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	2019-003774-41
Trial protocol	FR HU
Global end of trial date	03 February 2022

Results information

Result version number	v1 (current)
This version publication date	17 February 2025
First version publication date	19 February 2023

Trial information

Trial identification

Sponsor protocol code	EFC16459

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04183335
WHO universal trial number (UTN)	U1111-1241-8153

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	03 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2022
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: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2019
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: 3
Country: Number of subjects enrolled	Argentina: 21
Country: Number of subjects enrolled	China: 15
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	151
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	117
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 58 active sites in 8 countries. A total of 200 subjects were screened from 12 December 2019 to 11 May 2021, out of which 49 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 151 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 topical corticosteroids/topical calcineurin inhibitors (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	76	75
Treated	75	75
Completed	63	72
Not completed	13	3
Adverse event	1	-
Withdrawal by subject	12	3

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 topical corticosteroids/topical calcineurin inhibitors (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	76	75	151
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	51.1	49.2	
standard deviation	± 15.8	± 17.4	-
Gender categorical			
Units: Subjects			
Female	48	52	100
Male	28	23	51
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2	3	5
Asian	25	29	54
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	8	11
White	45	35	80
More than one race	0	0	0
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 topical corticosteroids/topical calcineurin inhibitors (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 Improvement (Reduction) in Worst Itch Numeric Rating Scale (WI-NRS) by Greater Than or Equal to (>=) 4 From Baseline to Week 24

End point title	Percentage of Subjects With Improvement (Reduction) in Worst Itch Numeric Rating Scale (WI-NRS) by Greater Than or Equal to (>=) 4 From Baseline to 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 improvement (reduction) in WI-NRS scores by >=4 from Baseline to Week 24 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 and were 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 24	

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of subjects				
number (not applicable)	18.4	60.0		

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 are reported and continued when primary endpoint was statistically significant at two-sided 0.05.	
Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.78
upper limit	15.41

Notes:

[1] - Threshold of significance at 0.05.

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 prurigo nodularis (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	76	75		
Units: percentage of subjects				
number (not applicable)	18.4	48.0		

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 are reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	8.98

Notes:

[2] - Threshold of significance at 0.05.

Secondary: Percentage of Subjects With Both an Improvement (Reduction) in WI-NRS by >=4 Points and an IGA PN-S Scores 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 Scores 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 scores by >=4 Points (from Baseline) and an IGA PN-S scores 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	76	75		
Units: percentage of subjects				
number (not applicable)	9.2	38.7		

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 are reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	19.05

Notes:

[3] - Threshold of significance at 0.05.

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

End point title	Percent Change From Baseline in WI-NRS 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 evaluable 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	66	75		
Units: percent change				
least squares mean (standard error)	-22.22 (± 5.74)	-48.89 (± 5.61)		

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 are reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-26.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.44
upper limit	-14.9

Notes:

[4] - Threshold of significance at 0.05.

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

End point title	Change From Baseline in Health-Related Quality of Life (HRQoL) 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 subjects' HRQoL over the previous week. Responses to each question were assessed on a scale of 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 evaluable 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	69	75		
Units: score on a scale				
least squares mean (standard error)	-5.77 (± 1.05)	-11.97 (± 1.02)		

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 are reported and continued when endpoint measure was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-6.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.34
upper limit	-4.05

Notes:

[5] - Threshold of significance at 0.05.

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 evaluable 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	66	75		
Units: score on a scale				
least squares mean (standard error)	-2.16 (± 0.44)	-4.33 (± 0.43)		

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 are reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.07
upper limit	-1.28

Notes:

[6] - Threshold of significance at 0.05.

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 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 evaluable 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	69	75		
Units: score on a scale				
least squares mean (standard error)	-2.02 (± 0.94)	-4.62 (± 0.93)		

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 are reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082 [7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.52
upper limit	-0.67

Notes:

[7] - Threshold of significance at 0.05.

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

End point title	Probability of Subjects With an Improvement (Reduction) in WI-NRS Scores 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 scores 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	76	75		
Units: probability of subjects				
number (confidence interval 95%)	0.363 (0.253 to 0.473)	0.667 (0.548 to 0.761)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in WI-NRS Scores at Week 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 evaluable 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	72	75		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=72,75)	-1.84 (± 0.38)	-3.87 (± 0.38)		
Week 24 (n=66,75)	-2.28 (± 0.43)	-4.56 (± 0.42)		

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 evaluable 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	75	75		
Units: percent change				
least squares mean (standard error)				
Week 2 (n=75,75)	-7.98 (± 3.70)	-13.57 (± 3.64)		
Week 4 (n=75,75)	-9.09 (± 4.07)	-22.23 (± 4.00)		
Week 12 (n=72,75)	-17.05 (± 5.31)	-41.05 (± 5.21)		

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 evaluable for this endpoint.

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	76	75		
Units: percent change				
least squares mean (standard error)				
Week 1 (n=76,75)	-5.77 (± 2.24)	-6.68 (± 2.21)		
Week 2 (n=75,75)	-7.98 (± 3.70)	-13.57 (± 3.64)		
Week 3 (n=75,75)	-9.27 (± 3.92)	-17.67 (± 3.86)		
Week 4 (n=75,75)	-9.09 (± 4.07)	-22.23 (± 4.00)		
Week 5 (n=74,74)	-8.49 (± 4.43)	-23.87 (± 4.36)		
Week 6 (n=74,75)	-10.56 (± 4.79)	-26.94 (± 4.71)		
Week 7 (n=73,75)	-12.22 (± 5.02)	-29.20 (± 4.93)		
Week 8 (n=73,75)	-13.78 (± 5.06)	-32.51 (± 4.97)		
Week 9 (n=72,75)	-15.34 (± 5.14)	-34.26 (± 5.03)		
Week 10 (n=72,75)	-16.32 (± 5.12)	-36.96 (± 5.00)		
Week 11 (n=73,75)	-16.71 (± 5.35)	-38.06 (± 5.22)		
Week 12 (n=72,75)	-17.05 (± 5.31)	-41.05 (± 5.21)		
Week 13 (n=73,75)	-17.66 (± 5.35)	-41.23 (± 5.26)		
Week 14 (n=73,75)	-18.64 (± 5.40)	-40.55 (± 5.30)		
Week 15 (n=72,75)	-19.69 (± 5.51)	-42.37 (± 5.42)		
Week 16 (n=71,75)	-18.10 (± 5.54)	-43.29 (± 5.44)		
Week 17 (n=71,75)	-19.06 (± 5.62)	-42.33 (± 5.52)		

Week 18 (n=71,75)	-19.93 (± 5.75)	-43.27 (± 5.65)		
Week 19 (n=70,74)	-20.99 (± 5.80)	-43.35 (± 5.69)		
Week 20 (n=69,75)	-19.90 (± 5.83)	-43.79 (± 5.72)		
Week 21 (n=68,75)	-20.51 (± 5.80)	-44.85 (± 5.69)		
Week 22 (n=68,75)	-23.30 (± 5.90)	-44.84 (± 5.78)		
Week 23 (n=68,75)	-23.08 (± 5.79)	-48.65 (± 5.68)		
Week 24 (n=66,75)	-22.22 (± 5.74)	-48.89 (± 5.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement (Reduction) in WI-NRS Scores >=4 Points From Baseline at Week 12

End point title	Percentage of Subjects With Improvement (Reduction) in WI-NRS Scores >=4 Points From Baseline 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 improvement (reduction) in WI-NRS score by >=4 from Baseline to Week 12 is reported in this endpoint. Analysis was performed on ITT population.

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	76	75		
Units: percentage of subjects				
number (not applicable)	15.8	44.0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Improvement (Reduction) in WI-NRS Scores >=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 scores 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	76	75		
Units: percentage of subjects				
number (not applicable)	3.9	18.7		

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:

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	76	75		
Units: percentage of subjects				
number (not applicable)				
Week 1	0	4.0		
Week 2	2.6	10.7		
Week 3	3.9	12.0		

Week 4	3.9	18.7		
Week 5	5.3	21.3		
Week 6	6.6	33.3		
Week 7	7.9	29.3		
Week 8	10.5	33.3		
Week 9	13.2	38.7		
Week 10	10.5	40.0		
Week 11	14.5	44.0		
Week 12	15.8	44.0		
Week 13	13.2	50.7		
Week 14	19.7	45.3		
Week 15	18.4	52.0		
Week 16	17.1	50.7		
Week 17	21.1	50.7		
Week 18	21.1	54.7		
Week 19	22.4	54.7		
Week 20	21.1	54.7		
Week 21	18.4	56.0		
Week 22	22.4	56.0		
Week 23	19.7	58.7		
Week 24	18.4	60.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Onset of Action Based on Change From Baseline in WI-NRS Scores at Week 3

End point title	Onset of Action Based on Change From Baseline in WI-NRS Scores at Week 3

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. LS means and SE were obtained from ANCOVA model. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 3

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	75		
Units: score on a scale				
least squares mean (standard error)	-1.10 (± 0.27)	-1.80 (± 0.26)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo
Comparison groups	Dupilumab 300 mg Q2W v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.15

Notes:

[8] - Threshold of significance at <0.05 level.

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

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

End point values	Placebo	Dupilumab 300 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of subjects				
number (not applicable)				
Week 4	1.3	9.3		
Week 8	3.9	16.0		
Week 12	11.8	32.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IGA PN-S Scores of 0 and 1 at Weeks 4, 8, 12, and 24

End point title	Change From Baseline in IGA PN-S Scores of 0 and 1 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 evaluable 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	74	75		
Units: score on a scale				
least squares mean (standard error)				
Week 4 (n=70,74)	-0.15 (± 0.10)	-0.44 (± 0.10)		
Week 8 (n=72,72)	-0.29 (± 0.13)	-0.79 (± 0.13)		
Week 12 (n=74,75)	-0.52 (± 0.15)	-1.13 (± 0.15)		
Week 24 (n=69,75)	-0.62 (± 0.17)	-1.59 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Investigator's Global Assessment for PN-Activity (IGA PN-A) 0 or 1 Score 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	76	75		
Units: percentage of subjects				
number (not applicable)				
Week 4	3.9	10.7		
Week 8	3.9	22.7		
Week 12	14.5	34.7		
Week 24	19.7	60.0		

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 scale of 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 evaluable 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	74	75		
Units: score on a scale				
least squares mean (standard error)	-5.67 (± 0.90)	-10.95 (± 0.89)		

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 (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 and 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	75	75		
Units: subjects				
TEAEs	47	53		
TESAEs	8	5		

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 intervention and had at least one non-missing ADA result after first dose of IMP. 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	67	68		
Units: subjects				
Treatment-emergent ADAs	3	8		
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	8 / 75 (10.67%)	5 / 75 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's Disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary Thyroid Cancer			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol Poisoning			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal Ulcer Perforation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory Bowel Disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteritis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Neurodermatitis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (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			
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
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	15 / 75 (20.00%)	14 / 75 (18.67%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	2 / 75 (2.67%)	5 / 75 (6.67%)	
occurrences (all)	2	5	
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 6	4 / 75 (5.33%) 9	
Skin and subcutaneous tissue disorders Neurodermatitis subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 8	2 / 75 (2.67%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	4 / 75 (5.33%) 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, permitted and prohibited concomitant medications and rescue medication; 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 prostaglandin D2 metabolite" into urinalysis; updated the AE and SAE recording; removed the "Acceptable methods" in contraception guidance; added the copyright information.
21 October 2021	Following changes were made: promoted "proportion of subjects with improvement (reduction) in WI-NRS by >= 4 from Baseline to Week 24 as primary endpoint and moved "proportion of subjects with improvement (reduction) in WI-NRS by >= 4 from Baseline to Week 12" to a secondary endpoint. Updated sample size calculation based on the observed effect sizes from EFC16460. Updated the primary analysis considerations to Week 24 timepoint. Updated Week 24 timepoint as the primary endpoint. Removed the sentence "A key secondary endpoint will be the responder analyses of itch improvement of at least 4 points at Week 24." as it was now the primary endpoint, and provided rationale for choosing the primary endpoint timepoint at Week 24 with the following language: "The timing of the primary assessment, i.e., at Week 24, was based on the results of the primary analysis of EFC16460, showing that the effect of dupilumab over time showed continuous improvement after Week 12 across all endpoints, with a similar time course of improvement in both itch and lesion endpoints through at least Week 24. Since improvement of itch and lesions may occur prior to Week 24, responder analyses assessments will be performed at earlier time points as well, starting at Week 2 for itch, and Week 4 for lesions." Specified that the rationale for a 24-week duration of the trial was an appropriate duration based on data observed from EFC16460 and removed references to atopic dermatitis trials. Reflected that the primary endpoint timepoint was Week 24. Removed the the possibility of re-evaluating the timing of the primary database lock of EFC16459 based on the observed treatment effect size in EFC16460, that was added per Amendment 02 and consequently removed the 2 populations (ITT-Week 12 and ITT-Week 24) that were added per Amendment 02. Minor editorial and formatting changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported