Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study Investigating the Efficacy, Safety, Pharmacokinetic and Biomarker Profiles of Dupilumab (REGN668, SAR231893) Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2012-003651-11
Trial protocol	HU CZ DE PL
Global end of trial date	10 September 2014

Results information

Result version number	v1
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	R668-AD-1021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01859988
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 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)	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	09 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of multiple dupilumab dose-regimens, compared to placebo, in adult patients 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 Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

Topical corticosteroids

Evidence for comparator: -

Actual start date of recruitment	15 May 2013
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: 35
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	United States: 112
Country: Number of subjects enrolled	Canada: 54
Country: Number of subjects enrolled	Japan: 58
Worldwide total number of subjects	380
EEA total number of subjects	156

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)	372
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 95 study sites in 7 countries. A total of 452 subjects were screened between 15 May 2013 and 10 January 2014. 380 subjects were randomized and 379 were treated. 72 subjects were screen failures mainly due to exclusion and inclusion criteria not met.

Pre-assignment

Screening details:

Randomization was stratified by disease severity (moderate Investigator's global assessment [IGA] = 3 versus severe IGA = 4 atopic dermatitis and region (Japan versus rest of world). Assignment to arms was done centrally in 1:1:1:1:1:1 ratio for Dupilumab (300 mg qw; 300 mg q2w; 200 mg q2w; 300 mg q4w & 100 mg 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	Dupilumab 300 mg qw

Arm description:

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

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

Dosage and administration details:

Subcutaneous injection (300 mg/2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Arm title	Dupilumab 300 mg q2w

Arm description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab every 2 weeks (q2w) from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection (300 mg/2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

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 (2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Arm title	Dupilumab 200 mg q2w

Arm description:

Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 200 mg injection of Dupilumab q2w from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection (200 mg/2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

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 (2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Arm title	Dupilumab 300 mg q4w

Arm description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab every 4 weeks (q4w) and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection (300 mg/2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

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 (2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Arm title	Dupilumab 100 mg q4w

Arm description:

Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single 100 mg injection of Dupilumab q4w and Placebo (for Dupilumab) qw when

Dupilumab not administered from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection (100 mg/2 ml & 200 mg/2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Arm title	Placebo

Arm description:

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

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 (2 ml) in the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs.

Number of subjects in period 1	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Started	63	64	62
Treated	63	64	61
Completed	52	52	34
Not completed	11	12	28
Consent withdrawn by subject	6	3	4
Physician decision	1	3	1
Protocol violation	-	-	1
Adverse event	2	1	3
Other than specified	-	2	11
Lost to follow-up	1	2	3
Lack of efficacy	1	1	5

Number of subjects in period 1	Dupilumab 300 mg q4w	Dupilumab 100 mg q4w	Placebo
Started	65	65	61
Treated	65	65	61
Completed	55	42	42
Not completed	10	23	19
Consent withdrawn by subject	3	2	2
Physician decision	3	4	1

Protocol violation	-	-	-
Adverse event	1	2	2
Other than specified	3	5	3
Lost to follow-up	-	3	2
Lack of efficacy	-	7	9

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab 300 mg qw
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection every week (qw) from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab every 2 weeks (q2w) from Week 1 to Week 15.	
Reporting group title	Dupilumab 200 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 200 mg injection of Dupilumab q2w from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q4w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab every 4 weeks (q4w) and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.	
Reporting group title	Dupilumab 100 mg q4w
Reporting group description:	
Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single 100 mg injection of Dupilumab q4w and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.	
Reporting group title	Placebo
Reporting group description:	
Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection qw from Week 1 to Week 15.	

Reporting group values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Number of subjects	63	64	62
Age categorical Units: Subjects			
Age continuous			
Data is reported for the 379 treated subjects included in the efficacy and safety analyses.			
Units: years arithmetic mean standard deviation	 36.2 ± 10.74	 39.4 ± 12.06	 35.8 ± 14.9
Gender categorical Units: Subjects			
Female	20	23	26
Male	43	41	36

Reporting group values	Dupilumab 300 mg q4w	Dupilumab 100 mg q4w	Placebo
Number of subjects	65	65	61

Age categorical Units: Subjects			

Age continuous			
Data is reported for the 379 treated subjects included in the efficacy and safety analyses.			
Units: years			
arithmetic mean	36.8	36.6	37.2
standard deviation	± 10.77	± 11.55	± 13.1
Gender categorical Units: Subjects			
Female	25	31	21
Male	40	34	40

Reporting group values	Total		
Number of subjects	380		
Age categorical Units: Subjects			

Age continuous			
Data is reported for the 379 treated subjects included in the efficacy and safety analyses.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	146		
Male	234		

End points

End points reporting groups

Reporting group title	Dupilumab 300 mg qw
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection every week (qw) from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab every 2 weeks (q2w) from Week 1 to Week 15.	
Reporting group title	Dupilumab 200 mg q2w
Reporting group description:	
Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 200 mg injection of Dupilumab q2w from Week 1 to Week 15.	
Reporting group title	Dupilumab 300 mg q4w
Reporting group description:	
Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab every 4 weeks (q4w) and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.	
Reporting group title	Dupilumab 100 mg q4w
Reporting group description:	
Two subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single 100 mg injection of Dupilumab q4w and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.	
Reporting group title	Placebo
Reporting group description:	
Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection qw from Week 1 to Week 15.	

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

End point title	Percent Change in Eczema Area and Severity Index Score (EASI) From Baseline to Week 16
End point description:	
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. Analysis was performed on full analysis set (FAS) included all randomized subjects who received at least 1 dose of study drug. Here, number of subjects analyzed = subjects with EASI score assessment at specified time-points. Efficacy data was set to missing after use of rescue medication. Missing values imputed by last observation carried forward (LOCF). Here 'n' signifies number of subjects with available data for each specified category: (Score at) Baseline; (Score at) Week 16; (Percent) Change at Week 16	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	65
Units: Percent change				
arithmetic mean (standard deviation)				
Baseline (n=63,64,61,65,65,61)	30.1 (± 11.23)	33.8 (± 14.52)	32.9 (± 15.5)	29.4 (± 11.48)
Week 16 (n=61,63,60,65,64,61)	7.2 (± 8.83)	10.7 (± 12.89)	10.9 (± 12.41)	9.8 (± 11.16)
Change at Week 16 (n=61,63,60,65,64,61)	-75.5 (± 26.86)	-70.5 (± 35.09)	-67.4 (± 31.97)	-64.9 (± 37.21)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percent change				
arithmetic mean (standard deviation)				
Baseline (n=63,64,61,65,65,61)	32.2 (± 13.49)	32.9 (± 13.77)		
Week 16 (n=61,63,60,65,64,61)	17.4 (± 15.28)	25.6 (± 18.32)		
Change at Week 16 (n=61,63,60,65,64,61)	-46.7 (± 41.96)	-20.2 (± 46.15)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

LS mean and standrad error were obtained using analysis of covariance(ANCOVA) model with treatment and randomization strata(moderate vs severe;Japan vs rest of world) and relevant baseline values as covariates. Multiplicity was controlled using hierarchical testing procedure: highest dose vs. placebo was tested first.Comparison order was 300 mg qw, 300 mg q2w, 200 mg q2w, 300 mg q4w & 100 mg q4w, vs placebo respectively.Testing continues only if previous comparison was statistically significant.

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-55.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.9
upper limit	-42.4
Variability estimate	Standard error of the mean
Dispersion value	6.74

Notes:

[1] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-50.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.3
upper limit	-37
Variability estimate	Standard error of the mean
Dispersion value	6.67

Notes:

[2] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 200 mg q2w vs Placebo

Statistical analysis description:

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

Comparison groups	Dupilumab 200 mg q2w v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-47.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.6
upper limit	-34.1
Variability estimate	Standard error of the mean
Dispersion value	6.76

Notes:

[3] - Threshold for significance at 0.05.

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).

Comparison groups	Dupilumab 300 mg q4w v Placebo

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-45.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.5
upper limit	-32.3
Variability estimate	Standard error of the mean
Dispersion value	6.66

Notes:

[4] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 100 mg q4w vs Placebo

Statistical analysis description:

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

Comparison groups	Dupilumab 100 mg q4w v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-26.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.8
upper limit	-13.7
Variability estimate	Standard error of the mean
Dispersion value	6.65

Notes:

[5] - Threshold for significance at 0.05.

Secondary: Percentage of Subjects Who Achieved Investigator's Global Assessment (IGA) Response at Week 16

End point title	Percentage of Subjects Who Achieved Investigator's Global Assessment (IGA) Response at Week 16

End point description:

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

End point type	Secondary

End point timeframe:

Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	65
Units: Percentage of subjects				
number (confidence interval 95%)	33.3 (21.95 to 46.34)	29.7 (18.91 to 42.42)	27.9 (17.15 to 40.83)	21.5 (12.31 to 33.49)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percentage of subjects				
number (confidence interval 95%)	12.3 (5.47 to 22.82)	1.6 (0.04 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved IGA Score Reduction of ≥2 at Week 16

End point title	Percentage of Subjects Who Achieved IGA Score Reduction of ≥2 at Week 16

End point description:

Values after first rescue medication were set to missing and subjects with missing IGA score at Week 16 were treated as a non-responders. Analysis was done on FAS.

End point type	Secondary

End point timeframe:

Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	65
Units: Percentage of subjects				
number (confidence interval 95%)	50.8 (37.89 to 63.62)	46.9 (34.28 to 59.77)	42.6 (30.04 to 55.94)	35.4 (23.92 to 48.23)

End point values	Dupilumab 100	Placebo		

	mg q4w			
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percentage of subjects				
number (confidence interval 95%)	20 (11.1 to 31.77)	9.8 (3.7 to 20.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Peak Weekly Averaged Pruritus Numerical Rating Scores (NRS) From Baseline to Week 16

End point title	Percent Change in Peak Weekly Averaged Pruritus Numerical Rating Scores (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]). Analysis was performed on FAS. Here, number of subjects analyzed = subjects with pruritus NRS assessment at specified time-points. Efficacy data was set to missing after use of rescue medication. Missing values imputed by LOCF. Here 'n' signifies number of subjects with available data for specified category. (Score at) Baseline; (Score at) Week 16; (Percent) Change at Week 16

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	64
Units: Percent change				
arithmetic mean (standard deviation)				
Baseline (n=62,63,59,63,64,58)	6.54 (± 1.54)	6.74 (± 2.072)	6.98 (± 2.315)	6.84 (± 1.853)
Week 16 (n=63,64,61,64,65,61)	3.07 (± 2.148)	3.64 (± 2.388)	4.21 (± 2.763)	3.99 (± 2.449)
Change at Week 16 (n=62,63,58,63,64,58)	-52.85 (± 31.368)	-46.22 (± 31.964)	-40.6 (± 33.073)	-38.69 (± 38.366)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percent change				
arithmetic mean (standard deviation)				
Baseline (n=62,63,59,63,64,58)	6.71 (± 1.882)	6.34 (± 1.832)		
Week 16 (n=63,64,61,64,65,61)	5.26 (± 2.465)	6.05 (± 2.312)		

Change at Week 16 (n=62,63,58,63,64,58)	-21.47 (± 32.952)	-0.43 (± 38.423)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Peak Weekly Averaged Pruritus NRS From Baseline to Week 16

End point title	Absolute Change in Peak Weekly Averaged Pruritus NRS From Baseline to Week 16

End point description:

Analysis was performed on FAS. Here, number of subjects analyzed = subjects with pruritus NRS assessment at specified time-points. Efficacy data was set to missing after use of rescue medication. Missing values imputed by LOCF. Here 'n' signifies number of subjects with available data for specified category. (Score at) Baseline; (Score at) Week 16; (Absolute) Change at Week 16

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	64
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=62,63,59,63,64,58)	6.54 (± 1.54)	6.74 (± 2.072)	6.98 (± 2.315)	6.84 (± 1.853)
Week 16 (n=63,64,61,64,65,61)	3.07 (± 2.148)	3.64 (± 2.388)	4.21 (± 2.763)	3.99 (± 2.449)
Change at Week 16 (n=62,63,59,63,64,58)	-3.48 (± 2.32)	-3.16 (± 2.467)	-2.77 (± 2.595)	-2.79 (± 2.609)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=62,63,59,63,64,58)	6.71 (± 1.882)	6.34 (± 1.832)		
Week 16 (n=63,64,61,64,65,61)	5.26 (± 2.465)	6.05 (± 2.312)		
Change at Week 16 (n=62,63,59,63,64,58)	-1.46 (± 2.038)	-0.27 (± 2.28)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Analysis was performed on FAS. Here, number of subjects analyzed = subjects with EASI score assessment at specified time-points. Efficacy data was set to missing after use of rescue medication. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	60	65
Units: Units on a scale				
least squares mean (standard error)	-23.1 (± 1.7)	-21.1 (± 1.68)	-20.7 (± 1.71)	-20.4 (± 1.62)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61		
Units: Units on a scale				
least squares mean (standard error)	-13.8 (± 1.64)	-5.8 (± 1.71)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change in SCORing Atopic Dermatitis (SCORAD) Scores from Baseline to 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]). Analysis was performed on FAS. Here, number of subjects analyzed = subjects with SCORAD score assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	60	65
Units: Percent change				
least squares mean (standard deviation)	-56.9 (± 4.12)	-51.2 (± 4.05)	-46 (± 4.12)	-48.8 (± 3.95)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	60		
Units: Percent change				
least squares mean (standard deviation)	-26.6 (± 3.98)	-13.8 (± 4.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in SCORAD Scores From Baseline to Week 16

End point title	Absolute Change in SCORAD Scores From Baseline to Week 16

End point description:

Analysis was performed on FAS. Here, number of subjects analyzed = subjects with SCORAD score assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	60	65
Units: Units on a scale				
least squares mean (standard error)	-38.2 (± 2.76)	-34.4 (± 2.71)	-30.9 (± 2.76)	-33.1 (± 2.64)

End point values	Dupilumab 100 mg q4w	Placebo		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	60		
Units: Units on a scale				
least squares mean (standard error)	-18 (± 2.66)	-10.5 (± 2.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved 50%, 75% and 90% Reduction from Baseline in EASI Score (EASI-50, EASI-75 and EASI-90 Respectively) at Week 16

End point title	Percentage of Subjects Who Achieved 50%, 75% and 90% Reduction from Baseline in EASI Score (EASI-50, EASI-75 and EASI-90 Respectively) at Week 16

End point description:

Analysis was performed on FAS. Subjects with a missing EASI score at Week 16 were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	65
Units: Percentage of participants				
number (confidence interval 95%)				
Reduction of 50%	82.5 (70.9 to 90.95)	78.1 (66.03 to 87.49)	62.3 (48.96 to 74.39)	70.8 (58.17 to 81.4)
Reduction of 75%	60.3 (47.2 to 72.43)	53.1 (40.23 to 65.72)	55.7 (42.45 to 68.45)	49.2 (36.6 to 61.93)
Reduction of 90%	36.5 (24.73 to 49.6)	29.7 (18.91 to 42.42)	31.1 (19.9 to 44.29)	29.3 (18.6 to 41.83)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percentage of participants				
number (confidence interval 95%)				
Reduction of 50%	44.6 (32.27 to 57.47)	29.5 (18.52 to 42.57)		
Reduction of 75%	29.2 (18.6 to 41.83)	11.5 (4.74 to 22.22)		
Reduction of 90%	15.4 (7.63 to 26.48)	3.3 (0.4 to 11.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved 50%, 75% and 90% Reduction From Baseline in SCORAD Score (SCORAD-50, SCORAD-75 and SCORAD-90 Respectively) at Week 16

End point title	Percentage of Subjects Who Achieved 50%, 75% and 90% Reduction From Baseline in SCORAD Score (SCORAD-50, SCORAD-75 and SCORAD-90 Respectively) at Week 16

End point description:

Analysis was performed on FAS. Subjects with a missing SCORAD score at Week 16 were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	61	65
Units: Percentage of participants				
number (confidence interval 95%)				
Reduction of 50%	68.3 (55.3 to 79.4)	59.4 (46.4 to 71.5)	52.5 (39.3 to 65.4)	55.4 (42.5 to 67.7)
Reduction of 75%	23.8 (14 to 36.2)	25 (15 to 37.4)	16.4 (8.2 to 28.1)	21.5 (12.3 to 33.5)
Reduction of 90%	6.3 (1.8 to 15.5)	6.3 (1.7 to 15.2)	4.9 (1 to 13.7)	3.1 (0.4 to 10.7)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Percentage of participants				
number (confidence interval 95%)				
Reduction of 50%	26.2 (16 to 38.5)	19.7 (10.6 to 31.8)		
Reduction of 75%	7.7 (2.5 to 17)	3.3 (0.4 to 11.3)		
Reduction of 90%	3.1 (0.4 to 10.7)	0 (0 to 5.9)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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 to 28 (high score indicative of poor quality of life [QOL]). Analysis was performed on FAS. Here, number of subjects analyzed = subjects with POEM score assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	59	65
Units: Percent change				
least squares mean (standard error)	-57.3 (± 4.52)	-44 (± 4.44)	-49.2 (± 5.54)	-46.6 (± 4.33)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	59		
Units: Percent change				
least squares mean (standard error)	-14.2 (± 4.35)	0.2 (± 4.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in POEM Scores from Baseline to Week 16

End point title	Absolute Change in POEM Scores from Baseline to Week 16

End point description:

Analysis was performed on FAS. Here, number of subjects analyzed = subjects with POEM score

assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	59	65
Units: Units on a scale				
least squares mean (standard error)	-12.1 (± 0.88)	-9.8 (± 0.87)	-10.4 (± 0.89)	-9.9 (± 0.85)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	59		
Units: Units on a scale				
least squares mean (standard error)	-3.3 (± 0.85)	-1.1 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Global Individual Signs Score (GISS) Components (Erythema, Infiltration/Papulation, Excoriations, and Lichenification) From Baseline to Week 16

End point title	Changes in Global Individual Signs Score (GISS) Components (Erythema, Infiltration/Papulation, Excoriations, and Lichenification) From Baseline to Week 16

End point description:

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. Analysis was performed on FAS. Here, number of subjects analyzed = subjects with GISS score assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	60	65
Units: Units on a scale				
least squares mean (standard error)				
Erythema	-0.9 (± 0.1)	-0.9 (± 0.1)	-0.8 (± 0.1)	-0.8 (± 0.1)
Infiltration/papulation	-1.2 (± 0.11)	-1.1 (± 0.11)	-1 (± 0.11)	-1.1 (± 0.1)
Excoriations	-1.4 (± 0.11)	-1.4 (± 0.11)	-1.1 (± 0.11)	-1.3 (± 0.11)
Lichenification	-1.1 (± 0.12)	-1.1 (± 0.11)	-1 (± 0.12)	-1.1 (± 0.11)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61		
Units: Units on a scale				
least squares mean (standard error)				
Erythema	-0.4 (± 0.1)	-0.2 (± 0.1)		
Infiltration/papulation	-0.6 (± 0.11)	-0.3 (± 0.11)		
Excoriations	-0.6 (± 0.11)	-0.4 (± 0.11)		
Lichenification	-0.7 (± 0.11)	-0.3 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in GISS Cumulative Score from Baseline to Week 16

End point title	Changes in GISS Cumulative Score from Baseline to Week 16

End point description:

Analysis was performed on FAS. Here, number of subjects analyzed = subjects with GISS score assessment at specified time-points. Missing values imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Dupilumab 300 mg qw	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	63	60	65
Units: Units on a scale				
least squares mean (standard error)	-4.6 (± 0.38)	-4.5 (± 0.37)	-3.9 (± 0.38)	-4.3 (± 0.37)

End point values	Dupilumab 100 mg q4w	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61		
Units: Units on a scale				
least squares mean (standard error)	-2.3 (± 0.37)	-1.2 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Baseline to Week 32) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

TEAEs that developed during the treatment and follow-up period (time period from the administration of first dose of study drug to the EOS visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects who received 2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection qw from Week 1 to Week 15.

Reporting group title	Dupilumab 100 mg q4w

Reporting group description:

Subjects who received 2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single 100 mg injection of Dupilumab q4w and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.

Reporting group title	Dupilumab 300 mg q4w

Reporting group description:

Subjects who received 2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab q4w and Placebo (for Dupilumab) qw when Dupilumab not administered from Week 1 to Week 15.

Reporting group title	Dupilumab 200 mg q2w

Reporting group description:

Subjects who received 2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 200 mg injection of Dupilumab q2w from Week 1 to Week 15.

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

Subjects who received 2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single injection of Placebo (for Dupilumab) alternating with single 300 mg injection of Dupilumab q2w from Week 1 to Week 15.

Reporting group title	Dupilumab 300 mg qw

Reporting group description:

Subjects who received 2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection qw from Week 1 to Week 15.

Serious adverse events	Placebo	Dupilumab 100 mg q4w	Dupilumab 300 mg q4w
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 61 (6.56%)	5 / 65 (7.69%)	3 / 65 (4.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Congenital, familial and genetic disorders			
Hip dysplasia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	0 / 65 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	0 / 65 (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 shock			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	0 / 65 (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			
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	0 / 65 (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
Skin and subcutaneous tissue disorders			

Dermatitis atopic			
subjects affected / exposed	1 / 61 (1.64%)	4 / 65 (6.15%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	0 / 65 (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
Peritonsillar abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	0 / 65 (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 200 mg q2w	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 61 (1.64%)	2 / 64 (3.13%)	1 / 63 (1.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Hip dysplasia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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			
Tachycardia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 64 (0.00%)	0 / 63 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 61 (0.00%)	1 / 64 (1.56%)	0 / 63 (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
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 61 (1.64%)	0 / 64 (0.00%)	0 / 63 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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 failure			

subjects affected / exposed	1 / 61 (1.64%)	0 / 64 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 64 (1.56%)	0 / 63 (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
Dermatitis exfoliative			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Peritonsillar abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	0 / 63 (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
Viral infection			

subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dupilumab 100 mg q4w	Dupilumab 300 mg q4w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 61 (62.30%)	38 / 65 (58.46%)	39 / 65 (60.00%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 61 (3.28%)	7 / 65 (10.77%)	5 / 65 (7.69%)
occurrences (all)	2	18	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 61 (4.92%)	0 / 65 (0.00%)	4 / 65 (6.15%)
occurrences (all)	3	0	4
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 65 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Conjunctivitis allergic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 65 (1.54%)	3 / 65 (4.62%)
occurrences (all)	2	1	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 61 (1.64%)	4 / 65 (6.15%)	0 / 65 (0.00%)
occurrences (all)	1	4	0
Vomiting			
subjects affected / exposed	3 / 61 (4.92%)	0 / 65 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	10 / 61 (16.39%)	11 / 65 (16.92%)	10 / 65 (15.38%)
occurrences (all)	12	13	12
Urticaria			
subjects affected / exposed	0 / 61 (0.00%)	4 / 65 (6.15%)	0 / 65 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	5 / 61 (8.20%)	3 / 65 (4.62%)	2 / 65 (3.08%)
occurrences (all)	5	3	5
Infections and infestations			
Herpes simplex			
subjects affected / exposed	0 / 61 (0.00%)	5 / 65 (7.69%)	1 / 65 (1.54%)
occurrences (all)	0	7	1
Nasopharyngitis			
subjects affected / exposed	16 / 61 (26.23%)	20 / 65 (30.77%)	21 / 65 (32.31%)
occurrences (all)	23	29	29
Oral herpes			
subjects affected / exposed	0 / 61 (0.00%)	5 / 65 (7.69%)	3 / 65 (4.62%)
occurrences (all)	0	8	4
Upper respiratory tract infection			
subjects affected / exposed	11 / 61 (18.03%)	5 / 65 (7.69%)	5 / 65 (7.69%)
occurrences (all)	11	7	6
Urinary tract infection			
subjects affected / exposed	2 / 61 (3.28%)	2 / 65 (3.08%)	3 / 65 (4.62%)
occurrences (all)	2	2	3

Non-serious adverse events	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Total subjects affected by non-serious adverse events			

subjects affected / exposed	34 / 61 (55.74%)	34 / 64 (53.13%)	35 / 63 (55.56%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 64 (1.56%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 61 (14.75%)	5 / 64 (7.81%)	8 / 63 (12.70%)
occurrences (all)	24	13	40
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 61 (1.64%)	1 / 64 (1.56%)	2 / 63 (3.17%)
occurrences (all)	1	1	2
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 64 (1.56%)	4 / 63 (6.35%)
occurrences (all)	0	1	5
Conjunctivitis allergic			
subjects affected / exposed	6 / 61 (9.84%)	2 / 64 (3.13%)	3 / 63 (4.76%)
occurrences (all)	9	4	5
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 61 (0.00%)	2 / 64 (3.13%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	4 / 61 (6.56%)	0 / 64 (0.00%)	1 / 63 (1.59%)
occurrences (all)	7	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 61 (3.28%)	4 / 64 (6.25%)	4 / 63 (6.35%)
occurrences (all)	2	4	4
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	8 / 61 (13.11%)	13 / 64 (20.31%)	8 / 63 (12.70%)
occurrences (all)	10	19	9
Urticaria			

subjects affected / exposed	1 / 61 (1.64%)	0 / 64 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 61 (6.56%)	4 / 64 (6.25%)	1 / 63 (1.59%)
occurrences (all)	5	4	1
Back pain			
subjects affected / exposed	0 / 61 (0.00%)	2 / 64 (3.13%)	2 / 63 (3.17%)
occurrences (all)	0	3	16
Infections and infestations			
Herpes simplex			
subjects affected / exposed	3 / 61 (4.92%)	2 / 64 (3.13%)	1 / 63 (1.59%)
occurrences (all)	4	2	1
Nasopharyngitis			
subjects affected / exposed	16 / 61 (26.23%)	16 / 64 (25.00%)	16 / 63 (25.40%)
occurrences (all)	25	18	23
Oral herpes			
subjects affected / exposed	2 / 61 (3.28%)	3 / 64 (4.69%)	0 / 63 (0.00%)
occurrences (all)	4	5	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 61 (3.28%)	6 / 64 (9.38%)	5 / 63 (7.94%)
occurrences (all)	2	8	7
Urinary tract infection			
subjects affected / exposed	6 / 61 (9.84%)	3 / 64 (4.69%)	0 / 63 (0.00%)
occurrences (all)	7	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2013	It included the following changes: -The enrollment period for subjects at clinical sites in Japan was changed; - Exclusion criteria was clarified to define the potential subject population; - The prohibited medications and procedures section was reorganized and the text was clarified; - The timing of the primary analysis was changed.
27 June 2013	- The length of screening period was increased to 28 days; - Added a section for study committees; - Modified the time points for some of the assessments: photographs, periostin, and serum pregnancy test; - Specified that photographs were taken only at selected sites; - The inclusion/exclusion criteria was clarified to further define the subject population; - Permitted/prohibited medications text was modified to improve clarity regarding the use of prescription moisturizers or moisturizers containing additives; - Expanded description of skin barrier function tests; - Reporting period for any pregnancy was redefined occurring in a female subject of female partner of a male subject during the study; - PK variables were modified; - Modifications to statistical plan.
03 December 2013	- Added a provision for an interim analysis; - Added description and criteria for subjects to undergo reduced follow-up duration and transition into an open-label extension study; - The definition of FAS was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported