Clinical trial results:
A phase 3 study investigating the efficacy, safety, and tolerability of Dupilumab administered to adult patients with severe atopic dermatitis who are not adequately controlled with or are intolerant to oral cyclosporine A, or when this treatment is not medically advisable

Summary

EudraCT number	2015-002653-35
Trial protocol	DE PL BE GB NL SK AT IE ES
Global end of trial date	29 March 2017

Results information

Result version number	v2
This version publication date	15 July 2020
First version publication date	06 February 2019
Version creation reason	• Correction of full data set Minor updates made to align with source and other registry

Trial information

Trial identification

Sponsor protocol code	R668-AD-1424

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02755649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States,
Public contact	Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc.,, clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Administrator, 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 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult subjects with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable.

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	27 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 107
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Germany: 142
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	325
EEA total number of subjects	309

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	316
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 73 sites in Europe. A total of 390 subjects were screened between 28 Jan 2016 and 14 Sep 2016. Of those, 325 subjects were enrolled into the study and randomized. Sixty subjects were considered screen failures, mostly due to unmet eligibility criteria.

Pre-assignment

Screening details:

After providing informed consent, subjects were assessed for study eligibility. Screening assessments were performed between day -28 & day -15, prior to randomization. Subjects who met eligibility criteria at baseline (day 1) were randomized in a 1:1:1 ratio to receive dupilumab (weekly[QW] or every 2 weeks[Q2W]) or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QW + TCS

Arm description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Arm type	Experimental
Investigational medicinal product name	Topical corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

Investigational medicinal product name	Placebo (Matched to Dupilumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of placebo matching to dupilumab QW following a loading dose on Day 1 from Week 1 to Week 15.

Arm title	Dupilumab 300 mg Q2W + TCS

Arm description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label

extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Arm type	Experimental
Investigational medicinal product name	Dupilumab 300 mg
Investigational medicinal product code	REGN668
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received one SC injection of Dupilumab every 2 weeks (Q2W) (following two SC injections on day 1) from Week 1 to Week 15.

Investigational medicinal product name	Topical corticosteroids (TCS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received treatment with topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

Arm title	Dupilumab 300 mg QW + TCS

Arm description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Arm type	Experimental
Investigational medicinal product name	Topical corticosteroids (TCS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received treatment with topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

Investigational medicinal product name	Dupilumab 300 mg
Investigational medicinal product code	REGN668
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received one SC injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15.

Number of subjects in period 1	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
Started	108	107	110
Completed (Week 16 - Treatment Period)	107	106	109
Completed	7	8	8
Not completed	101	99	102
Consent withdrawn by subject	-	1	-
Physician decision	-	-	2
Rolled over into OLE study	99	98	100
Currently undecided	1	-	-
Did not complete follow-up visits	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QW + TCS
Reporting group description:	
Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).	
Reporting group title	Dupilumab 300 mg Q2W + TCS
Reporting group description:	
Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).	
Reporting group title	Dupilumab 300 mg QW + TCS
Reporting group description:	
Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).	

Reporting group values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
Number of subjects	108	107	110
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	38.9	37.5	38.7
standard deviation	± 13.35	± 12.89	± 13.21
Gender categorical			
Units: Subjects			
Female	40	42	44
Male	68	65	66
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	1	5
Not Hispanic or Latino	101	99	101
Unknown or Not Reported	4	7	4
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	2

Native Hawaiian or Other pacific Islander	0	0	0
Black or African American	0	0	2
White	104	104	105
More than one race	2	0	1
Unknown is Not Reported	0	1	0
Region of Enrollment Units: Subjects			
Austria	2	2	3
Belgium	4	4	3
Germany	51	48	43
Ireland	0	1	1
Netherlands	4	6	6
Poland	33	39	35
Russia	7	0	9
Slovakia	1	2	1
Spain	2	1	0
United Kingdom	4	4	9
Investigator's Global Assessment (IGA) score Units: Subjects			
IGA score = 3	56	57	58
IGA score = 4	52	50	52
Eczema Area and Severity Index (EASI) Score Units: units on a scale			
arithmetic mean	32.9	33.3	33.1
standard deviation	± 10.80	± 9.93	± 11.02
Peak weekly averaged pruritus Numerical Rating Scale (NRS) score Units: subjects			
arithmetic mean	6.4	6.6	6.2
standard deviation	± 2.23	± 2.10	± 2.01
Body Surface Area (BSA) involvement of atopic dermatitis Units: units on a scale			
arithmetic mean	55.0	56.1	56.0
standard deviation	± 20.51	± 17.83	± 19.26
SCORing Atopic Dermatitis (SCORAD) score Units: units on a scale			
arithmetic mean	67.0	68.6	66.0
standard deviation	± 12.20	± 11.91	± 12.70
Global Individual Signs Score (GISS) Units: Units on a scale			
arithmetic mean	9.4	9.3	9.1
standard deviation	± 1.63	± 1.64	± 1.63
Dermatology Life Quality Index (DLQI) Total Score Units: units on a scale			
arithmetic mean	13.2	14.5	13.8
standard deviation	± 7.60	± 7.63	± 8.03
Patient Oriented Eczema Measure (POEM)			

Units: units on a scale			
arithmetic mean	19.1	19.3	18.6
standard deviation	± 5.99	± 6.21	± 6.97
Total Hospital Anxiety Depression Scale (HADS)			
Units: units on a scale			
arithmetic mean	13.0	12.8	13.3
standard deviation	± 7.85	± 8.01	± 8.15

Reporting group values	Total		
Number of subjects	325		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	126		
Male	199		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	301		
Unknown or Not Reported	15		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	6		
Native Hawaiian or Other pacific Islander	0		
Black or African American	2		
White	313		
More than one race	3		
Unknown is Not Reported	1		
Region of Enrollment			
Units: Subjects			
Austria	7		
Belgium	11		
Germany	142		
Ireland	2		
Netherlands	16		
Poland	107		
Russia	16		
Slovakia	4		
Spain	3		
United Kingdom	17		
Investigator's Global Assessment (IGA) score			
Units: Subjects			

IGA score = 3	171		
IGA score = 4	154		

Eczema Area and Severity Index (EASI) Score			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Peak weekly averaged pruritus Numerical Rating Scale (NRS) score			
Units: subjects			
arithmetic mean			
standard deviation	-		
Body Surface Area (BSA) involvement of atopic dermatitis			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
SCORing Atopic Dermatitis (SCORAD) score			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Global Individual Signs Score (GISS)			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		
Dermatology Life Quality Index (DLQI) Total Score			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Patient Oriented Eczema Measure (POEM)			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Total Hospital Anxiety Depression Scale (HADS)			
Units: units on a scale			
arithmetic mean			
standard deviation	-		

End points reporting groups

Reporting group title	Placebo QW + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Dupilumab 300 mg Q2W + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Dupilumab 300 mg QW + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Primary: Percentage of Subjects With Eczema Area and Severity Index (EASI) 75 (≥75% Improvement From Baseline) at Week 16

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

End point description:

The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16. The analysis population for efficacy analyses is the Full Analysis Set (FAS) which included all randomized subjects. Efficacy analyses were based on the treatment allocated (as randomized).

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of Subjects				
number (not applicable)	29.6	62.6	59.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across 2 dose regimens. Difference is Dupilumab minus placebo. Confidence Interval (CI) calculated using normal approximation. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	29.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.87
upper limit	42.05

Notes:

[1] - Threshold for significance at 0.05 level. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by disease severity (IGA 3 vs IGA 4) and prior Cyclosporine A (CSA) use (Yes, No).

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across 2 dose regimens. Difference is Dupilumab minus placebo. Confidence Interval (CI) calculated using normal approximation. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated.

Comparison groups	Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	33
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.41
upper limit	45.57

Notes:

[2] - Threshold for significance at 0.05 level. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by disease severity (IGA 3 vs IGA 4) and prior Cyclosporine A (CSA) use (Yes, No).

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

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

End point description:

The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. The analysis population for efficacy analyses is the FAS which included all randomized subjects. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	105	
Units: Percent change				
least squares mean (standard error)	-46.6 (± 2.76)	-79.8 (± 2.59)	-78.2 (± 2.55)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

Hierarchical testing approach to control Type-1 error rate at 0.05 across 2 dose regimens.CI w/p-value is based on treatment difference(dupilumab vs placebo) of LS mean percent change using multiple imputation (MI) w/ANCOVA model w/baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by MI

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-31.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.85
upper limit	-24.3

Notes:

[3] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-33.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.42
upper limit	-25.88

Notes:

[4] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects With Eczema Area and Severity Index (EASI) Score (≥75% Improvement From Baseline) at Week 16 for subjects With Prior CSA Use

End point title	Percentage of Subjects With Eczema Area and Severity Index (EASI) Score (≥75% Improvement From Baseline) at Week 16 for subjects With Prior CSA Use

End point description:

The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	69	69	
Units: Percentage of subjects				
number (not applicable)	26.4	58.0	56.5	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Dupilumab 300 mg QW + TCS v Placebo QW + TCS
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	30.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.63
upper limit	45.64

Notes:

[5] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	31.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.11
upper limit	47.05

Notes:

[6] - Threshold for significance at 0.05 level.

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

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

End point description:

The Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	102	103	
Units: Percent change				
least squares mean (standard error)	-25.4 (± 3.39)	53.9 (± 3.14)	-51.7 (± 3.09)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Dupilumab 300 mg QW + TCS v Placebo QW + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-26.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.07
upper limit	-17.41

Notes:

[7] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference]
Point estimate	-28.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.34
upper limit	-19.68

Notes:

[8] - Threshold for significance at 0.05 level

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

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

End point description:

Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	94	94	
Units: Percentage of subjects				
number (not applicable)	14.3	45.7	40.4	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Dupilumab 300 mg QW + TCS v Placebo QW + TCS
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.89
upper limit	38.39

Notes:

[9] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	31.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.08
upper limit	43.83

Notes:

[10] - Threshold for significance at 0.05 level.

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

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

End point description:

Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject's 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]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint. Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 2

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	105	110	
Units: Percent change				
least squares mean (standard error)	-10.0 (± 2.24)	-17.2 (± 2.25)	-19.7 (± 2.21)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	-3.66

Notes:

[11] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0214 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.31
upper limit	-1.06

Notes:

[12] - Threshold for significance at 0.05 level

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

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

End point description:

The SCORAD is a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	104	
Units: Percent change				
least squares mean (standard error)	-29.5 (± 2.55)	-62.4 (± 2.48)	-58.3 (± 2.45)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.56
upper limit	-21.93

Notes:

[13] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.7
upper limit	-26.06

Notes:

[14] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects Achieving SCORAD 50 (≥50% Improvement From Baseline) at Week 16

End point title	Percentage of Subjects Achieving SCORAD 50 (≥50% Improvement From Baseline) at Week 16

End point description:

The SCORAD is a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). 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). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	25.9	66.4	55.5	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	29.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.1
upper limit	41.96

Notes:

[15] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	40.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.24
upper limit	52.61

Notes:

[16] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Percent Body Surface Area (BSA) Involvement With Atopic Dermatitis (AD) at Week 16

End point title	Change From Baseline in Percent Body Surface Area (BSA) Involvement With Atopic Dermatitis (AD) at Week 16

End point description:

BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	104	
Units: Percent BSA				
least squares mean (standard error)	-19.57 (± 1.798)	-39.23 (± 1.715)	-37.52 (± 1.690)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment,randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-17.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.706
upper limit	-13.197

Notes:

[17] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-19.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.431
upper limit	-14.895

Notes:

[18] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects With Investigator Global Assessment (IGA) 0 or 1 (on the 0 to 4 IGA Scale) and a Reduction From Baseline of ≥2 Points at Week 16

End point title	Percentage of Subjects With Investigator Global Assessment (IGA) 0 or 1 (on the 0 to 4 IGA Scale) and a Reduction From Baseline of ≥2 Points 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). Subjects with IGA score of "0" or "1" and a reduction from baseline of ≥2 points at Week 16 were reported. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized).

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	13.9	40.2	39.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.99
upper limit	36.41

Notes:

[19] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	26.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	14.95
upper limit	37.65

Notes:

[20] - Threshold for significance at 0.05 level

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

End point title	Change From Baseline in the Dermatology Life Quality Index (DLQI) at Week 16

End point description:

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); a high score is indicative of a poor QOL. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	104	
Units: Units on a scale				
least squares mean (standard error)	-4.5 (± 0.49)	-9.5 (± 0.46)	-8.8 (± 0.45)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	-3.04

Notes:

[21] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No])as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	-3.74

Notes:

[22] - Threshold for significance at 0.05 level

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

End point title	Change From Baseline in the Patient Oriented Eczema Measure (POEM) at 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 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	103	104	
Units: units on a scale				
least squares mean (standard error)	-4.3 (± 0.62)	-11.9 (± 0.60)	-11.4 (± 0.59)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No])as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.29
upper limit	-5.97

Notes:

[23] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No])as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.78
upper limit	-5.47

Notes:

[24] - Threshold for significance at 0.05 level

Secondary: Change From Baseline in Mean Weekly Dose of Topical Corticosteroid (TCS) Use During Treatment Period

End point title	Change From Baseline in Mean Weekly Dose of Topical Corticosteroid (TCS) Use During Treatment Period

End point description:

The type, amount, frequency, and potency of topical products used during the study were recorded at home by subjects in a medication diary. Subjects returned TCS tubes at each clinic visit up until week 16, and these tubes were weighed by the site staff to determine the actual amount of TCS used. During the 16-week placebo-controlled study treatment period, medium-potency TCS dosing frequency was symptom-based (IGA score) adjusted every 4 weeks per the protocol-specified tapering algorithm. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Grams				
least squares mean (standard error)	25.1 (± 1.48)	15.0 (± 1.51)	17.5 (± 1.49)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [25]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.64
upper limit	-3.51

Notes:

[25] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.15
upper limit	-5.95

Notes:

[26] - Threshold for significance at 0.05 level

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

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

End point description:

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. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	104	
Units: units on a scale				
least squares mean (standard error)	-2.3 (± 0.56)	-6.1 (± 0.54)	-5.2 (± 0.53)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	-2.4

Notes:

[27] - Threshold for significance at 0.05 level

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [28]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.41
upper limit	-1.43

Notes:

[28] - Threshold for significance at 0.05 level

Secondary: Percent Change From Baseline in the Total Global Individual Signs Score (GISS) at Week 16 (Erythema, Infiltration/ Papulation, Excoriations, Lichenification)

End point title	Percent Change From Baseline in the Total Global Individual Signs Score (GISS) at Week 16 (Erythema, Infiltration/ Papulation, Excoriations, Lichenification)

End point description:

Individual components of the AD lesions (erythema, infiltration/ papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0= none, 1= mild, 2= moderate and 3= severe) using the EASI severity grading criteria. Total score ranges from 0 (absent disease) to 12 (severe disease). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Full Analysis Set (FAS) included all randomized. Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	103	104	
Units: Percent change				
least squares mean (standard error)	-29.0 (± 2.75)	-55.2 (± 2.66)	-53.3 (± 2.65)	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab group vs. placebo)of LS mean percent change using MI with ANCOVA with baseline measurement as covariate & treatment,randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use[Yes,No])as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.63
upper limit	-16.88

Notes:

[29] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-26.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.49
upper limit	-18.86

Notes:

[30] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) From Baseline Through Week 28

End point title	Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) From Baseline Through Week 28

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 16]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Safety analysis set (SAF) included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	8.3	1.9	3.6	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1486
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.97
upper limit	1.58

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0319
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	-6.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.27
upper limit	-0.65

Secondary: Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) Through Week 28

End point title	Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) Through Week 28

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 16]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Baseline to week 28

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	1.9	1.9	1.8	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9829
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	3.53

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	3.63

Secondary: Percentage of Subjects Having at Least One Treatment-Emergent Adverse Event (TEAE) Leading to Treatment Discontinuation Through Week 28

End point title	Percentage of Subjects Having at Least One Treatment-Emergent Adverse Event (TEAE) Leading to Treatment Discontinuation Through Week 28

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 28]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Baseline to week 28

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	0.9	0	1.8	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3241
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	0.88

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5619
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	3.97

Secondary: Percentage of Subjects With Treatment-Emergent Adverse Events Through Week 28

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events Through Week 28

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 28]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Baseline to week 28

End point values	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	107	110	
Units: Percentage of subjects				
number (not applicable)	69.4	72.0	69.1	

Statistical analyses

Statistical analysis title	Dupilumab 300 mg QW + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg QW + TCS
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9518
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	11.9

Statistical analysis title	Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

Comparison groups	Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6833
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentages
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.64
upper limit	14.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of informed consent form up to end of study (EOS), Week 28, regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Pre-treatment AEs were AEs that developed/worsened in severity during pre-treatment period (from informed consent to first dose of study drug); All AEs collected during treatment and follow-up period were considered TEAEs. TEAEs were AEs that developed or worsened in severity compared to baseline during treatment and follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo QW + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Dupilumab 300 mg Q2W + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Dupilumab 300 mg QW + TCS

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Serious adverse events	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 108 (1.85%)	2 / 107 (1.87%)	3 / 110 (2.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Uterine leiomyoma			
subjects affected / exposed	0 / 108 (0.00%)	0 / 107 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 107 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 108 (0.00%)	1 / 107 (0.93%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 108 (0.00%)	1 / 107 (0.93%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	1 / 108 (0.93%)	0 / 107 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 108 (0.00%)	0 / 107 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 107 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 108 (41.67%)	54 / 107 (50.47%)	51 / 110 (46.36%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 108 (9.26%)	10 / 107 (9.35%)	11 / 110 (10.00%)
occurrences (all)	17	20	13
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	7 / 108 (6.48%)	16 / 107 (14.95%)	10 / 110 (9.09%)
occurrences (all)	9	18	11
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 108 (0.93%)	7 / 107 (6.54%)	4 / 110 (3.64%)
occurrences (all)	2	8	7
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	18 / 108 (16.67%)	8 / 107 (7.48%)	10 / 110 (9.09%)
occurrences (all)	26	10	15
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 108 (3.70%)	12 / 107 (11.21%)	8 / 110 (7.27%)
occurrences (all)	4	14	8
Nasopharyngitis			
subjects affected / exposed	18 / 108 (16.67%)	22 / 107 (20.56%)	18 / 110 (16.36%)
occurrences (all)	26	29	24

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2016	1. Extended the treatment period from 16 weeks to 24 weeks and add week 24 endpoints to meet the criteria for dupilumab to be considered for chronic use in the treatment of AD. 2. The introduction was modified to provide support for the safety of a 24-week treatment period. 3. As a result, endpoints for week 24 corresponding to those for week 16 have been added and the hierarchy modified accordingly. 4. As the treatment period is extended from 16 weeks to 24 weeks and there is a 1-step analysis after the last patient completes 16 weeks of treatment, planned interim analysis section has been modified to state that the results of the 1-step analysis will not be used to change the conduct and integrity of the study. 1-step analysis has also been modified to accommodate the extension of the treatment period and the addition of week 24 endpoints. 5. Removed the endpoint "Percent change from baseline to week 16 in the GISS". 6. Exclusion criterion #4 was changed from "within 8 weeks prior to the screening visit" to "within 4 weeks of the baseline visit". The original wording would have resulted in automatic exclusion of all patients on systemic treatments (which is common in a population with severe AD) who present for screening. The revised criterion is now also consistent with all other AD protocols. 7. The secondary endpoint "Topical treatment for AD – medication-free days" was added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported