Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of Multiple Dupilumab Dose Regimens Administered as Monotherapy for Maintaining Treatment Response in Patients With Atopic Dermatitis

Summary

EudraCT number	2014-003384-38
Trial protocol	LT EE DE FI SE GB DK ES BG PL IT
Global end of trial date	18 October 2016

Results information

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

Trial information

Trial identification

Sponsor protocol code	R668-AD-1415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02395133
WHO universal trial number (UTN)	-
Other trial identifiers	Investigational New Drug: IND 107969

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States,
Public contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 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 is to assess the ability of different Dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of initial treatment with Dupilumab monotherapy compared to placebo.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2015
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	Poland: 19
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	United States: 153
Country: Number of subjects enrolled	Japan: 28
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Canada: 39
Worldwide total number of subjects	422
EEA total number of subjects	172

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)	397
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 15 countries between 25 March 2015 and 18 October 2016. A total of 422 subjects were randomized in the study.

Pre-assignment

Screening details:

Out of the 475 subjects, 422 were randomized and received Dupilumab. Subjects were randomized in 2:1:1:1 ratio to receive Dupilumab 300 milligram (mg) once weekly/twice weekly (QW/Q2W), Dupilumab 300 mg four times a week (Q4W), Dupilumab 300 mg eight times a week (Q8W) and

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QW

Arm description:

Subcutaneous injection of Placebo (for Dupilumab) was administered weekly (QW) from Week 1 (Day 1) to Week 36.

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 Q8W

Arm description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every eight week (Q8W) from Week 1 to Week 36.

Arm type	Experimental
Investigational medicinal product name	Dupilumab 300 mg
Investigational medicinal product code	REGN668
Other name	SAR231893
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 Q4W

Arm description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every four week (Q4W) from Week 1 to Week 36.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668
Other name	SAR231893
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/QW

Arm description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every week (QW) or twice a week (Q2W) from Week 1 to Week 36.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668
Other name	SAR231893
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 Q8W	Dupilumab 300 mg Q4W
Started	83	84	86
Completed	69	75	76
Not completed	14	9	10
Physician decision	-	-	-
Consent withdrawn with personal reason	-	1	-
Pregnancy	-	-	3
Adverse event	4	1	3
Other than specified	5	2	2
Sponsor decision	2	-	-
Lost to follow-up	-	1	1
Consent withdrawn with no reason given	1	3	-
Lack of efficacy	1	-	1
Protocol deviation	1	1	-

Number of subjects in period 1	Dupilumab 300 mg Q2W/QW
Started	169
Completed	155
Not completed	14
Physician decision	1

Consent withdrawn with personal reason	3
Pregnancy	-
Adverse event	-
Other than specified	4
Sponsor decision	-
Lost to follow-up	-
Consent withdrawn with no reason given	2
Lack of efficacy	1
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QW
Reporting group description:	
Subcutaneous injection of Placebo (for Dupilumab) was administered weekly (QW) from Week 1 (Day 1) to Week 36.	
Reporting group title	Dupilumab 300 mg Q8W
Reporting group description:	
Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every eight week (Q8W) from Week 1 to Week 36.	
Reporting group title	Dupilumab 300 mg Q4W
Reporting group description:	
Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every four week (Q4W) from Week 1 to Week 36.	
Reporting group title	Dupilumab 300 mg Q2W/QW
Reporting group description:	
Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every week (QW) or twice a week (Q2W) from Week 1 to Week 36.	

Reporting group values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W
Number of subjects	83	84	86
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	38.1	37.3	38.5
standard deviation	± 13.64	± 13.98	± 16.76
Gender categorical			
Units: Subjects			
Female	32	33	43
Male	51	51	43
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	3	1
Not Hispanic or Latino	75	81	85
Unknown or Not Reported	6	0	0
Race (NIH/OMB)			
Units: Subjects			

American Indian or Alaska Native	0	0	0
Asian	17	18	16
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	8	4
White	54	56	64
More than one race	0	0	0
Unknown or Not Reported	5	2	2
Region of Enrollment Units: Subjects			
North America	38	39	38
Japan	12	11	12
Europe	33	34	36
Eczema Area and Severity Index (EASI) score			
The EASI score was used to measure the severity and extent of atopic dermatitis (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 range from 0 (minimum) to 72 (maximum) points,with the higher scores reflecting the worse severity of AD.			
Units: units on a scale			
arithmetic mean	2.5	2.3	2.8
standard deviation	± 2.31	± 2.33	± 3.31
Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is an assessment tool that is used to report the intensity of subjects'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]).			
Units: units on a scale			
arithmetic mean	2.8	2.7	3.1
standard deviation	± 2.11	± 2.27	± 2.16
Body Surface Area (BSA) Involvement with AD			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined.			
Units: percentage of body surface area			
arithmetic mean	8.1	7.9	9.3
standard deviation	± 8.21	± 9.04	± 10.51
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.) were assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease).			
Units: units on a scale			
arithmetic mean	16.8	17.1	17.5
standard deviation	± 10.03	± 9.41	± 10.59
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]).			
Units: units on a scale			
arithmetic mean	6.1	6.8	6.1
standard deviation	± 5.43	± 5.88	± 5.11

Dermatology Life Quality Index (DLQI) Score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on 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 indicative of a poor QOL.			
Units: units on a scale			
arithmetic mean	3.4	3	3.2
standard deviation	± 4.25	± 3.76	± 3.93
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 a scale			
arithmetic mean	5.9	7.1	7.3
standard deviation	± 6.36	± 6.87	± 7.53

Reporting group values	Dupilumab 300 mg Q2W/QW	Total	
Number of subjects	169	422	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	38.5		
standard deviation	± 13.94	-	
Gender categorical			
Units: Subjects			
Female	87	195	
Male	82	227	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	10	16	
Not Hispanic or Latino	155	396	
Unknown or Not Reported	4	10	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	31	82	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	7	26	

White	124	298	
More than one race	0	0	
Unknown or Not Reported	7	16	
Region of Enrollment Units: Subjects			
North America	77	192	
Japan	23	58	
Europe	69	172	
Eczema Area and Severity Index (EASI) score			
The EASI score was used to measure the severity and extent of atopic dermatitis (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 range from 0 (minimum) to 72 (maximum) points,with the higher scores reflecting the worse severity of AD.			
Units: units on a scale			
arithmetic mean	2.6		
standard deviation	± 2.92	-	
Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is an assessment tool that is used to report the intensity of subjects'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]).			
Units: units on a scale			
arithmetic mean	2.8		
standard deviation	± 1.92	-	
Body Surface Area (BSA) Involvement with AD			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined.			
Units: percentage of body surface area			
arithmetic mean	7.9		
standard deviation	± 9.02	-	
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.) were assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease).			
Units: units on a scale			
arithmetic mean	17.1		
standard deviation	± 10.49	-	
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]).			
Units: units on a scale			
arithmetic mean	6.4		
standard deviation	± 5.3	-	
Dermatology Life Quality Index (DLQI) Score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on 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 indicative of a poor QOL.			

Units: units on a scale			
arithmetic mean	3.4		
standard deviation	± 4.21	-	
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 a scale			
arithmetic mean	6.4		
standard deviation	± 5.94	-	

End points

End points reporting groups

Reporting group title	Placebo QW

Reporting group description:

Subcutaneous injection of Placebo (for Dupilumab) was administered weekly (QW) from Week 1 (Day 1) to Week 36.

Reporting group title	Dupilumab 300 mg Q8W

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every eight week (Q8W) from Week 1 to Week 36.

Reporting group title	Dupilumab 300 mg Q4W

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every four week (Q4W) from Week 1 to Week 36.

Reporting group title	Dupilumab 300 mg Q2W/QW

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every week (QW) or twice a week (Q2W) from Week 1 to Week 36.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injection of Placebo (for Dupilumab) was administered weekly (QW) from Week 1 (Day 1) to Week 36.

Subject analysis set title	Dupilumab 300 mg Q8W
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every eight week (Q8W) from Week 1 to Week 36.

Subject analysis set title	Dupilumab 300 mg Q4W
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every four week (Q4W) from Week 1 to Week 36.

Subject analysis set title	Dupilumab 300 mg Q2W/QW
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every week (QW) or twice a week (Q2W) from Week 1 to Week 36.

Primary: Difference Between Current Study Baseline and Week 36 in Percent Change in EASI From Parent Study Baseline (NCT02277743 and NCT02277769)

End point title	Difference Between Current Study Baseline and Week 36 in Percent Change in EASI From Parent Study Baseline (NCT02277743 and NCT02277769)

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. Difference of percent change in EASI between current study baseline and week 36 in from parent study baseline (NCT02277743 and NCT02277769) was reported. Values after first rescue treatment used were set to missing before multiple imputation (MI). Full analysis set (FAS) population included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline (Parent Study), Baseline (Current Study) and Week 36 (Current study)

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: percent change				
least squares mean (standard error)	21.67 (± 3.134)	6.84 (± 2.434)	3.84 (± 2.283)	0.06 (± 1.736)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q8W vs Placebo QW

Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the co-primary and key secondary efficacy endpoints in a pre-specified order. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Analysis was performed using ANCOVA method.

Comparison groups	Dupilumab 300 mg Q8W v Placebo QW
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [1]
Method	ANCOVA
Parameter estimate	Percent Change Difference
Point estimate	-14.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.34
upper limit	-7.33

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo QW

Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the co-primary and key secondary efficacy endpoints in a pre-specified order. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Analysis was performed using ANCOVA method.

Comparison groups	Dupilumab 300 mg Q4W v Placebo QW

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Percent Change Difference
Point estimate	-17.83
Confidence interval	
sides	2-sided
lower limit	-25.33
upper limit	-10.34

Notes:

[2] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W/QW vs Placebo QW

Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the co-primary and key secondary efficacy endpoints in a pre-specified order. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Analysis was performed using ANCOVA method.

Comparison groups	Dupilumab 300 mg Q2W/QW v Placebo QW
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Percent Change Difference
Point estimate	-21.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.36
upper limit	-14.87

Notes:

[3] - Threshold for significance at 0.05 level.

Primary: Percentage of Subjects With Eczema Area and Severity Index Greater than or Equal to (>=) 75% (EASI-75) at Baseline of Current Study Maintaining EASI-75 at Week 36

End point title	Percentage of Subjects With Eczema Area and Severity Index Greater than or Equal to (>=) 75% (EASI-75) at Baseline of Current Study Maintaining EASI-75 at Week 36

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 at Week 36. Values after first rescue treatment used were set to missing. Subjects with missing value at week 36 were considered as a non- responder. FAS population was used. Here, number of subjects analyzed = subjects with EASI-75 at baseline.

End point type	Primary

End point timeframe:

Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	84	162
Units: percentage of subjects				
number (not applicable)	30.4	54.9	58.3	71.6

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q8W vs Placebo QW

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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q8W v Placebo QW
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.7
upper limit	39.29

Notes:

[4] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W vs Placebo QW

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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q4W v Placebo QW
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	28

Confidence interval	
level	95 %
sides	2-sided
lower limit	13.32
upper limit	42.58

Notes:

[5] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W/QW vs on Placebo QW

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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q2W/QW v Placebo QW
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	41.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.93
upper limit	53.52

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Maintaining Investigator Global Assessment (IGA) Response Within 1 Point of Baseline at Week 36

End point title	Percentage of Subjects Maintaining Investigator Global Assessment (IGA) Response Within 1 Point of Baseline at Week 36

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 36 were reported. Values after first rescue treatment used were set to missing. Subjects with missing value at a visit were considered as a non-responder. FAS population was used. Here, number of subjects analyzed = subjects with IGA 0 or 1 at Baseline from Interactive voice response system (IVRS).

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	66	126
Units: percentage of subjects				
number (not applicable)	28.6	50	62.1	70.6

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q8W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q8W v Placebo QW
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.86
upper limit	38

Notes:

[7] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q4W v Placebo QW
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	33.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.38
upper limit	49.72

Notes:

[8] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W/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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q2W/QW v Placebo QW
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	42.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.36
upper limit	55.76

Notes:

[9] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Maintaining Investigator Global Assessment (IGA) Response at 0 or 1 Point at Week 36

End point title	Percentage of Subjects Maintaining Investigator Global Assessment (IGA) Response at 0 or 1 Point at Week 36

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 at week 36 were reported as responders. Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 36 were considered as non-responders. FAS population was used. Here, number of subjects analyzed = subjects with IGA 0 or 1 at Baseline from IVRS.

End point type	Secondary

End point timeframe:

Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	66	126
Units: Percentage of Subjects				
number (not applicable)	14.3	32.8	43.9	54

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q8W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q8W v Placebo QW
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.14
upper limit	32.91

Notes:

[10] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q4W v Placebo QW
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	29.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.89
upper limit	44.42

Notes:

[11] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W/QW vs on 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q2W/QW v Placebo QW

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	39.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.42
upper limit	51.95

Notes:

[12] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects With Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score Increased by 3 or More Points From Baseline to Week 35

End point title	Percentage of Subjects With Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) Score Increased by 3 or More Points From Baseline to Week 35

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subjects'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]). Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 35 were considered as non-responders. FAS population was used. Here, number of subjects analyzed = subjects with NRS <= 7 at Baseline.

End point type	Secondary

End point timeframe:

Baseline up to Week 35

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	81	83	168
Units: Percentage of Subjects				
number (not applicable)	70	55.6	49.4	33.9

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q8W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q8W v Placebo QW

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1048 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.21
upper limit	0.32

Notes:

[13] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q4W 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q4W v Placebo QW
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0107 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-20.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.32
upper limit	-5.89

Notes:

[14] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W/QW vs on 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, baseline disease severity and Dupilumab regimen received in parent studies.

Comparison groups	Dupilumab 300 mg Q2W/QW v Placebo QW
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-36.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.4
upper limit	-23.74

Notes:

[15] - Threshold for significance at 0.05 level.

Secondary: Time to First Event of Investigator's Global Assessment (IGA) >= 2 for Subjects With IGA 0 or 1 at Baseline

End point title	Time to First Event of Investigator's Global Assessment (IGA) >= 2 for Subjects With IGA 0 or 1 at Baseline

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). FAS population was used. Here, number of subjects analyzed = subjects with IGA 0 or 1 at Baseline from IVRS.

End point type	Secondary

End point timeframe:

Baseline up to Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	66	126
Units: days				
median (confidence interval 95%)	57 (56 to 58)	85 (59 to 113)	80 (55 to 85)	114 (85 to 169)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Increased Investigator's Global Assessment (IGA) Score 3 or 4 at Week 36

End point title	Percentage of Subjects With Increased Investigator's Global Assessment (IGA) Score 3 or 4 at Week 36

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). Values after first rescue treatment were set to missing and subjects with missing IGA scores at Week 36 were considered as responders (i.e. having a increase 3 or 4 of IGA value). FAS population was used. Here, number of subjects analyzed = subjects with IGA 0 or 1 at Baseline from IVRS.

End point type	Secondary

End point timeframe:

Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	66	126
Units: Percentage of Subjects				
number (not applicable)	66.7	48.4	34.8	26.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Eczema Area and Severity Index-50 (EASI-50) (>= 50% Reduction in EASI Score) at Week 36

End point title	Percentage of Subjects With Eczema Area and Severity Index-50 (EASI-50) (>= 50% Reduction in EASI Score) at Week 36

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 from baseline to Week 36. Values after first rescue treatment were set to missing and subjects with missing EASI-50 scores at Week 36 were considered as non-responders. FAS population was used.

End point type	Secondary

End point timeframe:

Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: Percentage of subjects				
number (not applicable)	39.8	54.8	60.5	73.4

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Eczema Area and Severity Index (EASI) at Week 36

End point title	Absolute Change From Baseline in Eczema Area and Severity Index (EASI) at Week 36

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. Values after first rescue treatment were set to missing and subjects with missing Values at Week 36 were imputed by using multiple imputation method. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	6.61 (± 0.799)	1.75 (± 0.738)	1.37 (± 0.735)	0.09 (± 0.511)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 36

End point title	Absolute Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 36

End point description:

SCORAD is 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). Values after first rescue treatment used were set to missing (censoring) before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	18.61 (± 2.107)	6.62 (± 2.010)	2.25 (± 1.899)	0.99 (± 1.350)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Peak Daily Pruritus Numerical Rating Scale (NRS) Score at Week 35

End point title	Absolute Change From Baseline in Peak Daily Pruritus Numerical Rating Scale (NRS) Score at Week 35

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subjects's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subjects 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]). Values after first rescue treatment used were set to missing before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline, Week 35

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	2.5 (± 0.29)	1.1 (± 0.27)	0.6 (± 0.25)	-0.1 (± 0.20)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Body Surface Area (BSA) Through Week 36

End point title	Absolute Change From Baseline in Percent Body Surface Area (BSA) Through Week 36

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. Values after first rescue treatment used were set to missing (censoring) before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: meter square				
least squares mean (standard error)	9.16 (± 1.642)	2.74 (± 1.530)	1.74 (± 1.457)	-1.27 (± 1.044)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline Through in Patient Oriented Eczema Measure (POEM) Through Week 36

End point title	Absolute Change From Baseline Through in Patient Oriented Eczema Measure (POEM) Through Week 36

End point description:

The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Values after first rescue treatment used were set to missing (censoring) before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	7 (± 0.9)	2.8 (± 0.78)	0.8 (± 0.73)	-0.3 (± 0.56)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Dermatology Life Quality Index (DLQI) Through Week 36

End point title	Absolute Change From Baseline in Dermatology Life Quality Index (DLQI) Through Week 36

End point description:

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Values after first rescue treatment used were set to missing before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	3.1 (± 0.52)	1.5 (± 0.46)	0.3 (± 0.48)	-0.2 (± 0.33)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Hospital Anxiety Depression Scale (HADS) Through Week 36

End point title	Absolute Change From Baseline in Hospital Anxiety Depression Scale (HADS) Through Week 36

End point description:

HADS is 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. Values after first rescue treatment used were set to missing before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through Week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: units on a scale				
least squares mean (standard error)	0.8 (± 0.6)	0.7 (± 0.52)	0.2 (± 0.54)	-0.8 (± 0.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between Current Study Baseline and Week 36 in Percent Change in SCORAD From Parent Study Baseline

End point title	Difference Between Current Study Baseline and Week 36 in Percent Change in SCORAD From Parent Study Baseline

End point description:

SCORAD is 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). Values after first rescue treatment used were set to missing before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline (Parent Study), Baseline (Current Study) and Week 36 (Current study)

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: Percent change				
least squares mean (standard error)	28.97 (± 3.683)	10.42 (± 2.988)	2.21 (± 2.743)	0.33 (± 2.092)

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between Current Study Baseline and Week 35 in Percent Change in Peak Weekly Pruritus NRS From Parent Study Baseline

End point title	Difference Between Current Study Baseline and Week 35 in Percent Change in Peak Weekly Pruritus NRS From Parent Study Baseline

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]). Values after first rescue treatment used were set to missing before MI. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline (Parent Study), Baseline (Current Study) and Week 35 (Current study)

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: percent change				
least squares mean (standard error)	35.6 (± 4.32)	16.7 (± 4.09)	8.6 (± 4.02)	-0.1 (± 3.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Event Rate of Skin Infection Treatment- Emergent Adverse Events (TEAEs)

End point title	Annualized Event Rate of Skin Infection Treatment- Emergent Adverse Events (TEAEs)

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 36]). 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 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: events per year				
median (confidence interval 95%)	0.12 (0.044 to 0.338)	0.07 (0.024 to 0.226)	0.02 (0.005 to 0.12)	0.02 (0.007 to 0.083)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Event Rate of Flares

End point title	Annualized Event Rate of Flares

End point description:

Rate of Flares defined as worsening of disease requiring initiation or escalation of rescue treatment. FAS population was used.

End point type	Secondary

End point timeframe:

Baseline through week 36

End point values	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	84	86	169
Units: events per year				
median (confidence interval 95%)	0.75 (0.465 to 1.214)	0.6 (0.363 to 0.977)	0.39 (0.231 to 0.661)	0.24 (0.146 to 0.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Well-Controlled Weeks During the On-treatment Period

End point title	Percentage of Well-Controlled Weeks During the On-treatment Period

End point description:

Well-controlled weeks are those in which subjects during their weekly IVRS call completion has their eczema been well-controlled over the last week during which no rescue treatments were administered. Percentage of well-controlled weeks during the on-treatment period were reported. The safety analysis set (SAF) included all randomized subjects who received any amount of study drug. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through Week 36

End point values	Placebo	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W	Dupilumab 300 mg Q2W/QW
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	82	87	165
Units: percentage of weeks				
arithmetic mean (standard deviation)	40.9 (± 30.35)	53.2 (± 32.95)	52.3 (± 35.96)	63.6 (± 32.08)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 36) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events that developed/worsened during the 'on-treatment period' (time form the first dose of study drug up to the end of study [Week 36]). The safety analysis set (SAF) included all randomized subjects who received any amount of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo QW

Reporting group description:

Subcutaneous injection of Placebo (for Dupilumab) was administered weekly (QW) from Week 1 (Day 1) to Week 36.

Reporting group title	Dupilumab 300 mg Q8W

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every eight week (Q8W) from Week 1 to Week 36.

Reporting group title	Dupilumab 300 mg Q4W

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every four week (Q4W) from Week 1 to Week 36.

Reporting group title	Dupilumab 300 mg Q2W/QW

Reporting group description:

Subcutaneous injection of Dupilumab 300 mg alternatively with placebo (matched to Dupilumab) once every week (QW) or twice a week (Q2W) from Week 1 to Week 36.

Serious adverse events	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 82 (1.22%)	3 / 84 (3.57%)	4 / 87 (4.60%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 82 (0.00%)	2 / 84 (2.38%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			

subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ligament rupture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 84 (1.19%)	0 / 87 (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
Open fracture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia induced cardiomyopathy			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Biochemical pregnancy			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	0 / 87 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 300 mg Q2W/QW		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 167 (3.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Gun shot wound			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle injury			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Open fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia induced cardiomyopathy			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Biochemical pregnancy			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Osteoarthritis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo QW	Dupilumab 300 mg Q8W	Dupilumab 300 mg Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 82 (67.07%)	43 / 84 (51.19%)	47 / 87 (54.02%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 82 (2.44%)	3 / 84 (3.57%)	5 / 87 (5.75%)
occurrences (all)	6	3	7
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	2 / 82 (2.44%)	3 / 84 (3.57%)	2 / 87 (2.30%)
occurrences (all)	22	10	8
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	40 / 82 (48.78%)	27 / 84 (32.14%)	30 / 87 (34.48%)
occurrences (all)	60	34	43
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	5 / 87 (5.75%)
occurrences (all)	1	0	6
Influenza			
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	5 / 87 (5.75%)
occurrences (all)	1	0	7
Nasopharyngitis			
subjects affected / exposed	11 / 82 (13.41%)	11 / 84 (13.10%)	11 / 87 (12.64%)
occurrences (all)	13	14	14
Oral herpes			
subjects affected / exposed	3 / 82 (3.66%)	5 / 84 (5.95%)	2 / 87 (2.30%)
occurrences (all)	4	10	5
Upper respiratory tract infection			

subjects affected / exposed	6 / 82 (7.32%)	7 / 84 (8.33%)	5 / 87 (5.75%)
occurrences (all)	6	7	6

Non-serious adverse events	Dupilumab 300 mg Q2W/QW		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 167 (43.11%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 167 (4.79%)		
occurrences (all)	12		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	10 / 167 (5.99%)		
occurrences (all)	62		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	34 / 167 (20.36%)		
occurrences (all)	43		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences (all)	4		
Influenza			
subjects affected / exposed	4 / 167 (2.40%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	32 / 167 (19.16%)		
occurrences (all)	41		
Oral herpes			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences (all)	10		
Upper respiratory tract infection			
subjects affected / exposed	13 / 167 (7.78%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2015	Following changes were made: 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 to add Japan to the countries that will use the co-primary endpoints, • Changed "other endpoints" to "other secondary endpoints" for clarity and consistency with the terminology used in the parent studies (R668-AD-1334 and -1416), • Moved the endpoint "change in SCORing Atopic Dermatitis (SCORAD) from baseline to week 36" from key secondary endpoints section to the "other secondary endpoints" section, and revised the endpoint from "change … from baseline …" to "percent change … from baseline …" • Added per protocol set (PPS) for efficacy analysis, • Clarified the description, using language consistent with that used in the parent studies (R668-AD-1334 and -1416), of methods for missing data imputation (multiple imputation [MI] Statistical Analysis Software [SAS] procedure with Markov Monte Carlo algorithm) and data analysis.
23 February 2015	• Clarified that subjects who completed the end of treatment visit in SOLO-1 (R668 AD 1334) and SOLO-2, (R668-AD-1416) and who fulfill eligibility criteria, were enrolled in the current study, • Further clarified the definition of adequate birth control for sexually active women of reproductive potential in the "Exclusion Criteria" • Provided more specific guidance on escalation of rescue treatment, • Updated information regarding infections requiring systemic treatment under "Reasons for Temporary Discontinuation of Study Drug" to improve clarity and accuracy, as oral treatment was also a systemic route of administration, • Added an additional restriction to "Prohibited Medications and Procedures" to include all atopic dermatitis (AD) treatments, including off-label treatments, with the exception of those specifically allowed in the protocol, • Removed ACQ-5 and Sinonasal Outcome Test (SNOT)-22 questionnaires from the study visit descriptions of visit 4 and visit 7 to align with the schedule of events • Corrected study drug administration up through week 35, instead of week 36 • Changed the anti-drug antibody (ADA) variables and text throughout the protocol to distinguish between transient and persistent ADA responses, • Made changes throughout the protocol to the follow-up of subjects with positive ADA titer at their last study visit to ensure that subjects with ADA positive titer were not lost to follow-up, • Provided text to clarify the relationship between rescue medications and prohibited medications, • Increased the clarity and accuracy of the conditions for the early termination visit, • Clarified that the sample size was an estimate, based on the anticipated number of eligible subjects enrolled from the SOLO-1 (R668-AD-1334) and SOLO-2 (R668-AD-1416) clinical trials, and not based on a predefined quota.

12 October 2016	The purpose of amendment 3 was to update and revised the protocol sections addressing study endpoints and statistical considerations, and to ensure concordance with the final Statistical Analysis Plan (SAP). The primary objective of the study was to assess the ability of different Dupilumab dose regimens, administered as monotherapy, to maintain the treatment response achieved after 16 weeks of initial treatment. One of the current co-primary endpoints, IGA(0,1) had been helpful to assess initial treatment response but lacks adequate sensitivity to optimally characterize maintenance of response over time for different dosing regimens. As such, a more sensitive co-primary endpoint had been selected to better support the above study objective. The main changes were as follows: • Downgraded the Investigator's Global Assessment (IGA)(0,1) from co-primary to a key secondary endpoint. This endpoint could not be analyzed in the entire randomized population (required subset analysis in subjects with IGA 0,1 at baseline), it did not adequately characterize Dupilumab's clinical effect over time, and it lacked the sensitivity necessary to support the objective of the study, which was to differentiate between the treatment groups analyzed with respect to maintenance vs. loss of response • Added a co-primary endpoint based on percent change in Eczema Area and Severity Index (EASI) score, which was analyzed in the entire randomized population (full analysis set [FAS]). This endpoint provided improved sensitivity to differentiate between maintenance vs. loss of response and better support for the study objective. • Changed the statistical testing methodology of multiplicity control, ie, from parallel testing of each of the 3 dose groups vs. placebo (with a 3-way alpha split and 0.0167 significance level) to hierarchical testing at a 0.05 significance level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported