Clinical trial results:
Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Dupilumab Monotherapy in Patients 12 to <18 Years of Age, With Moderate-to-severe Atopic Dermatitis

Summary

EudraCT number	2015-004458-16
Trial protocol	Outside EU/EEA
Global end of trial date	05 June 2018

Results information

Result version number	v1
This version publication date	19 December 2018
First version publication date	06 February 2019

Trial information

Trial identification

Sponsor protocol code	R668-AD-1526

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03054428
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001501-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 June 2018
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 as a monotherapy in subjects ≥12 years to <18 years of age with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study was to assess the safety of dupilumab as a monotherapy in subjects ≥12 years to <18 years of age with moderate-to-severe AD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2017
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	United States: 220
Country: Number of subjects enrolled	Canada: 31
Worldwide total number of subjects	251
EEA total number of subjects	0

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)	251
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 50 sites in the United States and Canada between 21 March 2017 and 04 Jun 2018. A total of 295 subjects were screened in the study. The most common causes for screening failures were lack of adequate disease severity and lack of willingness to comply with study visits and procedures.

Pre-assignment

Screening details:

Out of 295 subjects, 251 were enrolled and randomized in an approximate 1:1:1 ratio to 1 of 3 treatment groups: Dupilumab once every 2 weeks (Q2W), Dupilumab once every 4 weeks (Q4W) and Placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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 Q4W

Arm description:

Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	REGN668
Pharmaceutical forms	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 200 mg or 300 mg Q2W

Arm description:

Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	REGN668
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W
Started	85	84	82
Completed Week 16	80	81	79
Completed	2	4	3
Not completed	83	80	79
Consent withdrawn by subject	3	2	3
Physician decision	-	1	1
Discontinued for R668-AD-1434, but did not enroll	1	-	-
Transitioned to R668-AD-1434 (open-label)	-	-	73
Discontinued to enroll in R668-AD-1434	-	-	1
Lost to follow-up	-	-	1
Transitioned to R668-AD-1434 open-label study	76	76	-
Lack of efficacy	3	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).	
Reporting group title	Dupilumab 300 mg Q4W
Reporting group description:	
Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given.	
Reporting group title	Dupilumab 200 mg or 300 mg Q2W
Reporting group description:	
Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.	

Reporting group values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W
Number of subjects	85	84	82
Age categorical Units: Subjects			
≥12-<15	41	45	43
≥15-<18	44	39	39
Age continuous Units: years			
arithmetic mean	14.5	14.4	14.5
standard deviation	± 1.78	± 1.59	± 1.74
Gender categorical Units: Subjects			
Female	32	32	39
Male	53	52	43
Race Units: Subjects			
White	48	55	54
Black or African American	15	8	7
Asian	13	13	12
Other	6	8	7
Not Reported/Missing	3	0	2
Ethnicity Units: Subjects			
NOT HISPANIC OR LATINO	72	64	69
HISPANIC OR LATINO	13	20	13

Investigator's Global Assessment (IGA) Score			
IGA is an assessment scale used to determine severity of atopic dermatitis (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: Scores on a scale			
arithmetic mean	3.5	3.5	3.5
standard deviation	± 0.50	± 0.50	± 0.50
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: Scores on a scale			
arithmetic mean	35.5	35.8	35.3
standard deviation	± 13.97	± 14.82	± 13.84
Peak weekly averaged pruritus Numerical Rating Scale (NRS) Score			
Peak Pruritus NRS is an assessment tool used by subjects to report intensity of pruritus (itch) during a 24-hour recall period. Subjects were asked the following questions: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your itch at the worst moment during the previous 24 hours?" Baseline NRS was the prorated average of NRSs reported continuously for 7 days right before and on the baseline visit (ie, study day -6 to day 1).			
Units: Peak weekly average score			
arithmetic mean	7.7	7.5	7.5
standard deviation	± 1.62	± 1.84	± 1.52
Body Surface Area (BSA) of 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	56.4	56.9	56.0
standard deviation	± 24.13	± 23.51	± 21.40
Scoring Atopic Dermatitis (SCORAD) Score			
SCORAD is 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.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease).			
Units: Scores on a scale			
arithmetic mean	70.4	69.8	70.6
standard deviation	± 13.25	± 14.12	± 13.89
Children's Dermatology Life Quality Index (CDLQI) Total Score			
The CDLQI is a 10-item questionnaire used to measure how much a subject's skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant 1 = Only a little 2 = Quite a lot 3 = Very much = yes = prevent school			
Units: Scores on a scale			
arithmetic mean	13.1	14.8	13.0
standard deviation	± 6.72	± 7.38	± 6.21

Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4= 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor QOL.			
Units: Scores on a scale			
arithmetic mean	21.1	21.1	21.0
standard deviation	± 5.38	± 5.47	± 5.01
Total Hospital Anxiety and Depression Scale (HADS)			
The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.'			
Units: Scores on a scale			
arithmetic mean	11.6	13.3	12.6
standard deviation	± 7.76	± 8.17	± 8.04

Reporting group values	Total		
Number of subjects	251		
Age categorical			
Units: Subjects			
≥12-<15	129		
≥15-<18	122		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	103		
Male	148		
Race			
Units: Subjects			
White	157		
Black or African American	30		
Asian	38		
Other	21		
Not Reported/Missing	5		
Ethnicity			
Units: Subjects			
NOT HISPANIC OR LATINO	205		
HISPANIC OR LATINO	46		
Investigator's Global Assessment (IGA) Score			
IGA is an assessment scale used to determine severity of atopic dermatitis (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: Scores on a scale			
arithmetic mean			

standard deviation	-		
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: Scores on a scale arithmetic mean standard deviation	- -		
Peak weekly averaged pruritus Numerical Rating Scale (NRS) Score			
Peak Pruritus NRS is an assessment tool used by subjects to report intensity of pruritus (itch) during a 24-hour recall period. Subjects were asked the following questions: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your itch at the worst moment during the previous 24 hours?" Baseline NRS was the prorated average of NRSs reported continuously for 7 days right before and on the baseline visit (ie, study day -6 to day 1).			
Units: Peak weekly average score arithmetic mean standard deviation	- -		
Body Surface Area (BSA) of 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 is 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.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease).			
Units: Scores on a scale arithmetic mean standard deviation	- -		
Children's Dermatology Life Quality Index (CDLQI) Total Score			
The CDLQI is a 10-item questionnaire used to measure how much a subject's skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant 1 = Only a little 2 = Quite a lot 3 = Very much = yes = prevent school			
Units: Scores on a scale arithmetic mean standard deviation	- -		
Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4= 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor QOL.			
Units: Scores on a scale			

arithmetic mean standard deviation	- 		
Total Hospital Anxiety and Depression Scale (HADS)			
The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.'			
Units: Scores on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

Reporting group title	Dupilumab 300 mg Q4W

Reporting group description:

Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given.

Reporting group title	Dupilumab 200 mg or 300 mg Q2W

Reporting group description:

Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.

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

End point description:

IGA is an assessment scale used to determine severity of atopic dermatitis (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). Subjects with IGA "0" or "1" and a reduction from baseline of ≥2 points at Week 16 were reported.

Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Subject considered non-responder after rescue treatment use – Full analysis set (FAS). FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Primary

End point timeframe:

At Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percentage of subjects				
number (not applicable)	2.4	17.9	24.4	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Analysis was performed using Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (less than [<] 60 kilogram [kg] vs greater than or equal to [≥] 60 kg).

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	22
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.2
upper limit	31.87

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (<60 kg vs >= 60 kg).

Comparison groups	Placebo v Dupilumab 300 mg Q4W
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	24.31

Notes:

[2] - Threshold for significance at 0.05 level.

Primary: Percentage of Subjects with Eczema Area and Severity Index (EASI)-75

(≥75% Improvement from Baseline) at Week 16

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

End point description:

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. EASI--75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16.

Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Subject considered nonresponder after rescue treatment use – Full analysis set (FAS). FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Primary

End point timeframe:

At Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percentage of Subjects				
number (not applicable)	8.2	38.1	41.5	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (< 60 kg vs >= 60 kg).

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	33.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.07
upper limit	45.39

Notes:

[3] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (< 60 kg vs >=60 kg).

Comparison groups	Dupilumab 300 mg Q4W v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	29.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.94
upper limit	41.78

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in EASI Score at Week 16

End point title	Percent Change from Baseline in EASI Score at Week 16

End point description:

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.

[Multiple imputation (MI) Method with Data Set to Missing after Rescue Treatment Use – Full analysis set (FAS). FAS included all randomized subjects. Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered as non-¬responders.]

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percent change				
least squares mean (standard error)	-23.6 (± 5.49)	-64.8 (± 4.51)	-65.9 (± 3.99)	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs. Placebo) of the LS mean percent change using analysis of covariance (ANCOVA) model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-42.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.6
upper limit	-29.04

Notes:

[5] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs. Placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

Comparison groups	Dupilumab 300 mg Q4W v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-41.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.44
upper limit	-28.02

Notes:

[6] - Threshold for significance at 0.05 level.

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

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

End point description:

revise to weekly average post-baseline

[MI Method with Data Set to Missing after Rescue Treatment Use – FAS. Values after first rescue

treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: percent change				
least squares mean (standard error)	-19.0 (± 4.09)	-45.5 (± 3.54)	-47.9 (± 3.43)	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs. Placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.54
upper limit	-18.38

Notes:

[7] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs. Placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

Comparison groups	Dupilumab 300 mg Q4W v Placebo

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.45
upper limit	15.63

Notes:

[8] - Threshold for significance at 0.05 level.

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

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

End point description:

Pruritus NRS is an assessment tool that is 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 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.

[Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥3.]

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: percentage of subjects				
number (not applicable)	9.4	38.6	48.8	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by

CMH test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	39.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.9
upper limit	51.84

Notes:

[9] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

Comparison groups	Dupilumab 300 mg Q4W v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.97
upper limit	41.32

Notes:

[10] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 Points From Baseline to Week 16

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

End point description:

revise

[Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥ 4.

End point type	Secondary

End point timeframe:
Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	82	
Units: Percentage of subjects				
number (not applicable)	4.8	26.5	36.6	

Statistical analyses

Statistical analysis title	Dupilumab 200 mg or 300 mg Q2W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

Comparison groups	Dupilumab 200 mg or 300 mg Q2W v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	31.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.45
upper limit	43.2

Notes:

[11] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

Comparison groups	Dupilumab 300 mg Q4W v Placebo

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	21.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.21
upper limit	32.28

Notes:

[12] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with EASI-50 at Week 16

End point title	Percentage of Subjects with EASI-50 at 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. EASI-50 responders were the subjects who achieved >=50% overall improvement in EASI score at Week 16. Values after first rescue treatment used were set to missing. Subjects with missing value at week 16 were considered as a non-responder. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: percentage of subjects				
number (not applicable)	12.9	54.8	61.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With EASI-90 at Week 16

End point title	Percentage of Subjects With EASI-90 at 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. EASI-90 responders were the subjects who achieved >=90% overall improvement in EASI score at Week 16. Values after first rescue treatment used were set to

missing. Subjects with missing value at week 16 were considered as a non-responder. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: percentage of subjects				
number (not applicable)	2.4	19.0	23.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >=3 From Baseline

End point title	Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >=3 From Baseline

End point description:

It was measured by percentage of subjects with improvement of weekly average of daily peak pruritus numerical rating scale (NRS) score increased by 3 or more points from baseline. 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]). FAS included all randomized subjects. Here, number of subjects analyzed=subjects with available data for specified endpoint.

End point type	Secondary

End point timeframe:

Baseline up to week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: weeks				
arithmetic mean (standard deviation)	11.4 (± 5.63)	8.4 (± 5.92)	7.7 (± 5.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >=4 From Baseline

End point title	Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >=4 From Baseline

End point description:

It was measured by percentage of subjects with improvement of weekly average of daily peak pruritus numerical rating scale (NRS) score increased by 4 or more points from baseline. 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]). FAS included all randomized subjects. Here, number of subjects analyzed=subjects with available data for specified endpoint.

End point type	Secondary

End point timeframe:

Baseline up to week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	82	
Units: weeks				
arithmetic mean (standard deviation)	12.8 (± 4.90)	9.9 (± 5.87)	10.6 (± 5.50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Body Surface Area (BSA) at week 16

End point title	Change From Baseline in Percent Body Surface Area (BSA) at 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. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: percentage of body surface area				
least squares mean (standard error)	-11.66 (± 2.720)	-33.41 (± 2.330)	-30.11 (± 2.337)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Score at Week 16

End point title	Percent Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Score at Week 16

End point description:

SCORAD is 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.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percent change				
least squares mean (standard error)	-17.6 (± 3.76)	-47.5 (± 3.21)	-51.6 (± 3.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children’s Dermatology Life Quality Index (CDLQI) Total Score at Week 16

End point title	Change From Baseline in Children’s Dermatology Life Quality Index (CDLQI) Total Score at Week 16

End point description:

The CDLQI is a 10-item questionnaire used to measure how much a subject’s skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant, 1 = Only a little, 2 = Quite a lot, 3 = Very much = yes = prevent school. FAS included all randomized subjects.

End point type	Secondary
End point timeframe: Baseline, Week 16	

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Scores on a scale				
least squares mean (standard error)	-5.1 (± 0.62)	-8.8 (± 0.53)	-8.5 (± 0.50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Oriented Eczema Measure (POEM) at Week 16

End point title	Change From Baseline in Patient Oriented Eczema Measure (POEM) at Week 16

End point description:

The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4= 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor quality of life (QOL). FAS included all randomized subjects.

End point type	Secondary
End point timeframe: Baseline, Week 16	

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Scores on a scale				
least squares mean (standard error)	-3.8 (± 0.96)	-9.5 (± 0.86)	-10.1 (± 0.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at

Week 16

End point title	Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 16

End point description:

revise

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Scores on a scale				
least squares mean (standard error)	-1.54 (± 0.303)	-3.44 (± 0.260)	-3.70 (± 0.250)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 4

End point title	Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 4

End point description:

Pruritus NRS scale is an assessment tool that is 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 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]). FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percent change				
least squares mean (standard error)	-12.5 (± 3.06)	-33.1 (± 3.05)	-34.7 (± 2.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Hospital Anxiety and Depression Scale (HADS) at Week 16

End point title	Change From Baseline in Total Hospital Anxiety and Depression Scale (HADS) at Week 16

End point description:

The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each sub-scale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either sub-scale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.' FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Scores on a scale				
least squares mean (standard error)	-2.5 (± 0.80)	-5.2 (± 0.73)	-3.8 (± 0.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >= 4 From Baseline at Week 4

End point title	Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS >= 4 From Baseline at 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]). FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

From baseline to Week 4

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	82	
Units: Percentage of Subjects				
number (not applicable)	4.8	20.5	22.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Skin-infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) Through Week 16

End point title	Percentage of Subjects With Skin-infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) Through Week 16

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 causal relationship with this treatment. Treatment-emergent adverse events (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 the end of study [Week 16]). 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 subjects with both serious and non-serious AEs. FAS included all randomized subjects. Here, number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: Percentage of subjects				
number (not applicable)	18.8	9.6	9.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Serious TEAEs Through Week 16

End point title	Percentage of Subjects With Serious TEAEs Through Week 16

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 causal relationship with this treatment. Treatment-emergent adverse events (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 the end of study [Week 28]). 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 subjects with both serious and non-serious AEs. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: Percentage of subjects				
number (not applicable)	1.2	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Day 197) regardless of seriousness or relationship to investigational product (IP).

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs (TEAEs) that developed/worsened during 'on treatment period' (from 1st dose of IP up to Day 113). TEAEs were collected for the 16-week treatment & follow-up period up to 12 weeks. After completing the treatment period, all were offered an opportunity to enroll in open-label extension (OLE) study R668-AD-1434.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Dupilumab 300 mg Q4W

Reporting group description:

Dupilumab 300 mg Q4W

Reporting group title	Dupilumab 200 mg or 300 mg

Reporting group description:

Dupilumab 200 mg or 300 mg

Serious adverse events	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	0 / 82 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dupilumab 300 mg Q4W	Dupilumab 200 mg or 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 85 (47.06%)	34 / 83 (40.96%)	39 / 82 (47.56%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 85 (10.59%)	4 / 83 (4.82%)	9 / 82 (10.98%)
occurrences (all)	14	5	11
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	21 / 85 (24.71%)	16 / 83 (19.28%)	15 / 82 (18.29%)
occurrences (all)	29	27	21
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 85 (4.71%)	0 / 83 (0.00%)	5 / 82 (6.10%)
occurrences (all)	4	0	6
Nasopharyngitis			
subjects affected / exposed	4 / 85 (4.71%)	10 / 83 (12.05%)	5 / 82 (6.10%)
occurrences (all)	5	16	8
Pharyngitis streptococcal			
subjects affected / exposed	0 / 85 (0.00%)	5 / 83 (6.02%)	2 / 82 (2.44%)
occurrences (all)	0	5	2
Upper respiratory tract infection			
subjects affected / exposed	15 / 85 (17.65%)	7 / 83 (8.43%)	10 / 82 (12.20%)
occurrences (all)	23	9	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2015	Following changes were made: - Added a 200 mg Q2W regimen (with a loading dose of 400 mg on day 1) to the Q2W treatment group. Subjects below 60 kg received 200 mg Q2W, while subjects >=60 kg received 300 mg Q2W (with a loading dose of 600 mg on day 1). This weight-adjusted dosing better fulfilled the conventional therapeutic objective to utilize the minimum effective dose. - Changed duration of treatment period from 12 weeks to 16 weeks. - Revised inclusion and exclusion criteria. - Added a clarifying note that subjects who had a positive drug test due to a prescription drug being used for medical reasons, would still be eligible for enrollment into the study. - Removed the endpoint hierarchy under Multiplicity Considerations; details were specified in the SAP. - Removed the endpoint hierarchy under Multiplicity Considerations; details were specified in the SAP. - Updated all endpoints previously being assessed at 12 weeks to be assessed at 16 weeks (to align with increase in duration of treatment period from 12 weeks to 16 weeks). - Revised the number of imputations used to generate a complete data set for missing data from the FAS from 50 times to multiple times. - Corrected the IND number. - Added that "Regulatory approvals were also obtained where required by local legislation." - Updated the Introduction to include more current information about completed and ongoing trials in the dupilumab program. - Revised the Biomarker Procedures section to align with the new procedures for collection, use, and storage of biomarker serum and plasma samples and DNA/RNA samples for the optional genomics sub-study. - Revised the definition of concomitant medications and procedures. - Deleted the section on Cytochrome P450. - Clarified the definition of the ADA analysis set. - Included that ADA positive samples would be further characterized for the presence of neutralizing antibody response.
05 July 2017	- Added an exclusion criterion. - Corrected the expellable volume for 200 mg to 1.14 mL instead of 1.0 mL. - Clarified the text indicating where moisturizers should be applied by the deletion of the following text in the third sentence "on the area(s) of nonlesional skin designated for such assessments". - Added the medication crisaborole to the list of prohibited agents because it is a treatment for atopic dermatitis and would interfere with the efficacy evaluation. - Added crisaborole to the list of prohibited medications to prevent any confounding of efficacy assessment for the study drug. - Added the medication crisaborole to the list of prohibited agents because it is a treatment for atopic dermatitis and would interfere with the efficacy evaluation. - Added crisaborole to the list of prohibited medications to prevent any confounding of efficacy assessment for the study drug. -Removed hematology and chemistry assessments at week 2 and week 12. - Removed the Pain Assessment with VAS from phone visit 16 for accuracy. - Added the IGA scale to the protocol. - The scale was already included in the efficacy procedures and in the Study Manual and was added to Appendix 2 for further clarification. - As per FDA request, provided further details on the methodology for multiple imputation of the continuous endpoints and deleted text related to missing data from the FAS. - For continuous endpoints, added that the MI with ANCOVA model would be used "as the primary analysis method."
23 February 2018	- Key secondary endpoints were added. - Revision was made in Inclusion Criterion. - The biomarker sample type was changed from "serum/plasma" to "serum" based on clarification letter previously sent to investigators, regulatory authorities, ethic committees and independent review boards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported