59.34 (± 6.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement (Reduction) in WI-NRS >=4 Points From Baseline at Week 4

End point title	Percentage of Subjects With Improvement (Reduction) in WI-NRS >=4 Points From Baseline at Week 4

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. Percentage of subjects with improvement (Reduction) in WI-NRS scale by >=4 Points at Week 4 is reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)	7.3	16.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving >=4 Points Improvement (Reduction) From Baseline in WI-NRS Scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24

End point title	Percentage of Subjects Achieving >=4 Points Improvement (Reduction) From Baseline in WI-NRS Scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24

End point description:

WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated more severity. Percentage of subjects achieving >=4 points improvement (reduction) from Baseline in WI-NRS scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 is reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)				
Week 1	1.2	1.3		
Week 2	1.2	5.1		
Week 3	6.1	12.8		
Week 4	7.3	16.7		
Week 5	4.9	17.9		
Week 6	13.4	23.1		
Week 7	15.9	24.4		
Week 8	14.6	28.2		
Week 9	24.4	32.1		
Week 10	18.3	32.1		
Week 11	17.1	33.3		
Week 12	22.0	37.2		
Week 13	19.5	39.7		
Week 14	22.0	39.7		
Week 15	20.7	44.9		
Week 16	19.5	44.9		
Week 17	23.2	47.4		
Week 18	24.4	48.7		
Week 19	23.2	51.3		
Week 20	20.7	51.3		
Week 21	20.7	48.7		
Week 22	22.0	50.0		
Week 23	20.7	55.1		
Week 24	19.5	57.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Onset of Action Based on Change From Baseline in WI-NRS at Week 4

End point title	Onset of Action Based on Change From Baseline in WI-NRS at Week 4

End point description:

Onset of action was defined as the first $p<0.05$ difference from placebo in the weekly average WI-NRS that remained significant at subsequent measurements. WI-NRS is a validated measure of itch severity. Subjects were asked daily to rate the intensity of their worst pruritus (itch) over the past 24 hours, using a 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). Higher scores indicated greater severity. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	77		
Units: score on a scale				
least squares mean (standard error)	-1.94 (± 0.33)	-2.55 (± 0.34)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo
Comparison groups	Placebo v Dupilumab 300 mg Q2W
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037 [10]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.04

Notes:

[10] - Threshold of significance was <0.05.

Secondary: Percentage of Subjects With Investigator's Global Assessment for PN-Stage (IGA PN-S) Score of 0 or 1 at Weeks 4 and 8

End point title	Percentage of Subjects With Investigator's Global Assessment for PN-Stage (IGA PN-S) Score of 0 or 1 at Weeks 4 and 8

End point description:

IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4: where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. Higher scores indicate severe PN. In this endpoint, percentage of subjects with IGA PN-S score of either 0 (clear) or 1 (almost clear) has been reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

At Weeks 4 and 8

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)				
Week 4	6.1	7.7		
Week 8	9.8	15.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IGA PN-S Scores at Weeks 4, 8, 12, and 24

End point title	Change From Baseline in IGA PN-S Scores at Weeks 4, 8, 12, and 24

End point description:

IGA PN-S is an instrument used to assess the overall number and thickness of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4: where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. Higher scores indicate severe PN. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, and 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: score on a scale				
least squares mean (standard error)				
Week 4 (n=80,77)	-0.54 (± 0.13)	-0.69 (± 0.13)		
Week 8 (n=76,76)	-0.79 (± 0.17)	-1.19 (± 0.17)		
Week 12 (n=78,77)	-0.86 (± 0.18)	-1.47 (± 0.18)		
Week 24 (n=74,77)	-1.07 (± 0.20)	-2.03 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Investigator's Global Assessment for PN-Activity (IGA PN-A) Score of 0 or 1 at Weeks 4, 8, 12 and 24

End point title	Percentage of Subjects With Investigator's Global Assessment for PN-Activity (IGA PN-A) Score of 0 or 1 at Weeks 4, 8, 12 and 24

End point description:

The IGA PN-A is an instrument used to assess the overall activity of PN lesions at a given time point, as determined by the investigator. It consists of a 5-point scale ranging from 0 to 4: where 0 = clear (0% nodules showing excoriations/crusts), 1 = almost clear (up to 10% nodules showing excoriations/crusts), 2 = mild (11-25% nodules showing excoriations/crusts), 3 = moderate (26-75% nodules showing excoriations/crusts) and 4 = severe (76-100% of nodules showing excoriations/crusts). Higher scores indicate severe PN. In this endpoint, percentage of subjects with IGA PN-A score of either 0 (clear) or 1 (almost clear) has been reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

At Weeks 4, 8, 12 and 24

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	78		
Units: percentage of subjects				
number (not applicable)				
Week 4	4.9	14.1		
Week 8	15.9	23.1		
Week 12	19.5	42.3		
Week 24	18.3	51.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQoL, as Measured by DLQI at Week 12

End point title	Change From Baseline in HRQoL, as Measured by DLQI at Week 12

End point description:

DLQI is developed to measure dermatology specific HRQoL in adult subjects. It comprises of set of 10 questions assessing the impact of skin disease on subjects' HRQoL over the previous week. Responses to each question were assessed on a 4-point Likert scale which ranged from 0 (not at all) to 3 (very much). Scores from all 10 questions added up to give total DLQI scores ranged from 0 (not at all) to 30 (very much), higher scores indicated more impact on quality of life. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: score on a scale				
least squares mean (standard error)	-7.05 (± 1.12)	-12.07 (± 1.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily have to have a causal relationship with the treatment. Serious adverse events (SAEs) was defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the treatment-emergent (TE) period (time from the first investigational medicinal product [IMP] administration to the last IMP administration + 14 weeks). Analysis was performed on safety population which included all subjects who received at least 1 dose of study intervention analysed according to the intervention actually received.

End point type	Secondary

End point timeframe:

From the first IMP administration to the last IMP administration + 14 weeks (i.e., up to 36 weeks)

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	77		
Units: subjects				
TEAEs	47	47		
TESAEs	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent and Treatment Boosted Antidrug Antibodies (ADA)

End point title	Number of Subjects With Treatment-emergent and Treatment Boosted Antidrug Antibodies (ADA)

End point description:

ADA response was categorised as: Treatment emergent and Treatment-boosted. Treatment emergent ADAs were defined as a subject with no positive assay response at baseline but with a positive assay response during the entire TEAE period. Treatment boosted ADAs: defined as subjects with a positive ADA assay response at baseline and with at least a 4-fold increase in titer compared to baseline during the TE period (time from the first IMP administration to the last IMP administration + 14 weeks). Titer values were defined as low titer (< 1,000); moderate (1,000 <= titer <=10,000) and high titer (> 10,000). Analysis was performed on ADA population which included all subjects who received at least one dose of the study drug and had at least one non missing ADA result after first dose of study drug. Subjects were analysed according to the intervention actually received.

End point type	Secondary

End point timeframe:

From the first IMP administration to the last IMP administration + 14 weeks (i.e., up to 36 weeks)

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	76		
Units: subjects				
Treatment-emergent ADAs	1	7		
Treatment-boosted ADAs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first IMP administration to the last IMP administration + 14 weeks (i.e., up to 36 weeks)

Adverse event reporting additional description:

Reported AEs were TEAEs that developed/worsened in grade or became serious during TE period (defined as the time from the first IMP administration to the last IMP administration + 14 weeks). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to dupilumab 600 mg (loading dose), SC on Day 1 followed by placebo matched to dupilumab 300 mg q2w for 24 weeks added to background therapy of TCS/TCI at stable dose.

Reporting group title	Dupilumab 300 mg Q2W

Reporting group description:

Subjects received dupilumab at a loading dose of 600 mg, SC on Day 1 followed by dupilumab 300 mg q2w for 24 weeks added to background therapy of TCS/TCI at stable dose.

Serious adverse events	Placebo	Dupilumab 300 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 82 (4.88%)	2 / 77 (2.60%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cutaneous T-Cell Lymphoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Granular Lymphocytosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			

subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda Equina Syndrome			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator Cuff Syndrome			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pelvic Inflammatory Disease			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
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: 5 %

Non-serious adverse events	Placebo	Dupilumab 300 mg Q2W	
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 82 (12.20%)	11 / 77 (14.29%)	
Injury, poisoning and procedural complications Accidental Overdose subjects affected / exposed occurrences (all)	5 / 82 (6.10%) 5	4 / 77 (5.19%) 4	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 82 (6.10%) 9	4 / 77 (5.19%) 4	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 82 (0.00%) 0	4 / 77 (5.19%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2020	Following changes were made: added "proportion of subjects with Investigator's Global Assessment 0 or 1 score for PN-Stage (IGA PN-S) at Week 24" as another key secondary endpoint; corrected rescue medication use start date to Day 1 (Visit 2); removed the endpoint "Change from baseline in PAS total score at Week 4, Week 8, Week 12, and Week 24" in exploratory endpoint and modified exploratory endpoint regarding the healed lesions from PAS questionnaire analysis; broke out secondary endpoints with multiple measuring timepoints into individual endpoints; updated inclusion and exclusion criteria; clarified the use of non-investigational medicinal products and rescue medication; clarified permitted and prohibited concomitant medications; added that a pre-specified algorithm would be used to classify rescue and a blinded review of all post-baseline medications, based on medical judgment, would be performed to adjudicate rescue; clarified the treatment discontinuation criteria regarding the missing doses; updated assessments and procedures to describe alternative temporary mechanism that could be implemented in the study conduct in case of pandemic requiring public health emergency e.g., Coronavirus Disease-19 (COVID-19); updated the adverse event of special interest (AESI) "any type of conjunctivitis or blepharitis (severe or serious)" to "any severe type of conjunctivitis or blepharitis"; added the sensitivity analysis for secondary endpoints information, and separated key secondary endpoints in a different row; added covariate "baseline antidepressant use (yes or no)" to primary and secondary endpoint analyses; updated section other analyses; updated the unblinding plan to "Unblinding plan is not applicable for this study"; removed the description about false positivity; added "tetranor PGDM" into urinalysis; updated the AE and SAE recording; removed the "Acceptable methods" in contraception guidance; added the copyright information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported