Clinical trial results:
A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2014-001198-15
Trial protocol	EE DE ES FI DK BG
Global end of trial date	11 February 2016

Results information

Result version number	v2 (current)
This version publication date	27 February 2020
First version publication date	08 March 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	R668-AD-1334

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02277743
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: SOLO 1

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States,
Public contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.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	15 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult subjects with moderate-to-severe atopic dermatitis (AD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 106
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	United States: 238
Country: Number of subjects enrolled	Canada: 48
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Estonia: 54
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 124
Worldwide total number of subjects	671
EEA total number of subjects	265

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)	639
From 65 to 84 years	31
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 countries between 28 Oct 2014 and 12 Feb 2016. A total of 917 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 917 subjects, 671 were randomized and 669 were treated in the study. Subjects were randomize d in 1:1:1 ratio to receive dupilumab 300 mg once weekly (qw), dupilumab 300 mg every 2 weeks (q2w) or placebo qw.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Dupilumab 300 mg q2w

Arm description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668; SAR231893
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Dupilumab 300 mg qw

Arm description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15.

Arm type	Experimental

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668; SAR231893
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Number of subjects in period 1	Placebo	Dupilumab 300 mg q 2w	Dupilumab 300 mg qw
Started	224	224	223
Treated	223	223	223
Completed	184	208	197
Not completed	40	16	26
Adverse event	10	6	6
Other than specified	18	5	16
Protocol deviation	1	1	1
Lack of efficacy	11	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg qw
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15.	

Reporting group values	Placebo	Dupilumab 300 mg q 2w	Dupilumab 300 mg qw
Number of subjects	224	224	223
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	39.5	39.8	39.3
standard deviation	± 13.91	± 14.68	± 14.39
Gender categorical Units: Subjects			
Female	106	94	81
Male	118	130	142
Ethnicity Units: Subjects			
Not Hispanic or Latino	212	215	212
Hispanic or Latino	11	6	8
Not reported or missing	1	3	3
Race Units: Subjects			
White	146	155	149
Black or African American	16	10	20
Asian	56	54	51
Unknown or Not Reported	6	5	3
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
More than one race	0	0	0
Region Units: Subjects			
North and South America	95	95	96
Asia Pacific	40	42	38
Eastern Europe	23	22	24

Western Europe	66	65	65

Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. Data for EASI score was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Units on a scale			
arithmetic mean	34.5	33	33.2
standard deviation	± 14.47	± 13.57	± 13.98
Investigator's Global Assessment (IGA) Score			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Data for IGA score was reported for 670 subjects (n=223, 224 and 223).			
Units: Units on a scale			
arithmetic mean	3.5	3.5	3.5
standard deviation	± 0.5	± 0.5	± 0.5
Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is a tool used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hr recall period. Subjects were asked the following: how would a subject rate his itch at the worst moment during the previous 24 hrs (for maximum itch intensity on a scale of 0–10 [0=no itch; 10=worst itch imaginable]). Weekly average obtained in the 7-day period prior to baseline visit. Data for pruritus NRS score was reported for 669 subjects (n=224, 224 & 221). Number of subjects analyzed = subjects with available data for the baseline parameter.			
Units: Units on a scale			
arithmetic mean	7.4	7.2	7.2
standard deviation	± 1.77	± 1.89	± 2.06
Body Surface Area (BSA) Involvement with Atopic Dermatitis			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. Data for Body surface area was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Percentage of body surface area			
arithmetic mean	57.5	54.7	56.1
standard deviation	± 23.38	± 23.19	± 22.96
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is a tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: SCORAD index. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). Data for SCORAD score was reported for 669 subjects (n=223, 223 & 223). Number of subjects analyzed = subjects with available data for baseline parameter.			
Units: Units on a scale			
arithmetic mean	68.3	66.9	67.5
standard deviation	± 13.96	± 13.97	± 13.61
Dermatology Life Quality Index (DLQI) Score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Data for DLQI score was reported for 670 subjects (n=223, 224 and 223).			

Units: Units on a scale			
arithmetic mean	14.8	13.9	14.1
standard deviation	± 7.23	± 7.37	± 7.51
Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Data for POEM score was reported for 670 subjects (n=223, 224 and 223).			
Units: Units on a scale			
arithmetic mean	20.3	19.8	20.4
standard deviation	± 5.9	± 6.37	± 6.25
Global Individual Signs Score (GISS)			
Individual components of the AD lesions (erythema, infiltration/ papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. Data for GISS was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Units on a scale			
arithmetic mean	9	8.9	8.9
standard deviation	± 1.85	± 1.81	± 1.74
Total Hospital Anxiety Depression Scale (HADS)			
The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. Data for HADS score was reported for 615 subjects (n=204, 207 and 204).			
Units: Units on a scale			
arithmetic mean	12.6	12.2	12.6
standard deviation	± 8.33	± 7.26	± 7.95

Reporting group values	Total		
Number of subjects	671		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	281		
Male	390		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	639		
Hispanic or Latino	25		
Not reported or missing	7		
Race			
Units: Subjects			
White	450		
Black or African American	46		

Asian	161		
Unknown or Not Reported	14		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
More than one race	0		
Region Units: Subjects			
North and South America	286		
Asia Pacific	120		
Eastern Europe	69		
Western Europe	196		
Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. Data for EASI score was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Units on a scale arithmetic mean standard deviation	- -		
Investigator's Global Assessment (IGA) Score			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Data for IGA score was reported for 670 subjects (n=223, 224 and 223).			
Units: Units on a scale arithmetic mean standard deviation	- -		
Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is a tool used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hr recall period. Subjects were asked the following: how would a subject rate his itch at the worst moment during the previous 24 hrs (for maximum itch intensity on a scale of 0–10 [0=no itch; 10=worst itch imaginable]). Weekly average obtained in the 7-day period prior to baseline visit. Data for pruritus NRS score was reported for 669 subjects (n=224, 224 & 221). Number of subjects analyzed = subjects with available data for the baseline parameter.			
Units: Units on a scale arithmetic mean standard deviation	- -		
Body Surface Area (BSA) Involvement with Atopic Dermatitis			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. Data for Body surface area was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Percentage of body surface area arithmetic mean standard deviation	- -		
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is a tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: SCORAD index. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). Data for SCORAD score was reported for 669 subjects (n=223, 223 & 223). Number of subjects analyzed = subjects with available data for baseline			

parameter.			
Units: Units on a scale arithmetic mean standard deviation	- 	 	
Dermatology Life Quality Index (DLQI) Score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Data for DLQI score was reported for 670 subjects (n=223, 224 and 223).			
Units: Units on a scale arithmetic mean standard deviation	- 	 	
Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Data for POEM score was reported for 670 subjects (n=223, 224 and 223).			
Units: Units on a scale arithmetic mean standard deviation	- 	 	
Global Individual Signs Score (GISS)			
Individual components of the AD lesions (erythema, infiltration/ papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. Data for GISS was reported for 670 subjects (n=223, 224 and 223). Number of participants analyzed = participants with available data for the baseline parameter.			
Units: Units on a scale arithmetic mean standard deviation	- 	 	
Total Hospital Anxiety Depression Scale (HADS)			
The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. Data for HADS score was reported for 615 subjects (n=204, 207 and 204).			
Units: Units on a scale arithmetic mean standard deviation	- 	 	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg qw
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection qw from Week 1 to Week 15. One subject randomized to placebo but received Dupilumab, analyzed in Dupilumab 300 mg q2w arm.	
Subject analysis set title	Dupilumab 300 mg q2w
Subject analysis set type	Safety analysis
Subject analysis set description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15. One subject randomized to placebo and 5 subjects randomized to Dupilumab 300 mg qw arm, received Dupilumab 300 mg q2w and analyzed in Dupilumab 300 mg q2w arm.	
Subject analysis set title	Dupilumab 300 mg qw
Subject analysis set type	Safety analysis
Subject analysis set description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15. Five subjects randomized to Dupilumab qw arm, analyzed in Dupilumab 300 mg q2w arm.	

Primary: Percentage of Subjects with Eczema Area and Severity Index--75 (EASI--75) (≥75% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects with Eczema Area and Severity Index--75 (EASI--75) (≥75% Improvement from Baseline) at Week 16
End point description:	
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. EASI--75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16. Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered as non--responders. Full analysis set (FAS) included all randomized subjects.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	224	223	
Units: Percentage of subjects				
number (not applicable)	14.7	51.3	52.5	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	
Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity.	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	36.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.58
upper limit	44.63

Notes:

[1] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity.	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	37.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.7
upper limit	45.77

Notes:

[2] - Threshold for significance at 0.025 level.

Primary: Percentage of Subjects with Investigator's Global Assessment (IGA) Score of "0" or "1" (clear or almost clear) and Reduction from Baseline of ≥2 Points at Week 16

End point title	Percentage of Subjects with Investigator's Global Assessment (IGA) Score of "0" or "1" (clear or almost clear) and Reduction from Baseline of ≥2 Points at Week 16

End point description:

IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Subjects with IGA "0" or "1" and a reduction from baseline of ≥2 points at Week 16 were reported. Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 16 were counted as non-responders. Analysis was performed on FAS population.

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	224	223	
Units: Percentage of Subjects				
number (not applicable)	10.3	37.9	37.2	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity.

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.18
upper limit	35.17

Notes:

[3] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease

severity.

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	27
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.47
upper limit	34.44

Notes:

[4] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus Numerical Rating Scale (NRS) Score from Baseline to Week 16

End point title	Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus Numerical Rating Scale (NRS) Score from Baseline to Week 16

End point description:

Pruritus NRS scale is a tool used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hr recall period. Subjects were asked the following: how would a subject rate his itch at the worst moment during the previous 24 hrs (for maximum itch intensity on a scale of 0–10 [0=no itch; 10=worst itch imaginable]). Weekly average obtained in the 7-day period prior to baseline visit. Data for pruritus NRS score was reported for 669 subjects (n=224, 224 & 221). Number of subjects analyzed = subjects with available data for the baseline parameter.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	212	213	201	
Units: Percentage of subjects				
number (not applicable)	12.3	40.8	40.3	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.025 level.

Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.64
upper limit	36.52

Notes:

[5] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level.

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	28
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.94
upper limit	36.13

Notes:

[6] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Improvement (Reduction ≥3 Points) of Pruritus NRS Score from Baseline to Week 16

End point title	Percentage of Subjects with Improvement (Reduction ≥3 Points) of Pruritus NRS Score from Baseline to Week 16

End point description:

Subjects achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥3.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	220	211	
Units: Percentage of subjects				
number (not applicable)	17.2	46.8	51.7	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	29.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.36
upper limit	37.88

Notes:

[7] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.08
upper limit	42.84

Notes:

[8] - Threshold for significance at 0.025 level.

Secondary:
Percent Change from Baseline in Peak Daily Pruritus NRS Score to Week 16

End point title	Percent Change from Baseline in Peak Daily Pruritus NRS Score to Week 16

End point description:

Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	169	162	
Units: Percent change				
arithmetic mean (standard deviation)	-26.8 (± 28.38)	-51.1 (± 28.81)	-49 (± 33.45)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.26
upper limit	-17.52

Notes:

[9] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.33
upper limit	-15.33

Notes:

[10] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus NRS Score from Baseline to Week 4

End point title	Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus NRS Score from Baseline to Week 4

End point description:

Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 4 were reported. Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 4 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	212	213	201	
Units: Percentage of subjects				
number (not applicable)	6.1	16	23.4	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.95
upper limit	15.71

Notes:

[11] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.57
upper limit	23.93

Notes:

[12] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus NRS Score from Baseline to Week 2

End point title	Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus NRS Score from Baseline to Week 2

End point description:

Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 2 were reported. Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 2 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline pruritus NRS ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 2

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	212	213	201	
Units: Percentage of subjects				
number (not applicable)	3.3	9.4	9.5	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	10.68

Notes:

[13] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	10.86

Notes:

[14] - Threshold for significance at 0.025 level.

Secondary: Change From Baseline in Peak Daily Pruritus NRS Score to Week 16	
End point title	Change From Baseline in Peak Daily Pruritus NRS Score to Week 16

End point description:

Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	169	162	
Units: units on a scale				
arithmetic mean (standard deviation)	-2.13 (± 2.044)	-3.78 (± 2.325)	-3.72 (± 2.186)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.236
upper limit	-1.26

Notes:

[15] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.189
upper limit	-1.186

Notes:

[16] - Threshold for significance at 0.025 level.

Secondary: Percent Change From Baseline in EASI Score to Week 16

End point title	Percent Change From Baseline in EASI Score to Week 16

End point description:

Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	173	162	
Units: Percent change				
arithmetic mean (standard deviation)	-39.5 (± 33.66)	-73.9 (± 26.28)	-73.8 (± 26.41)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-34.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.35
upper limit	-26.88

Notes:

[17] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-34.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.17
upper limit	-26.56

Notes:

[18] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Eczema Area and Severity Index--50 (EASI--50) (≥50% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects with Eczema Area and Severity Index--50 (EASI--50) (≥50% Improvement from Baseline) at Week 16

End point description:

EASI-50 responders were the subjects who achieved ≥50% overall improvement in EASI score from baseline to Week 16. Values after first rescue treatment were set to missing and subjects with missing EASI--50 scores at Week 16 were counted as non-responders. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	224	223	
Units: Percentage of subjects				
number (not applicable)	24.6	68.8	61	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	44.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.91
upper limit	52.48

Notes:

[19] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	36.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.9
upper limit	44.96

Notes:

[20] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Eczema Area and Severity Index--90 (EASI--90) (≥90% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects with Eczema Area and Severity Index--

	90 (EASI--90) (≥90% Improvement from Baseline) at Week 16

End point description:

EASI-90 responders were the subjects who achieved ≥90% overall improvement in EASI score from baseline to Week 16. Values after first rescue treatment were set to missing and subjects with missing EASI-90 scores at Week 16 were counted as non-responders. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	224	223	
Units: Percentage of subjects				
number (not applicable)	7.6	35.7	33.2	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	28.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.96
upper limit	35.29

Notes:

[21] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo

Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage
Point estimate	25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.51
upper limit	32.68

Notes:

[22] - Threshold for significance at 0.025 level.

Secondary: Change from Baseline in Percent Body Surface Area (BSA) to Week 16

End point title	Change from Baseline in Percent Body Surface Area (BSA) to Week 16

End point description:

Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	173	162	
Units: Percentage of body surface area				
arithmetic mean (standard deviation)	-17.2 (± 17.381)	-33.72 (± 19.619)	-35.42 (± 19.926)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-17.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.487
upper limit	-13.353

Notes:

[23] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-18.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.125
upper limit	-14.65

Notes:

[24] - Threshold for significance at 0.025 level.

Secondary: Percent Change from Baseline in the SCORing Atopic Dermatitis (SCORAD) Score to Week 16

End point title	Percent Change from Baseline in the SCORing Atopic Dermatitis (SCORAD) Score to Week 16

End point description:

SCORAD is a tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: SCORAD index. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). Data for SCORAD score was reported for 669 subjects (n=223, 223 & 223). Number of subjects analyzed = subjects with available data for baseline parameter.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	172	161	
Units: Units on a scale				
arithmetic mean (standard deviation)	-28.9 (± 24.25)	-57.2 (± 24.03)	-56.7 (± 24.27)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.79
upper limit	-21.54

Notes:

[25] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.09
upper limit	-20.87

Notes:

[26] - Threshold for significance at 0.025 level.

Secondary: Change from Baseline in Dermatology Life Quality Index (DLQI) to Week 16

End point title	Change from Baseline in Dermatology Life Quality Index (DLQI) to Week 16

End point description:

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	173	162	
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.6 (± 5.86)	-9 (± 6.61)	-8.8 (± 6.79)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.16
upper limit	-2.8

Notes:

[27] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.87
upper limit	-2.49

Notes:

[28] - Threshold for significance at 0.025 level.

Secondary: Change from Baseline in Patient Oriented Eczema Measure (POEM) to Week 16

End point title	Change from Baseline in Patient Oriented Eczema Measure (POEM) to Week 16

End point description:

The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	173	162	
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.3 (± 6.24)	-11.5 (± 7.07)	-11.3 (± 6.36)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.02
upper limit	-5.01

Notes:

[29] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.44
upper limit	-4.32

Notes:

[30] - Threshold for significance at 0.025 level.

Secondary: Change from Baseline in Hospital Anxiety Depression Scale (HADS) to Week 16

End point title	Change from Baseline in Hospital Anxiety Depression Scale (HADS) to Week 16

End point description:

The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	159	146	
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.7 (± 4.4)	-4.8 (± 5.5)	-4.9 (± 5.36)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [31]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	-0.95

Notes:

[31] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [32]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	-1.03

Notes:

[32] - Threshold for significance at 0.025 level.

Secondary: Percent Change From Baseline in Global Individual Signs Score (GISS) to Week 16

End point title	Percent Change From Baseline in Global Individual Signs Score (GISS) to Week 16

End point description:

Individual components of the AD lesions (erythema, infiltration/ papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	173	162	
Units: Percent Change				
arithmetic mean (standard deviation)	-26.2 (± 25.7)	-52.5 (± 27.33)	-51.1 (± 26.58)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.04
upper limit	-18.91

Notes:

[33] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.06
upper limit	-18.12

Notes:

[34] - Threshold for significance at 0.025 level.

Secondary: Percent Change from Baseline in Peak Daily Pruritus NRS Score to Week 2

End point title	Percent Change from Baseline in Peak Daily Pruritus NRS Score to Week 2

End point description:

Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 2

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194	214	212	
Units: Percent Change				
arithmetic mean (standard deviation)	-4.2 (± 22.77)	-20.4 (± 21.4)	-18.9 (± 28.4)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.08
upper limit	-11.9

Notes:

[35] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.62
upper limit	-10.5

Notes:

[36] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with Skin Infection Treatment Emergent Adverse Events (TEAEs) Requiring Systemic Treatment from Baseline through Week 16

End point title	Percentage of Subjects with Skin Infection Treatment Emergent Adverse Events (TEAEs) Requiring Systemic Treatment from Baseline through Week 16

End point description:

Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug, and was analyzed as treated. Statistical significance in the hierarchical testing of secondary hypotheses was broken at this endpoint. Therefore, subsequent secondary efficacy endpoints were not tested for statistical significance.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	222	229	218	
Units: Percentage of Subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment Emergent Serious Adverse Events (TESAEs) from Baseline through Week 16

End point title	Percentage of Subjects with Treatment Emergent Serious Adverse Events (TESAEs) from Baseline through Week 16

End point description:

Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug, and was analyzed as treated. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	222	229	218	
Units: Percentage of Subjects				
number (not applicable)	5	3.1	0.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation from Baseline through Week 16

End point title	Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation from Baseline through Week 16

End point description:

Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug, and was analyzed as treated. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	222	229	218	
Units: Percentage of Subjects				
number (not applicable)	0.9	1.7	1.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 28) regardless of seriousness or relationship to investigational product.	
Adverse event reporting additional description:	
Reported adverse events are treatment-emergent adverse events that developed/worsened during the 'on-treatment period' (including the 16 week treatment period).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects exposed to Placebo (for Dupilumab) for 16 weeks (mean exposure of 14 weeks).	
Reporting group title	Dupilumab 300 mg qw
Reporting group description:	
Subjects exposed to Dupilumab 300 mg qw for 16 weeks (mean exposure of 15 weeks).	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Subjects exposed to Dupilumab 300 mg alternating with placebo qw for 16 weeks (mean exposure of 15 weeks).	

Serious adverse events	Placebo	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 222 (5.41%)	2 / 218 (0.92%)	7 / 229 (3.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			

subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 218 (0.46%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Limb operation			
subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	3 / 222 (1.35%)	0 / 218 (0.00%)	2 / 229 (0.87%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 222 (0.90%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 218 (0.46%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess sweat gland			
subjects affected / exposed	0 / 222 (0.00%)	0 / 218 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			

subjects affected / exposed	0 / 222 (0.00%)	1 / 218 (0.46%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 218 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 222 (43.69%)	90 / 218 (41.28%)	92 / 229 (40.17%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 222 (5.86%)	11 / 218 (5.05%)	21 / 229 (9.17%)
occurrences (all)	16	15	33

General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	13 / 222 (5.86%)	41 / 218 (18.81%)	19 / 229 (8.30%)
occurrences (all)	18	111	63
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	3 / 222 (1.35%)	8 / 218 (3.67%)	12 / 229 (5.24%)
occurrences (all)	3	11	13
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	66 / 222 (29.73%)	21 / 218 (9.63%)	35 / 229 (15.28%)
occurrences (all)	77	26	44
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 222 (9.91%)	26 / 218 (11.93%)	27 / 229 (11.79%)
occurrences (all)	30	34	32
Upper respiratory tract infection			
subjects affected / exposed	7 / 222 (3.15%)	12 / 218 (5.50%)	7 / 229 (3.06%)
occurrences (all)	7	14	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2014	-Clarified the required period for application of emollients prior to randomization was at least the 7 consecutive days immediately before randomization. -Added positive hepatitis B core antibody as an exclusion criterion in response to a health authority request. -Clarified the first step of rescue treatment should be limited to topical medications if possible. -Modified the list of medications leading to temporary or permanent discontinuation of study drug, and added possible resumption of study drug treatment after the medication leading to discontinuation was stopped. -Revised the list of prohibited medications, and the study periods in which they were prohibited. -Modified the frequency for subject self-assessment of pruritus. -Specified that fasting was recommended but not mandatory prior to collecting samples for laboratory testing. -Allowed retesting for bilirubin and creatine phosphokinase.
04 February 2015	-Clarified that emollients should not be applied to areas of non-lesional designated for assessment of skin dryness for at least 8 hours before each clinic visit. -Changed the terminology for the European reference market and indicated that Japan had been added to the countries that would use co-primary endpoint. -Reorganized the secondary endpoints into "Key" and "Other" categories. -Revised the definition of the Full Analysis Set, and added the Per Protocol Set. -Added description of methods for missing data imputation, and for data analysis for continuous secondary endpoints to be used in US and US reference market countries. -Added an inclusion criterion requiring a subject to have a baseline Pruritus NRS score ≥3 for weekly average of peak daily pruritus to be eligible to enroll in the study. -Clarified that non-invasive skin swabs were included in a sub-study that was conducted at selected sites. -Added a potential use for research samples: to study biomarkers that had predictive utility for response to dupilumab treatment. -Clarified that samples for exploratory biomarker testing had been banked. -Clarified the assessment of "Other" endpoints through week 16 that would include both absolute and percent changes. -For the primary efficacy analysis, added a sensitivity analysis using the Cochran-Mantel-Haenszel adjusted by randomization strata on observed values, regardless of rescue medication use or missing values.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported