Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Demonstrate the Efficacy and Long-Term Safety of Dupilumab in Adult Patients With Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2013-003254-24
Trial protocol	DE CZ IT HU NL LV BE PL ES RO FR
Global end of trial date	19 October 2016

Results information

Result version number	v1
This version publication date	24 August 2017
First version publication date	24 August 2017

Trial information

Trial identification

Sponsor protocol code	R668-AD-1224

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02260986
WHO universal trial number (UTN)	-

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	Interim
Date of interim/final analysis	27 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 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 administered concomitantly with topical corticosteroid (TCS) through Week 16 in adult subjects with moderate-to-severe atopic dermatitis (AD) compared to placebo administered concomitantly with TCS.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

All subjects were required to apply moisturizers (emollients) at least twice daily for at least 7 consecutive days immediately before randomization and to continue throughout the study. Starting on Day 1/baseline, all subjects were required to initiate treatment with a TCS using a standardized regimen. The type and amount of topical products (TCS and topical calcineurin inhibitors [TCI]) used during the study were recorded. It was recommended that subjects use triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment for medium potency, and hydrocortisone 1% cream for low potency.

Evidence for comparator: -

Actual start date of recruitment	16 September 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	Netherlands: 43
Country: Number of subjects enrolled	Poland: 144
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Australia: 41
Country: Number of subjects enrolled	Canada: 115
Country: Number of subjects enrolled	Japan: 117
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	United States: 139

Worldwide total number of subjects	740
EEA total number of subjects	297

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)	713
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 14 countries between 16 Sep 2014 and 19 Oct 2016. A total of 957 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 957 subjects, 740 subjects were randomized and treated in the study. Subjects were randomized in 3:1:3 ratio to receive Dupilumab 300 mg once weekly (qw) or Dupilumab 300 mg every 2 weeks (q2w) or placebo (for Dupilumab) 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	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo qw

Arm 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 51.

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:

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 placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab q2w from Week 1 to Week 51. During weeks in which Dupilumab was not administered, subjects received placebo.

Arm type	Experimental
Investigational medicinal product name	Dupilumab 300 mg q2w
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 51.

Arm type	Experimental

Investigational medicinal product name	Dupilumab 300 mg qw
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 qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Started	315	106	319
Completed	225	93	278
Not completed	90	13	41
Consent withdrawn by subject	17	4	9
Car accident	-	-	1
Pregnancy	2	-	-
Adverse event	24	-	11
Lack of investigation product supply	2	-	1
Lost to follow-up	4	-	3
Lack of efficacy	27	3	-
Protocol deviation	14	5	16
Incorrect randomization	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo qw
Reporting group 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 51.	
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 placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab q2w from Week 1 to Week 51. During weeks in which Dupilumab was not administered, subjects received placebo.	
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 51.	

Reporting group values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Number of subjects	315	106	319
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.6	39.6	36.9
standard deviation	± 13.01	± 13.98	± 13.67
Gender categorical Units: Subjects			
Female	122	44	128
Male	193	62	191
Ethnicity Units: Subjects			
Hispanic or Latino	10	2	5
Not Hispanic or Latino	299	103	309
Unknown or Not Reported	6	1	5
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	83	29	89
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	19	2	13
White	208	74	208
More than one race	0	0	0
Unknown or Not Reported	5	1	9
Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of 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 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD.			

Units: units on scale			
arithmetic mean	32.6	33.6	32.1
standard deviation	± 12.93	± 13.3	± 12.76
Investigator Global Assessment (IGA) Score			
IGA was 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 was an IGA score of 0 (clear) or 1 (almost clear).			
Units: units on scale			
arithmetic mean	3.5	3.5	3.5
standard deviation	± 0.5	± 0.5	± 0.5
Weekly Peak Averaged Pruritus Numeric Rating Scale (NRS)			
Pruritus NRS was an assessment tool that was used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at worst moment during previous 24 hours (for maximum itch intensity on a scale of 0–10 [0=no itch;10=worst itch imaginable]).			
Units: units on scale			
arithmetic mean	7.3	7.4	7.1
standard deviation	± 1.84	± 1.66	± 1.9
Body Surface Area (BSA) Involvement with Atopic Dermatitis (AD)			
BSA 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.			
Units: percentage of BSA			
arithmetic mean	56.9	59.5	54.1
standard deviation	± 21.69	± 20.84	± 21.76
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD was a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. 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 a total of 734 subjects (Placebo qw: 313; Dupilumab 300 mg q2w: 105 and Dupilumab 300 mg qw: 316).			
Units: units on a scale			
arithmetic mean	66	69.3	65.9
standard deviation	± 13.53	± 15.24	± 13.63
Dermatology Life Quality Index (DLQI) Total Score			
DLQI was 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.			
Units: units on scale			
arithmetic mean	14.7	14.5	14.4
standard deviation	± 7.37	± 7.31	± 7.17
Patient Oriented Eczema Measure (POEM)			
The POEM was a 7-item questionnaire that assessed 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 a total of 739 subjects (Placebo qw: 314; Dupilumab 300 mg q2w: 106 and Dupilumab 300 mg qw: 319).			
Units: units on a scale			
arithmetic mean	20	20.3	20.1
standard deviation	± 5.99	± 5.68	± 6.05
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. Total score ranges from 0 (absent disease) to 12 (severe disease).			
Units: units on scale			
arithmetic mean	8.7	8.9	8.9
standard deviation	± 1.84	± 2.04	± 1.8
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.			
Units: units on scale			
arithmetic mean	12.6	12.9	12.8
standard deviation	± 8.06	± 7.73	± 8.01

Reporting group values	Total		
Number of subjects	740		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	294		
Male	446		
Ethnicity			
Units: Subjects			
Hispanic or Latino	17		
Not Hispanic or Latino	711		
Unknown or Not Reported	12		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	201		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	34		
White	490		
More than one race	0		
Unknown or Not Reported	15		
Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of 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 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD.			
Units: units on scale			
arithmetic mean			
standard deviation	-		
Investigator Global Assessment (IGA)			

Score			
IGA was 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 was an IGA score of 0 (clear) or 1 (almost clear).			
Units: units on scale arithmetic mean standard deviation	- -		
Weekly Peak Averaged Pruritus Numeric Rating Scale (NRS)			
Pruritus NRS was an assessment tool that was used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at worst moment during previous 24 hours (for maximum itch intensity on a scale of 0–10 [0=no itch;10=worst itch imaginable]).			
Units: units on scale arithmetic mean standard deviation	- -		
Body Surface Area (BSA) Involvement with Atopic Dermatitis (AD)			
BSA 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.			
Units: percentage of BSA arithmetic mean standard deviation	- -		
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD was a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. 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 a total of 734 subjects (Placebo qw: 313; Dupilumab 300 mg q2w: 105 and Dupilumab 300 mg qw: 316).			
Units: units on a scale arithmetic mean standard deviation	- -		
Dermatology Life Quality Index (DLQI) Total Score			
DLQI was 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.			
Units: units on scale arithmetic mean standard deviation	- -		
Patient Oriented Eczema Measure (POEM)			
The POEM was a 7-item questionnaire that assessed 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 a total of 739 subjects (Placebo qw: 314; Dupilumab 300 mg q2w: 106 and Dupilumab 300 mg qw: 319).			
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. Total score ranges from 0 (absent disease) to 12 (severe disease).			
Units: units on 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.			
Units: units on scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Placebo qw
Reporting group 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 51.	
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 placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab q2w from Week 1 to Week 51. During weeks in which Dupilumab was not administered, subjects received placebo.	
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 51.	
Subject analysis set title	Placebo qw
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 51.	
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 (for Dupilumab) alternating with single 300 mg injection of Dupilumab q2w from Week 1 to Week 51. During weeks in which Dupilumab was not administered, subjects received placebo. Four subjects received fewer injections of Dupilumab 300 mg in Dupilumab 300 qw arm, were 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 51. Four subjects received fewer injections of Dupilumab 300 mg in Dupilumab 300 qw arm, were 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 (minimum) to 72 (maximum) 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. All efficacy analyses were performed on the Full Analysis Set (FAS), which included all randomized subjects. Efficacy analyses were based on the treatment allocated by interactive voice response system/ interactive web response system (IVRS/IWRS) at randomization (as randomized).	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percentage of subjects				
number (not applicable)	23.2	68.9	63.9	

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 (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	45.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.72
upper limit	55.66

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 (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	40.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	33.74
upper limit	47.81

Notes:

[2] - Threshold for significance at 0.025 level.

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

End point description:

IGA was 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 score "0" or "1" and a reduction from baseline of ≥2 points at Week 16 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). (Co-primary efficacy endpoints are for the European Union [EU], EU reference market countries, and Japan only).

End point type	Primary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percentage of subjects				
number (not applicable)	12.4	38.7	39.2	

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 (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.34
upper limit	36.26

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 (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.33
upper limit	33.28

Notes:

[4] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 16

End point title	Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 16

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	299	102	295	
Units: percentage of subjects				
number (not applicable)	19.7	58.8	50.8	

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 previous endpoint was statistically significant at 0.025 level for both comparisons.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	39.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.53
upper limit	49.65

Notes:

[5] - Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing peak NRS at Week 16 were considered as non-responders.
[6] - 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 for both comparisons.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	31.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	23.84
upper limit	38.39

Notes:

[7] - Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing peak NRS at Week 16 were considered as non-responders.
[8] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 16

End point title	Percentage of Subjects With Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 16

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥3.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306	105	309	
Units: percentage of subjects				
number (not applicable)	27.8	65.7	62.5	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing peak NRS at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw

Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	37.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.56
upper limit	48.31

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing peak NRS at Week 16 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	34.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.31
upper limit	42.05

Notes:

[10] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Investigator's Global Assessment (IGA) Score of "0" or "1" and Reduction From Baseline of ≥2 Points at Week 52

End point title	Percentage of Subjects With Investigator's Global Assessment (IGA) Score of "0" or "1" and Reduction From Baseline of ≥2 Points at Week 52

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 score of "0" or "1" and a reduction from baseline of ≥2 points at Week 52 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: percentage of subjects				
number (not applicable)	12.5	36	40	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	23.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.72
upper limit	34.19

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	27.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	20.42
upper limit	34.58

Notes:

[12] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Eczema Area and Severity Index-75 (EASI-75) (≥75% Improvement From Baseline) at Week 52

End point title	Percentage of Subjects With Eczema Area and Severity Index-75 (EASI-75) (≥75% Improvement From Baseline) at Week 52

End point description:

The EASI score was used to measure the severity and extent of AD and measured 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 (minimum) to 72 (maximum) 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 52. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: percentage of subjects				
number (not applicable)	21.6	65.2	64.1	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	43.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	32.5
upper limit	54.65

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	42.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.91
upper limit	50.06

Notes:

[14] - Threshold for significance at 0.025 level.

Secondary: Percent Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 16

End point title	Percent Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 16

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percent change				
least squares mean (standard error)	-30.3 (± 2.36)	-56.6 (± 3.95)	-57.1 (± 2.11)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-26.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.04
upper limit	-17.43

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-26.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.83
upper limit	-20.73

Notes:

[16] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 52

End point title	Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 52

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 52 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	86	249	
Units: percentage of subjects				
number (not applicable)	12.9	51.2	39	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	38.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	26.96
upper limit	49.66

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.76
upper limit	33.45

Notes:

[18] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 52

End point title	Percentage of Subjects With Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 52

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS score at Week 52 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥3.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	256	88	261	
Units: percentage of subjects				
number (not applicable)	15.6	55.7	42.9	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	40.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.76
upper limit	51.35

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 52 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	27.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.81
upper limit	34.76

Notes:

[20] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 24

End point title	Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 24

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 24 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	299	102	295	
Units: percentage of subjects				
number (not applicable)	16.1	53.9	43.7	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 24 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw

Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	37.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.34
upper limit	48.4

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 24 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.65
upper limit	34.7

Notes:

[22] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 4

End point title	Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 4

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 4 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	299	102	295	
Units: percentage of subjects				
number (not applicable)	16.4	37.3	27.1	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 4 were considered as non-responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.59
upper limit	31.15

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 4 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.15
upper limit	17.31

Notes:

[24] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 2

End point title	Percentage of Subjects With Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score From Baseline to Week 2

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 2 were reported. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with baseline peak pruritus NRS score ≥4.

End point type	Secondary

End point timeframe:

Baseline to Week 2

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	299	102	295	
Units: percentage of subjects				
number (not applicable)	8	17.6	13.6	

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 2 were considered as non-

responders.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0062 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	17.63

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). Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA baseline values: IGA=3 vs IGA=4). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 2 were considered as non-responders.

Comparison groups	Dupilumab 300 mg qw v Placebo qw
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0344 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	10.51

Notes:

[26] - Threshold for significance at 0.025 level.

Secondary: Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 16

End point title	Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 16

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: units on a scale				
least squares mean (standard error)	-2.36 (± 0.138)	-4.17 (± 0.207)	-4.27 (± 0.126)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.297
upper limit	-1.322

Notes:

[27] - Threshold for significance at 0.025 level.

Secondary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score to Week 16

End point title	Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score to Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measured 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 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percent change				
least squares mean (standard error)	-48.4 (± 3.82)	-80.5 (± 6.34)	-81.5 (± 5.78)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-32.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.37
upper limit	-17.82

Notes:

[28] - Threshold for significance at 0.025 level.

Secondary: Change From Baseline in Percent Body Surface Area (BSA) Affected by AD to Week 16

End point title	Change From Baseline in Percent Body Surface Area (BSA) Affected by AD to Week 16

End point description:

BSA 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percentage of BSA				
least squares mean (standard error)	-22.01 (± 1.158)	-40.39 (± 1.844)	-39.58 (± 1.065)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-18.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.583
upper limit	-14.187

Notes:

[29] - 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 was a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) were assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: percent change				
least squares mean (standard error)	-36.2 (± 1.66)	-63.9 (± 2.52)	-65.9 (± 1.49)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.46
upper limit	-21.9

Notes:

[30] - 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 was 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: units on a scale				
least squares mean (standard error)	-5.8 (± 0.34)	-10 (± 0.5)	-10.7 (± 0.31)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.31
upper limit	-3.02

Notes:

[31] - 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 was 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]). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: units on a scale				
least squares mean (standard error)	-5.3 (± 0.41)	-12.7 (± 0.64)	-12.9 (± 0.37)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.85
upper limit	-5.93

Notes:

[32] - 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:

HADS was a fourteen-item scale. Seven of the items relate to anxiety and seven items relate to depression. Each item on the questionnaire is scored from 0 (minimum score) - 3 (maximum score) 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: units on a scale				
least squares mean (standard error)	-4 (± 0.37)	-4.9 (± 0.58)	-5.4 (± 0.35)	

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). Analysis was performed using ANCOVA model with baseline measurements as covariate and the treatment, region and baseline IGA strata as fixed factors.

Comparison groups	Dupilumab 300 mg q2w v Placebo qw
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1596 [33]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.27
upper limit	0.37

Notes:

[33] - Threshold for significance at 0.025 level.

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

End point title	Percent Change From Baseline in Total 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. Total score ranges from 0 (absent disease) to 12 (severe disease). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: Percent Change				
least squares mean (standard error)	-33.3 (± 1.89)	-55.4 (± 2.69)	-59.3 (± 1.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Topical Atopic Dermatitis Medication-Free Days Through Week 52

End point title	Proportion of Topical Atopic Dermatitis Medication-Free Days Through Week 52

End point description:

Proportion of topical AD medication-free days through Week 52 was calculated as the number of days that a subject used neither topical corticosteroid (TCS)/ topical calcineurin inhibitors (TCI) nor system rescue therapy divided by the study days of each period. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline Up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: days				
arithmetic mean (standard deviation)	10.5 (± 23.68)	16.6 (± 30.08)	22.5 (± 33.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 2

End point title	Percent Change From Baseline in Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score to Week 2

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline to Week 2

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	315	106	319	
Units: Percent Change				
least squares mean (standard error)	-19.7 (± 1.58)	-27.3 (± 2.67)	-25.7 (± 1.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score to Week 52

End point title	Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score to Week 52

End point description:

The EASI score was used to measure the severity and extent of AD and measured 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 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: Percent Change				
least squares mean (standard error)	-60.9 (± 4.29)	-84.9 (± 6.73)	-87.8 (± 6.19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Body Surface Area (BSA) Affected by AD to Week 52

End point title	Change From Baseline in Percent Body Surface Area (BSA)

	Affected by AD to Week 52

End point description:

BSA 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: Percentage of BSA				
least squares mean (standard error)	-29.41 (± 1.443)	-43.75 (± 1.874)	-43.67 (± 1.143)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the SCORing Atopic Dermatitis (SCORAD) Score to Week 52

End point title	Percent Change From Baseline in the SCORing Atopic Dermatitis (SCORAD) Score to Week 52

End point description:

SCORAD was a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) were assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: Percent Change				
least squares mean (standard error)	-47.3 (± 2.18)	-69.7 (± 3.06)	-70.4 (± 1.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Global Individual Signs Score (GISS) to Week 52

End point title	Percent Change From Baseline in Global Individual Signs Score (GISS) to Week 52

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. Total score ranges from 0 (absent disease) to 12 (severe disease). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: Percent Change				
least squares mean (standard error)	-40.8 (± 2.72)	-62.8 (± 3.35)	-64.4 (± 2.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatology Life Quality Index (DLQI) to Week 52

End point title	Change From Baseline in Dermatology Life Quality Index (DLQI) to Week 52

End point description:

The DLQI was 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:
Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: units on a scale				
least squares mean (standard error)	-7.2 (± 0.4)	-11.4 (± 0.57)	-11.1 (± 0.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Oriented Eczema Measure (POEM) to Week 52

End point title	Change From Baseline in Patient Oriented Eczema Measure (POEM) to Week 52

End point description:

The POEM was 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]). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:
Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: units on a scale				
least squares mean (standard error)	-7 (± 0.57)	-14.2 (± 0.78)	-13.2 (± 0.45)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hospital Anxiety Depression Scale (HADS) to Week 52

End point title	Change From Baseline in Hospital Anxiety Depression Scale (HADS) to Week 52

End point description:

HADS was a fourteen-item scale. Seven of the items relate to anxiety and seven items relate to depression. Each item on the questionnaire is scored from 0 (minimum score) - 3 (maximum score) 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. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	89	270	
Units: units on a scale				
least squares mean (standard error)	-3.8 (± 0.47)	-5.5 (± 0.71)	-5.9 (± 0.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Flares Through Week 52

End point title	Number of Flares Through Week 52

End point description:

AD flares were defined as worsening of the disease that required escalation/intensification of AD treatment. Number of flares occurred in the subjects from first dose through Week 52 were reported. All safety analysis were performed on safety analysis set (SAF) that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: flares				
number (not applicable)	216	20	51	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Serious Treatment Emergent Adverse Events (TEAEs) Leading to Study Drug Discontinuation through Week 52

End point title	Number of Serious Treatment Emergent Adverse Events (TEAEs) Leading to Study Drug Discontinuation through Week 52

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of casual relationship with this treatment. A Serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included participants with both serious and non-serious AEs. All safety analysis were performed on SAF that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: events				
number (not applicable)	28	2	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Skin Infection TEAEs (excluding Herpetic Infections) from Baseline through Week 52

End point title	Percentage of Subjects With Skin Infection TEAEs (excluding Herpetic Infections) from Baseline through Week 52

End point description:

Any untoward medical occurrence in subjects who received IMP was considered an AE without regard to possibility of casual relationship with this treatment. TEAEs were defined as AEs that developed or worsened or became serious during "on-treatment period" (time from the first dose of study drug up to end of treatment at Week 52). Any TEAE included subjects with both serious and non-serious AEs. Skin infection TEAEs were identified based on blinded adjudication of all reported TEAEs under the 2 primary System Organ Classes (SOC): SOC = "Infection and Infestations" or SOC = "Skin and Subcutaneous Tissue Disorders". Blinded adjudication was performed and finalized by the study medical monitor before database lock. All safety analysis were performed on SAF that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: percentage of subjects				
number (not applicable)	17.8	10.9	8.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Skin Infection TEAEs (excluding Herpetic Infections) from Baseline through Week 52

End point title	Number of Skin Infection TEAEs (excluding Herpetic Infections) from Baseline through Week 52

End point description:

Any untoward medical occurrence in subjects who received IMP was considered an AE without regard to possibility of casual relationship with this treatment. TEAEs were defined as AEs that developed or worsened or became serious during "on-treatment period" (time from the first dose of study drug up to end of treatment at Week 52). Any TEAE included subjects with both serious and non-serious AEs. Skin infection TEAEs were identified based on blinded adjudication of all reported TEAEs under the 2 primary System Organ Classes (SOC): SOC = "Infection and Infestations" or SOC = "Skin and Subcutaneous Tissue Disorders". Blinded adjudication was performed and finalized by the study medical monitor before database lock. All safety analysis were performed on SAF that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: events				
number (not applicable)	80	15	29	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Skin Infection TEAEs (excluding Herpetic Infections) Requiring Systemic Treatment from Baseline through Week 52

End point title	Percentage of Subjects With Skin Infection TEAEs (excluding Herpetic Infections) Requiring Systemic Treatment from Baseline through Week 52

End point description:

Any untoward medical occurrence in subjects who received IMP was considered an AE without regard to possibility of casual relationship with this treatment. TEAEs were defined as AEs that developed or

worsened or became serious during "on-treatment period" (time from the first dose of study drug up to end of treatment at Week 52). Any TEAE included subjects with both serious and non-serious AEs. Skin infection TEAEs were identified based on blinded adjudication of all reported TEAEs under the 2 primary System Organ Classes (SOC): SOC = "Infection and Infestations" or SOC = "Skin and Subcutaneous Tissue Disorders". Blinded adjudication was performed and finalized by the study medical monitor before database lock. All safety analysis were performed on SAF that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: percentage of subjects				
number (not applicable)	9.5	5.5	3.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Skin Infection TEAEs (excluding Herpetic Infections) Requiring Systemic Treatment from Baseline through Week 52

End point title	Number of Skin Infection TEAEs (excluding Herpetic Infections) Requiring Systemic Treatment from Baseline through Week 52

End point description:

Any untoward medical occurrence in subjects who received IMP was considered an AE without regard to possibility of casual relationship with this treatment. TEAEs were defined as AEs that developed or worsened or became serious during "on-treatment period" (time from the first dose of study drug up to end of treatment at Week 52). Any TEAE included subjects with both serious and non-serious AEs. Skin infection TEAEs were identified based on blinded adjudication of all reported TEAEs under the 2 primary System Organ Classes (SOC): SOC = "Infection and Infestations" or SOC = "Skin and Subcutaneous Tissue Disorders". Blinded adjudication was performed and finalized by the study medical monitor before database lock. All safety analysis were performed on SAF that included all randomized subjects who received any study drug, and were analyzed as-treated.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	315	110	315	
Units: events				
number (not applicable)	44	7	13	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5) Score to Week 16

End point title	Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5) Score to Week 16

End point description:

ACQ-5 questionnaire was a validated questionnaire comprising of 5 questions for asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath, and wheeze. Subjects were asked to rate their asthma symptoms during the previous week on a 7-point scale as 0=no impairment, 6=maximum impairment. ACQ-5 score is the mean of the 5 questions and range between 0 (totally controlled) and 6 (severely uncontrolled) (a higher score indicated lower asthma control). All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). Here, number of subjects analyzed = subjects with ACQ-5 value at baseline. The ACQ-5 questionnaire was administered only to the subjects with a medical history of asthma.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	48	145	
Units: units on a scale				
least squares mean (standard error)	-0.12 (± 0.082)	-0.19 (± 0.113)	-0.36 (± 0.068)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Sinonasal Outcome Test (SNOT-22) Score to Week 16

End point title	Change From Baseline in Sinonasal Outcome Test (SNOT-22) Score to Week 16

End point description:

The SNOT 22 was a validated measure of health related quality of life in sinonasal disease. It is a 22 item questionnaire with each item assigned a score ranging from 0-5. The total score may range from 0 (no disease) -110 (worst disease) (lower scores represent better health related quality of life. All efficacy analyses were performed on the FAS, which included all randomized subjects. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). The SNOT-

22 was administered only to subjects with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 16

End point values	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	45	99	
Units: units on a scale				
least squares mean (standard error)	-4.77 (± 1.903)	-6.38 (± 2.445)	-10.39 (± 1.63)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Time-frame was 'On treatment (Week 52) period' defined time from administration of first dose of study drug to study completion date of Week 52 visit (365 days starting from first dose of study drug if the date of Week 52 visit was unavailable).

Adverse event reporting additional description:

All Adverse Events were collected from signature of informed consent form up to study completion date of the Week 52 visit regardless of seriousness or relationship to investigational product. Reported AEs and deaths are treatment-emergent that is AEs developed/worsened and deaths that occurred during 'On treatment (Week 52) period'.SAF population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo qw

Reporting group 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 51.

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 51. Four subjects received fewer injections of Dupilumab 300 mg in Dupilumab 300 qw arm, were analyzed in Dupilumab 300 mg q2w arm.

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 placebo (for Dupilumab) alternating with a single 300 mg injection of Dupilumab q2w from Week 1 to Week 51. During weeks in which Dupilumab was not administered, subjects received placebo. Four subjects received fewer injections of Dupilumab 300 mg in Dupilumab 300 qw arm, were analyzed in Dupilumab 300 mg q2w arm.

Serious adverse events	Placebo qw	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 315 (6.35%)	12 / 315 (3.81%)	4 / 110 (3.64%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Penile squamous cell carcinoma			

subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Squamous cell carcinoma			
subjects affected / exposed	1 / 315 (0.32%)	1 / 315 (0.32%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
General disorders and administration site conditions			
Soft tissue inflammation			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 315 (0.00%)	0 / 315 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Concussion			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Contusion			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Ligament rupture			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Limb traumatic amputation			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Road traffic accident			

subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Cerebral infarction			
subjects affected / exposed	0 / 315 (0.00%)	0 / 315 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Eye disorders			
Cataract			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Cystoid macular oedema			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Glaucoma			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 315 (0.32%)	1 / 315 (0.32%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Musculoskeletal and connective tissue disorders			
Pseudarthrosis			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Osteoarthritis			

subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Spondylolisthesis			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Appendicitis			
subjects affected / exposed	0 / 315 (0.00%)	1 / 315 (0.32%)	0 / 110 (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
Bronchitis			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Eczema herpeticum			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Pneumonia			
subjects affected / exposed	1 / 315 (0.32%)	0 / 315 (0.00%)	0 / 110 (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
Superinfection bacterial			
subjects affected / exposed	0 / 315 (0.00%)	0 / 315 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 qw	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	216 / 315 (68.57%)	228 / 315 (72.38%)	74 / 110 (67.27%)
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 315 (6.03%)	24 / 315 (7.62%)	5 / 110 (4.55%)
occurrences (all)	30	48	5
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	24 / 315 (7.62%)	60 / 315 (19.05%)	16 / 110 (14.55%)
occurrences (all)	102	224	34
Eye disorders			
Blepharitis			
subjects affected / exposed	3 / 315 (0.95%)	11 / 315 (3.49%)	6 / 110 (5.45%)
occurrences (all)	3	14	7
Conjunctivitis allergic			
subjects affected / exposed	19 / 315 (6.03%)	54 / 315 (17.14%)	13 / 110 (11.82%)
occurrences (all)	22	74	20
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	19 / 315 (6.03%)	7 / 315 (2.22%)	5 / 110 (4.55%)
occurrences (all)	23	7	5
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	161 / 315 (51.11%)	91 / 315 (28.89%)	40 / 110 (36.36%)
occurrences (all)	278	133	52
Infections and infestations			
Influenza			
subjects affected / exposed	17 / 315 (5.40%)	9 / 315 (2.86%)	4 / 110 (3.64%)
occurrences (all)	25	13	4
Nasopharyngitis			
subjects affected / exposed	62 / 315 (19.68%)	63 / 315 (20.00%)	26 / 110 (23.64%)
occurrences (all)	89	88	40
Oral herpes			

subjects affected / exposed	10 / 315 (3.17%)	17 / 315 (5.40%)	4 / 110 (3.64%)
occurrences (all)	15	31	9
Sinusitis			
subjects affected / exposed	9 / 315 (2.86%)	18 / 315 (5.71%)	2 / 110 (1.82%)
occurrences (all)	11	20	2
Upper respiratory tract infection			
subjects affected / exposed	34 / 315 (10.79%)	46 / 315 (14.60%)	11 / 110 (10.00%)
occurrences (all)	52	78	21
Urinary tract infection			
subjects affected / exposed	14 / 315 (4.44%)	16 / 315 (5.08%)	2 / 110 (1.82%)
occurrences (all)	16	22	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2014	Modification of study design: Dupilumab to be administered concomitantly with TCS; Incorporated the doses selected for phase 3 studies based on results of an interim analysis of a phase 2b dose-ranging study. The doses selected were 300 mg qw and 300 mg q2w; Increased the number of subjects to 700 and randomized in a 3:1:3 ratio to Dupilumab 300 mg qw, Dupilumab 300 mg q2w and matching placebo; Changed time of the assessment of the efficacy endpoints to week 16 from week 12; Clarified that different health authorities requested different primary endpoints although the study was to be conducted the same in all countries; Modified secondary endpoints and added exploratory endpoints. Modified Inclusion/Exclusion Criteria; Expanded section on prohibited medications; Modified section on study drug continuation rules; Modified assessments (Added Patient Global Assessment of Treatment; added Atopic keratoconjunctivitis [AKC], ACQ-5 and SNOT-22; added a second question for subject assessment of pruritus; added Hemoglobin A1c [HbA1c] to study assessments; changed frequency and timing of some assessments).
22 October 2014	Incorporated changes concerning the concomitant use of dupilumab and systemic corticosteroids that had already been made in the US-specific protocol (for global [R668-AD-1224.01] and UK-specific [R668-AD-1224.01GB] protocols only); Added positive HBcAb as an exclusion; Updated prohibited medications; Removed "treatment with a live (attenuated) vaccine" from the list of events that would lead to temporary discontinuation of study drug; Added "rescue treatment prior to week 2" to the list of events that would lead to permanent discontinuation of study drug; Modified the AKC assessment schedule; Added % BSA to the assessments to be completed prior to escalation of TCS treatment; Specified that fasting was recommended prior to obtaining laboratory samples; Clarified the description of IGA; Clarified subject population for SNOT-22 assessment; - Included an assessment of vital signs at visit 3; Changed reporting time for AEs leading to study withdrawal; Clarified reporting requirements for pregnancy or a complication of pregnancy in a female partner of a male subject; Modified statistics section for greater clarity and to expand on MMRM; Updated the cut-off date for earlier studies.

24 February 2015	Added text to indicate that for background treatment with moisturizers (emollients), to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit; Changed the terminology of "European Medicines Agency (EMA) reference market" to "European Union (EU) reference market", and "reference market submissions" to "reference market countries"; Made revisions to indicate that Japan had been added to the countries that would use the co-primary endpoints; Separated the secondary endpoints into 2 parts: Key Secondary Endpoints and Other Secondary Endpoints; Moved some of the secondary endpoint to the "key secondary endpoints" section; Added some endpoints in the "other secondary endpoints" section; Moved the following endpoint to the end of "other secondary endpoints": "incidence of skin-infection TEAEs requiring systemic treatment from baseline through Week 56; Revised the definition for the FAS and added per protocol set (PPS) for efficacy analysis; Added description of methods for missing data imputation and 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 average score for maximum itch intensity ≥3 to be eligible to enroll in the study; Changed one of recommended super high potency TCS from "betamethasone dipropionate 0.05% cream" to "betamethasone dipropionate 0.05% optimized ointment" to be consistent with the study reference manual, and made revision to clarify that the standardized low or median potency TCS daily regimen was once daily; Added a statement in the "Rescue Medications" section for clarity and to be consistent with the section of Reasons for Permanent Discontinuation of study drug; Clarified that ECGs should be performed before blood was drawn during visits requiring blood draws.
02 October 2015	Removed the requirement that no subjects would receive study drug from both vials and prefilled syringes; Indicated that the primary analysis, which would include the Week 16 primary and key secondary endpoints for all randomized subjects, would also contain Week 52 efficacy endpoints, which at a minimum would include all subjects randomized by 27 April 2015 and whose pertinent data (i.e. data required for Week 52 analyses) had been collected and validated; Modified and reorder key secondary efficacy endpoints, other secondary endpoints, and exploratory endpoints to match the SAP; Modified the statement regarding subjects with anti-drug antibody (ADA) titer of ≥240 at their last study visit returning to the clinic for additional samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported