



Clinical trial results:

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

Summary

EudraCT number	2014-002619-40
Trial protocol	DE LT IT GB SE PL FR
Global end of trial date	21 January 2016

Results information

Result version number	v1
This version publication date	23 February 2017
First version publication date	23 February 2017

Trial information

Trial identification

Sponsor protocol code	R668-AD-1416
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02277769
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: SOLO 2

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	25 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult subjects with moderate-to-severe Atopic Dermatitis (AD).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 97
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 87
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	United States: 238
Country: Number of subjects enrolled	Canada: 108
Country: Number of subjects enrolled	Korea, Republic of: 80
Country: Number of subjects enrolled	Hong Kong: 5
Worldwide total number of subjects	708
EEA total number of subjects	277

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)	676
From 65 to 84 years	30
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 countries between 03 December 2014 and 21 January 2016. A total of 962 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 962 subjects, 708 were randomized and 707 were treated in the study. Subjects were randomized in 1:1:1 ratio to receive dupilumab 300 mg weekly (qw), dupilumab 300 mg every 2 weeks (q2w) or placebo qw.

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

Arm description:

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

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

Dosage and administration details:

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

Arm title	Dupilumab 300 mg q2w
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Arm description:

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

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

Dosage and administration details:

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

Arm title	Dupilumab 300 mg qw
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Arm description:

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

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

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Started	236	233	239
Treated	235	233	239
Completed	190	220	221
Not completed	46	13	18
Adverse Event	14	2	4
Other than specified	12	8	5
Lack of efficacy	17	-	4
Protocol deviation	3	3	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

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

Reporting group title	Dupilumab 300 mg q2w
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Reporting group description:

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

Reporting group title	Dupilumab 300 mg qw
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Reporting group description:

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

Reporting group values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
Number of subjects	236	233	239
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	37.4 ± 14.09	36.9 ± 13.96	37.1 ± 14.51
Gender categorical Units: Subjects			
Female	104	96	100
Male	132	137	139
Ethnicity Units: Subjects			
Not Hispanic or Latino	219	218	220
Hispanic or Latino	8	7	12
Not reported/missing	9	8	7
Race Units: Subjects			
White	156	165	168
Asian	50	44	45
Black or African American	20	13	15
Other	3	5	7
Not reported/ missing	7	6	4
Region Units: Subjects			
North and South America	116	114	116
Western Europe	54	54	55
Eastern Europe	38	37	39
Asia Pacific	28	28	29

Eczema Area and Severity Index (EASI) score			
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD.			
Units: units on a scale			
arithmetic mean	33.6	31.8	31.9
standard deviation	± 14.31	± 13.08	± 12.7
Investigator's Global Assessment (IGA) score			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear).			
Units: units on a scale			
arithmetic mean	3.5	3.5	3.5
standard deviation	± 0.5	± 0.5	± 0.5
Weekly average of peak daily pruritus numerical rating scale (NRS)			
Pruritus NRS 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]). Weekly average obtained in the 7-day period prior to the baseline visit.			
Units: units on a scale			
arithmetic mean	7.5	7.6	7.5
standard deviation	± 1.85	± 1.6	± 1.81
Body surface area (BSA) involvement with atopic dermatitis			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined.			
Units: Percentage of Body Surface Area			
arithmetic mean	54.3	52.7	52.2
standard deviation	± 23.06	± 21.23	± 21.51
SCORing Atopic Dermatitis (SCORAD) score			
SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23-31. 1993). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]).			
Units: units on a scale			
arithmetic mean	69.2	67.2	67.5
standard deviation	± 14.91	± 13.48	± 13.1
Dermatology Life Quality Index (DLQI) score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 to 30; a high score was indicative of a poor QOL.			
Units: units on a scale			
arithmetic mean	15.4	15.4	16
standard deviation	± 7.69	± 7.07	± 7.33
Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]).			
Units: units on a scale			
arithmetic mean	21	20.8	20.9

standard deviation	± 5.94	± 5.49	± 5.59
Global Individual Signs Score (GISS)			
Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria.			
Units: units on a scale			
arithmetic mean	9.2	9	9
standard deviation	± 1.78	± 1.8	± 1.75
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	13.7	13.7	14.6
standard deviation	± 8.32	± 7.52	± 8.24

Reporting group values	Total		
Number of subjects	708		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	300		
Male	408		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	657		
Hispanic or Latino	27		
Not reported/missing	24		
Race			
Units: Subjects			
White	489		
Asian	139		
Black or African American	48		
Other	15		
Not reported/ missing	17		
Region			
Units: Subjects			
North and South America	346		
Western Europe	163		
Eastern Europe	114		
Asia Pacific	85		
Eczema Area and Severity Index (EASI) score			

The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk,

upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD.			
Units: units on a scale arithmetic mean standard deviation			
	-		
Investigator's Global Assessment (IGA) score			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear).			
Units: units on a scale arithmetic mean standard deviation			
	-		
Weekly average of peak daily pruritus numerical rating scale (NRS)			
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]). Weekly average obtained in the 7-day period prior to the baseline visit.			
Units: units on a scale arithmetic mean standard deviation			
	-		
Body surface area (BSA) involvement with atopic dermatitis			
Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined.			
Units: Percentage of Body Surface Area arithmetic mean standard deviation			
	-		
SCORing Atopic Dermatitis (SCORAD) score			
SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]).			
Units: units on a scale arithmetic mean standard deviation			
	-		
Dermatology Life Quality Index (DLQI) score			
The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 to 30; a high score was indicative of a poor QOL.			
Units: units on a scale arithmetic mean standard deviation			
	-		
Patient Oriented Eczema Measure (POEM)			
The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]).			
Units: units on a scale arithmetic mean standard deviation			
	-		
Global Individual Signs Score (GISS)			
Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and			

lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria.

Units: units on a scale arithmetic mean standard deviation	-		
Total Hospital Anxiety Depression Scale (HADS)			
The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.			
Units: units on a scale arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
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Reporting group description:

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

Reporting group title	Dupilumab 300 mg q2w
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Reporting group description:

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

Reporting group title	Dupilumab 300 mg qw
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Reporting group description:

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

Subject analysis set title	Placebo
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) for 16 weeks

Subject analysis set title	Dupilumab 300 mg q2w
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw for 16 weeks.

Subject analysis set title	Dupilumab 300 mg qw
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw for 16 weeks.

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

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

The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved $\geq 75\%$ overall improvement in EASI score from baseline to Week 16. The subjects withdrew from the study or used rescue treatment or had a missing value at Week 16, were counted as non-responders. Full analysis set (FAS) included all randomized subjects.

End point type	Primary
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End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	236	233	239	
Units: Percentage of Subjects				
number (not applicable)	11.9	44.2	48.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description: Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity.	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	32.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.75
upper limit	39.94

Notes:

[1] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description: Analysis was performed using Cochran-Mantel-Haenszel test stratified by region and baseline disease severity.	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	36.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.69
upper limit	43.81

Notes:

[2] - Threshold for significance at 0.025 level.

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

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

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

End point type	Primary
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End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	236	233	239	
Units: Percentage of Subjects				
number (not applicable)	8.5	36.1	36.4	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	27.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.46
upper limit	34.69

Notes:

[3] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

severity.

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	27.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.87
upper limit	34.99

Notes:

[4] - Threshold for significance at 0.025 level.

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

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

Pruritus NRS is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥ 4 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥ 4 .

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	225	228	
Units: Percentage of Subjects				
number (not applicable)	9.5	36	39	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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Statistical analysis description:

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

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.13
upper limit	33.87

Notes:

[5] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	29.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.11
upper limit	36.95

Notes:

[6] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	231	234	
Units: Percentage of subjects				
number (not applicable)	12.8	50.6	49.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	36.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.56
upper limit	44.06

Notes:

[7] - Threshold for significance at 0.025 level.

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	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	37.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.03
upper limit	45.6

Notes:

[8] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	195	182	
Units: Percent Change				
arithmetic mean (standard deviation)	-18.1 (\pm 27.66)	-47.2 (\pm 28.5)	-50.9 (\pm 30.56)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
----------------------------	--------------------------------

Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	Least Square (LS) mean difference
Point estimate	-32.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.2
upper limit	-25.49

Notes:

[9] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[10]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-28.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.04
upper limit	-21.83

Notes:

[10] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 4

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	225	228	
Units: Percentage of subjects				
number (not applicable)	6.3	22.7	27.6	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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
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Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.99
upper limit	22.68

Notes:

[11] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	21.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.66
upper limit	27.93

Notes:

[12] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 2

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	225	228	
Units: Percentage of Subjects				
number (not applicable)	0.9	10.7	12.7	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.31
upper limit	16.32

Notes:

[13] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.54
upper limit	13.98

Notes:

[14] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	195	182	
Units: units on a scale				
arithmetic mean (standard deviation)	-1.41 (\pm 1.973)	-3.56 (\pm 2.258)	-3.87 (\pm 2.426)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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
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Number of subjects included in analysis	300
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.0001 ^[15]
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Method	ANCOVA
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Parameter estimate	LS mean difference
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Point estimate	-2.1
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-2.605
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upper limit	-1.587
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Notes:

[15] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[16]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.982
upper limit	-1.957

Notes:

[16] - Threshold for significance at 0.025 level.

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

End point title	Percent Change From Baseline in EASI Score to Week 16
End point description:	Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.
End point type	Secondary
End point timeframe:	Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	197	181	
Units: Percent Change				
arithmetic mean (standard deviation)	-33.7 (± 33.45)	-69.6 (± 27.84)	-71.6 (± 27.08)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[17]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-36.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.46
upper limit	-28.86

Notes:

[17] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[18]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-38.2

Confidence interval

level	95 %
sides	2-sided
lower limit	-45.55
upper limit	-30.88

Notes:

[18] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with EASI-50 (≥50% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects with EASI-50 (≥50% Improvement from Baseline) at Week 16
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End point description:

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

End point type	Secondary
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End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	236	233	239	
Units: Percentage of Subjects				
number (not applicable)	22	65.2	61.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	43.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.12
upper limit	51.29

Notes:

[19] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	39.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.92
upper limit	47.19

Notes:

[20] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with EASI-90 (≥90% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects with EASI-90 (≥90% Improvement)
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from Baseline) at Week 16

End point description:

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

End point type Secondary

End point timeframe:

Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	236	233	239	
Units: Percentage of Subjects				
number (not applicable)	7.2	30	30.5	

Statistical analyses

Statistical analysis title Dupilumab 300 mg q2w vs Placebo

Statistical analysis description:

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

Comparison groups Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis 469

Analysis specification Pre-specified

Analysis type superiority

P-value < 0.0001 [21]

Method Cochran-Mantel-Haenszel

Parameter estimate difference in percentages

Point estimate 22.8

Confidence interval

level 95 %

sides 2-sided

lower limit 16.09

upper limit 29.59

Notes:

[21] - Threshold for significance at 0.025 level.

Statistical analysis title Dupilumab 300 mg qw vs Placebo

Statistical analysis description:

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

Comparison groups Dupilumab 300 mg qw v Placebo

Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	23.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.63
upper limit	30.05

Notes:

[22] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	197	181	
Units: Percentage of Body Surface Area				
arithmetic mean (standard deviation)	-14.48 (± 17.81)	-31.69 (± 19.614)	-32.97 (± 20.4)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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
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Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-17.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.06
upper limit	-13.92

Notes:

[23] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-19.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.491
upper limit	-15.529

Notes:

[24] - Threshold for significance at 0.025 level.

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

End point title	Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score to Week 16
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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 population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	193	178	
Units: Percent Change				
arithmetic mean (standard deviation)	-22.7 (\pm 25.48)	-53.5 (\pm 25.23)	-56 (\pm 25.53)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[25]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-33.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.75
upper limit	-27.8

Notes:

[25] - Threshold for significance at 0.025 level.

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	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[26]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-31.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.36
upper limit	-25.4

Notes:

[26] - Threshold for significance at 0.025 level.

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

End point title	Change From Baseline in Dermatology Life Quality Index (DLQI) to Week 16
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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 to 30; a high score was indicative of a poor QOL. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	197	181	
Units: units on a scale				
arithmetic mean (standard deviation)	-4 (± 5.75)	-9.7 (± 6.2)	-10.3 (± 6.75)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-4.72

Notes:

[27] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[28]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.86
upper limit	-4.47

Notes:

[28] - Threshold for significance at 0.025 level.

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

End point title	Change From Baseline in Patient Oriented Eczema Measure (POEM) to Week 16
End point description: The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]). Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe: Baseline to Week 16	

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	196	181	
Units: Units on a scael				
arithmetic mean (standard deviation)	-3.8 (± 6.07)	-10.7 (± 6.89)	-11.7 (± 7.13)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.36
upper limit	-5.57

Notes:

[29] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.36
upper limit	-6.64

Notes:

[30] - Threshold for significance at 0.025 level.

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

End point title	Change From Baseline in Hospital Anxiety Depression Scale (HADS) to Week 16
End point description:	
<p>The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.</p>	
End point type	Secondary
End point timeframe:	
Baseline to Week 16	

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	191	175	
Units: units on a scale				
arithmetic mean (standard deviation)	-1 (± 4.44)	-5.2 (± 5.42)	-6.2 (± 6.01)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg q2w v Placebo
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[31]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	-3.09

Notes:

[31] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[32]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.04
upper limit	-3.81

Notes:

[32] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	197	181	
Units: Percent Change				
arithmetic mean (standard deviation)	-20.3 (\pm 25.03)	-47.5 (\pm 27)	-48.4 (\pm 27.29)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
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Number of subjects included in analysis	286
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.0001 [33]
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Method	ANCOVA
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Parameter estimate	LS mean difference
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Point estimate	-28.9
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-35.03
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upper limit	-22.74
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Notes:

[33] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.73
upper limit	-21.7

Notes:

[34] - Threshold for significance at 0.025 level.

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

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

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

End point type	Secondary
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End point timeframe:

Baseline to Week 2

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	224	229	
Units: percent change				
arithmetic mean (standard deviation)	-6.3 (± 21.91)	-24.1 (± 21.22)	-21.2 (± 24.96)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo
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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
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Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[35]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.96
upper limit	-13.53

Notes:

[35] - Threshold for significance at 0.025 level.

Statistical analysis title	Dupilumab 300 mg qw vs Placebo
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Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg qw v Placebo
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[36]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.16
upper limit	-10.78

Notes:

[36] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) Requiring Systemic Treatment From Baseline Through Week 16

End point title	Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) Requiring Systemic Treatment From Baseline Through Week 16
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline up to Week 16

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	236	237	
Units: Percentage of Subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Serious Adverse Events (TESAEs) From Baseline Through Week 16

End point title	Percentage of Subjects With Treatment-Emergent Serious Adverse Events (TESAEs) From Baseline Through Week 16			
End point description:	Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug and analyzed based on the treatment received.			
End point type	Secondary			
End point timeframe:	Baseline up to Week 16			

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	236	237	
Units: Percentage of Subjects				
number (not applicable)	5.6	1.7	3.4	

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation from Baseline Through Week 16			
End point description:	Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug and analyzed based on the treatment received.			
End point type	Secondary			
End point timeframe:	Baseline up to Week 16			

End point values	Placebo	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	236	237	
Units: Percentage of Subjects				
number (not applicable)	2.1	0.8	1.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 28) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported adverse events are treatment emergent adverse events that developed/worsened during the 'on-treatment period' (including the 16 week treatment period).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects exposed to Placebo (for Dupilumab) for 16 weeks (mean exposure of 14 weeks).

Reporting group title	Dupilumab 300 mg qw
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Reporting group description:

Subjects exposed to Dupilumab 300 mg qw for 16 weeks (mean exposure of 15 weeks).

Reporting group title	Dupilumab 300 mg q2w
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Reporting group description:

Subjects exposed to Dupilumab 300 mg alternating with placebo qw for 16 weeks (mean exposure of 15 weeks).

Serious adverse events	Placebo	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 234 (6.84%)	9 / 237 (3.80%)	6 / 236 (2.54%)
number of deaths (all causes)	0	1	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Confusional state			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Delirium			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Mental status changes			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Psychotic disorder			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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

Schizophrenia, paranoid type subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Fall subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Radius fracture subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Nervous system disorders			
Cerebrovascular accident subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Headache subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-Ischaemic encephalopathy subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Subarachnoid haemorrhage subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Colonic pseudo-obstruction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	6 / 234 (2.56%)	1 / 237 (0.42%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 8	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			
subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 234 (0.85%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Endocarditis bacterial			

subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Erysipelas			
subjects affected / exposed	0 / 234 (0.00%)	1 / 237 (0.42%)	0 / 236 (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
Pyelonephritis			
subjects affected / exposed	0 / 234 (0.00%)	0 / 237 (0.00%)	1 / 236 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 234 (0.85%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic embolus			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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 infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (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
Tetany			
subjects affected / exposed	1 / 234 (0.43%)	0 / 237 (0.00%)	0 / 236 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Dupilumab 300 mg qw	Dupilumab 300 mg q2w
Total subjects affected by non-serious adverse events subjects affected / exposed	109 / 234 (46.58%)	90 / 237 (37.97%)	84 / 236 (35.59%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	12 / 234 (5.13%) 20	23 / 237 (9.70%) 50	18 / 236 (7.63%) 29
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	15 / 234 (6.41%) 17	31 / 237 (13.08%) 84	32 / 236 (13.56%) 58
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	82 / 234 (35.04%) 136	39 / 237 (16.46%) 49	34 / 236 (14.41%) 39
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	25 / 234 (10.68%) 26	22 / 237 (9.28%) 26	23 / 236 (9.75%) 25

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27690741>