Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Investigate The Efficacy and Safety of Dupilumab Administered Concomitantly With Topical Corticosteroids in Patients, 6 Years to < 12 Years of Age, With Severe Atopic Dermatitis

Summary

EudraCT number	2016-004997-16
Trial protocol	CZ DE GB PL
Global end of trial date	28 June 2019

Results information

Result version number	v1
This version publication date	26 March 2020
First version publication date	26 March 2020

Trial information

Trial identification

Sponsor protocol code	R668-AD-1652

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345914
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 107969

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS) in subjects greater than or equal to (≥) 6 years to less than (<) 12 years of age with 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 Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 93
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	United States: 221
Worldwide total number of subjects	367
EEA total number of subjects	130

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)	367

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 474 subjects were screened for study eligibility at multiple sites in the United States and Europe. Screen failure was mostly due to inclusion/exclusion criteria not met and "other" reasons. The majority of subjects (221/367) were enrolled at study sites in the United States.

Pre-assignment

Screening details:

A total of 474 subjects were screened, of which 367 subjects randomized in 1:1:1 ratio to 1 of 3 treatment groups. 5 randomized subjects were not treated (2 in the placebo + TCS group and 3 in the combined dupilumab + TCS group). Subjects randomized to receive Dupilumab 100 mg or 200 mg Q2W + TCS, Dupilumab 300 mg Q4W + TCS or matching placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + TCS

Arm description:

Subjects received matching placebo every 2 weeks (Q2W) or every 4 weeks (Q4W) during the 16-week double-blind treatment phase. Matching placebo was administered concomitantly with topical corticosteroids (TCS), including doubling the amount of placebo on Day 1 to match the loading dose.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injection of the study drug on different quadrants of the abdomen avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Arm title	Dupilumab 300 mg Q4W + TCS

Arm description:

Subjects received subcutaneous injections of 600 milligrams (mg) loading dose on Day 1, then 300 mg of Dupilumab every 4 weeks (Q4W) from Week 4 to Week 12. Topical corticosteroids (TCS) were administered concomitantly during the 16-week double-blind treatment phase.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injection of the study drug on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Arm title	Dupilumab 100 mg or 200 mg Q2W + TCS

Arm description:

Subjects received subcutaneous injections of 100 milligrams (mg) or 200 mg of Dupilumab every 2 weeks (Q2W). For 100 mg Q2W treatment group, subjects received a 200 mg loading dose on Day 1, then 100 mg Q2W from Week 2 to Week 14. For 200 mg Q2W treatment group, subjects received a 400 mg loading dose on Day 1, then 200 mg Q2W from Week 2 to Week 14. Topical corticosteroids (TCS) were administered concomitantly in all groups during the 16-week double-blind treatment phase.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injection of the study drug on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Number of subjects in period 1	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS
Started	123	122	122
Completed Week 16 Study Treatment	114	118	119
Completed Week 28 End of Study	0	0	0
Completed	0	0	0
Not completed	123	122	122
Physician decision	-	1	1
Not Specified	1	1	1
Ongoing	-	-	1
Transition to another study at week 16	80	86	78
Transition to another study during follow-up	37	33	39
Withdrawal by subject	5	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + TCS
Reporting group description:	
Subjects received matching placebo every 2 weeks (Q2W) or every 4 weeks (Q4W) during the 16-week double-blind treatment phase. Matching placebo was administered concomitantly with topical corticosteroids (TCS), including doubling the amount of placebo on Day 1 to match the loading dose.	
Reporting group title	Dupilumab 300 mg Q4W + TCS
Reporting group description:	
Subjects received subcutaneous injections of 600 milligrams (mg) loading dose on Day 1, then 300 mg of Dupilumab every 4 weeks (Q4W) from Week 4 to Week 12. Topical corticosteroids (TCS) were administered concomitantly during the 16-week double-blind treatment phase.	
Reporting group title	Dupilumab 100 mg or 200 mg Q2W + TCS
Reporting group description:	
Subjects received subcutaneous injections of 100 milligrams (mg) or 200 mg of Dupilumab every 2 weeks (Q2W). For 100 mg Q2W treatment group, subjects received a 200 mg loading dose on Day 1, then 100 mg Q2W from Week 2 to Week 14. For 200 mg Q2W treatment group, subjects received a 400 mg loading dose on Day 1, then 200 mg Q2W from Week 2 to Week 14. Topical corticosteroids (TCS) were administered concomitantly in all groups during the 16-week double-blind treatment phase.	

Reporting group values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects	123	122	122
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8.3	8.5	8.5
standard deviation	± 1.76	± 1.74	± 1.68
Gender categorical Units: Subjects			
Female	62	65	57
Male	61	57	65
Ethnicity Units: Subjects			
Not Hispanic or Latino	110	106	106
Hispanic or Latino	13	16	16
Race Units: Subjects			
White	77	89	88
Black or African American	23	19	20
Asian	13	5	10
Other	9	8	2
Not Reported/Missing	1	1	2
Eczema Area and Severity Index (EASI) Score			
The EASI assesses severity and extent of atopic dermatitis. Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) are assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs and lower limbs and converted to a score of 0 to 6.			

Units: Score on a Scale			
arithmetic mean	39.0	37.4	37.3
standard deviation	± 12.01	± 12.45	± 10.86
Investigator's Global Assessment (IGA) Score			
IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe).			
Units: Score on a Scale			
arithmetic mean	4.0	4.0	4.0
standard deviation	± 0.00	± 0.09	± 0.00
Weekly Average of Daily Worst Itch Score			
The worst itch scale is a simple assessment tool that subjects will use to report the intensity of their pruritus (itch). This is an 11-point scale (0 to 10) in which 0 indicates no itching while 10 indicates worst itching possible. Subjects will be asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score will be calculated as the worse of the scores for the 2 questions.			
Units: Score on a Scale			
arithmetic mean	7.7	7.8	7.8
standard deviation	± 1.54	± 1.58	± 1.52
Body Surface Area (BSA) of Atopic Dermatitis			
BSA affected by AD will be assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. The proportion assigned to different body regions is different in younger children as compared to older children (head and neck area is assigned a higher proportion in younger children as compared to older children).			
Units: Percentage of BSA			
arithmetic mean	60.2	54.8	57.8
standard deviation	± 21.46	± 21.58	± 20.04
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is used to assess the extent and severity of AD. Extent and severity of eczema as well as subjective symptoms (insomnia, etc) were assessed and scored. SCORAD total score range is from 0 (absent disease) to 103 (severe disease).			
Units: Score on a Scale			
arithmetic mean	72.9	75.6	72.3
standard deviation	± 12.01	± 11.71	± 10.83
Patient Oriented Eczema Measure (POEM)			
POEM is a 7-item, validated questionnaire used to assess disease symptoms in children and adults. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.			
Units: Score on a Scale			
arithmetic mean	20.7	21.3	20.5
standard deviation	± 5.48	± 5.51	± 5.50
Children's Dermatology Life Quality Index (CDLQI) Total Score			
CDLQI is a validated 10 question tool to measure the impact of skin disease on the quality of life (QOL) in children by assessing how much the skin problem has affected the subject over the past week. Nine questions are scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 has an added possible response, which is scored as 3. CDLQI equals the sum of the score of each question (maximum = 30, minimum = 0). Higher the score, the greater the impact on QOL. It can also be expressed as a percentage of the maximum possible score of 30.			
Units: Score on a Scale			
arithmetic mean	14.6	16.2	14.5
standard deviation	± 7.41	± 7.85	± 6.78

Dermatitis Family Index (DFI)			
DFI is a 10-item questionnaire with items inquiring about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver's life. The DFI questions are scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. Timeframe of reference is the past week. A higher DFI score indicates greater impairment in family QOL as affected by atopic dermatitis.			
Units: Score on a Scale			
arithmetic mean	15.0	16.9	14.9
standard deviation	± 7.54	± 8.65	± 7.05
Patient Reported Outcomes Measurements Information Systems (PROMIS) Anxiety Scale			
The PROMIS Anxiety instrument measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), & somatic symptoms related to arousal (racing heart, dizziness). Each question has five response options ranging in value from 1 to 5 (1 = Never, 2 = Almost never, 3 = Sometimes, 4 = Often, 5 = Almost Always). For an 8-item form, the lowest possible total raw score is 8; the highest possible total raw score is 40. For a 6-item form, the lowest possible total raw score is 6; the highest possible total raw score is 30.			
Units: Score on a Scale			
arithmetic mean	57.3	59.8	58.6
standard deviation	± 11.62	± 13.66	± 11.32
Patient Reported Outcomes Measurements Information Systems (PROMIS) Depression Scale			
PROMIS Depression instrument assesses: self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness) & social cognition (loneliness, interpersonal alienation), and decreased positive affect & engagement (loss of interest, meaning & purpose). Each question has 5 response options ranging in value from 1 to 5 (1=Never, 2=Almost never, 3=Sometimes, 4=Often, 5= Almost Always). For an 8-item form, lowest possible total raw score is 8; highest possible total raw score is 40. For a 6-item form, lowest possible total raw score is 6; highest possible total raw score is 30.			
Units: Score on a Scale			
arithmetic mean	55.0	58.1	56.3
standard deviation	± 12.05	± 12.77	± 11.22

Reporting group values	Total		
Number of subjects	367		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	184		
Male	183		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	322		
Hispanic or Latino	45		
Race			
Units: Subjects			
White	254		
Black or African American	62		
Asian	28		

Other	19		
Not Reported/Missing	4		

Eczema Area and Severity Index (EASI) Score			
The EASI assesses severity and extent of atopic dermatitis. Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) are assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs and lower limbs and converted to a score of 0 to 6.			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Investigator's Global Assessment (IGA) Score			
IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe).			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Weekly Average of Daily Worst Itch Score			
The worst itch scale is a simple assessment tool that subjects will use to report the intensity of their pruritus (itch). This is an 11-point scale (0 to 10) in which 0 indicates no itching while 10 indicates worst itching possible. Subjects will be asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score will be calculated as the worse of the scores for the 2 questions.			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Body Surface Area (BSA) of Atopic Dermatitis			
BSA affected by AD will be assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. The proportion assigned to different body regions is different in younger children as compared to older children (head and neck area is assigned a higher proportion in younger children as compared to older children).			
Units: Percentage of BSA			
arithmetic mean			
standard deviation	-		
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is used to assess the extent and severity of AD. Extent and severity of eczema as well as subjective symptoms (insomnia, etc) were assessed and scored. SCORAD total score range is from 0 (absent disease) to 103 (severe disease).			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Patient Oriented Eczema Measure (POEM)			
POEM is a 7-item, validated questionnaire used to assess disease symptoms in children and adults. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Children's Dermatology Life Quality			

Index (CDLQI) Total Score			
CDLQI is a validated 10 question tool to measure the impact of skin disease on the quality of life (QOL) in children by assessing how much the skin problem has affected the subject over the past week. Nine questions are scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 has an added possible response, which is scored as 3. CDLQI equals the sum of the score of each question (maximum = 30, minimum = 0). Higher the score, the greater the impact on QOL. It can also be expressed as a percentage of the maximum possible score of 30.			
Units: Score on a Scale arithmetic mean standard deviation	- -		
Dermatitis Family Index (DFI)			
DFI is a 10-item questionnaire with items inquiring about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver's life. The DFI questions are scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. Timeframe of reference is the past week. A higher DFI score indicates greater impairment in family QOL as affected by atopic dermatitis.			
Units: Score on a Scale arithmetic mean standard deviation	- -		
Patient Reported Outcomes Measurements Information Systems (PROMIS) Anxiety Scale			
The PROMIS Anxiety instrument measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), & somatic symptoms related to arousal (racing heart, dizziness). Each question has five response options ranging in value from 1 to 5 (1 = Never, 2 = Almost never, 3 = Sometimes, 4 = Often, 5 = Almost Always). For an 8-item form, the lowest possible total raw score is 8; the highest possible total raw score is 40. For a 6-item form, the lowest possible total raw score is 6; the highest possible total raw score is 30.			
Units: Score on a Scale arithmetic mean standard deviation	- -		
Patient Reported Outcomes Measurements Information Systems (PROMIS) Depression Scale			
PROMIS Depression instrument assesses: self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness) & social cognition (loneliness, interpersonal alienation), and decreased positive affect & engagement (loss of interest, meaning & purpose). Each question has 5 response options ranging in value from 1 to 5 (1=Never, 2=Almost never, 3=Sometimes, 4=Often, 5= Almost Always). For an 8-item form, lowest possible total raw score is 8; highest possible total raw score is 40. For a 6-item form, lowest possible total raw score is 6; highest possible total raw score is 30.			
Units: Score on a Scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo + TCS
Reporting group description:	
Subjects received matching placebo every 2 weeks (Q2W) or every 4 weeks (Q4W) during the 16-week double-blind treatment phase. Matching placebo was administered concomitantly with topical corticosteroids (TCS), including doubling the amount of placebo on Day 1 to match the loading dose.	
Reporting group title	Dupilumab 300 mg Q4W + TCS
Reporting group description:	
Subjects received subcutaneous injections of 600 milligrams (mg) loading dose on Day 1, then 300 mg of Dupilumab every 4 weeks (Q4W) from Week 4 to Week 12. Topical corticosteroids (TCS) were administered concomitantly during the 16-week double-blind treatment phase.	
Reporting group title	Dupilumab 100 mg or 200 mg Q2W + TCS
Reporting group description:	
Subjects received subcutaneous injections of 100 milligrams (mg) or 200 mg of Dupilumab every 2 weeks (Q2W). For 100 mg Q2W treatment group, subjects received a 200 mg loading dose on Day 1, then 100 mg Q2W from Week 2 to Week 14. For 200 mg Q2W treatment group, subjects received a 400 mg loading dose on Day 1, then 200 mg Q2W from Week 2 to Week 14. Topical corticosteroids (TCS) were administered concomitantly in all groups during the 16-week double-blind treatment phase.	

Primary: Percentage of Subjects with Investigator's Global Assessment (IGA) 0 or 1 at Week 16

End point title	Percentage of Subjects with Investigator's Global Assessment (IGA) 0 or 1 at Week 16
End point description:	
The IGA was an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The full analysis set (FAS) included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score at Week 16 were considered as a non-responder.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	11.4	32.8	29.5	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS
Statistical analysis description:	
A 2-sided hierarchical testing procedure was used for the primary and secondary endpoints in a pre-	

specified order. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level.

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.28
upper limit	27.97

Notes:

[1] - The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group (< 30 kilograms (kg) or ≥ 30 kg) and region (North America or Europe) was used for the analysis of percentage of subjects with IGA 0 or 1 at Week 16.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.36
upper limit	31.45

Notes:

[2] - The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group (< 30 kg or ≥ 30 kg) and region (North America or Europe) was used for the analysis of percentage of subjects with IGA 0 or 1 at Week 16.

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

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

End point description:

The EASI assesses severity and extent of atopic dermatitis (AD). Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) were assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score

at week 16 were considered as a non-responder.

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	26.8	69.7	67.2	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	40.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.95
upper limit	51.82

Notes:

[3] - The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group (< 30 kg or ≥ 30 kg) and region (North America or Europe) was used for the analysis of percentage of subjects with EASI-75 at Week 16.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	42.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.54
upper limit	54.15

Notes:

[4] - The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group (< 30 kg or ≥ 30 kg) and region (North America or Europe) was used for the analysis of percentage of subjects with EASI-75 at Week 16.

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 assesses severity and extent of AD. Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) were assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percent change				
least squares mean (standard error)	-48.6 (± 2.46)	-82.1 (± 2.37)	-78.4 (± 2.35)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.33
upper limit	-23.24

Notes:

[5] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.06
upper limit	-26.82

Notes:

[6] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Percent Change from Baseline in Weekly Average of Daily Worst Itch Score at Week 16

End point title	Percent Change from Baseline in Weekly Average of Daily Worst Itch Score at Week 16

End point description:

The worst itch scale was a simple assessment tool that subjects used to report the intensity of their pruritus (itch). This was an 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as the worse of the scores for the 2 questions. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percent change				
least squares mean (standard error)	-25.9 (± 2.90)	-54.6 (± 2.89)	-57.0 (± 2.77)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.76
upper limit	-23.26

Notes:

[7] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-28.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.47
upper limit	-20.82

Notes:

[8] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Percentage of Subjects with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Itch Score ≥3 Points at Week 16

End point title	Percentage of Subjects with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Itch Score ≥3 Points at Week 16

End point description:

The worst itch scale was a simple assessment tool that subjects used to report the intensity of their pruritus (itch). This was an 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as the worse of the scores for the 2 questions. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	121	120	
Units: Percentage of Subjects				
number (not applicable)	21.1	60.3	67.5	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	46.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.3
upper limit	57.42

Notes:

[9] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	39.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.88
upper limit	50.51

Notes:

[10] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Percentage of Subjects with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Itch Score ≥4 Points at Week 16

End point title	Percentage of Subjects with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Itch Score ≥4 Points at Week 16

End point description:

The worst itch scale was a simple assessment tool that subjects used to report the intensity of their pruritus (itch). This was an 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as the worse of the scores for the 2 questions. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	120	120	
Units: Percentage of Subjects				
number (not applicable)	12.3	50.8	58.3	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	46
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.47
upper limit	56.61

Notes:

[11] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	38.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.86
upper limit	49.21

Notes:

[12] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Percentage of Subjects Achieving Eczema Area and Severity Index - 50 (EASI-50) (≥ 50% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects Achieving Eczema Area and Severity Index - 50 (EASI-50) (≥ 50% Improvement from Baseline) at Week 16

End point description:

The EASI assessed severity and extent of AD. Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) were assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	43.1	91.0	82.8	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	39.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.68
upper limit	50.72

Notes:

[13] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Dupilumab 300 mg Q4W + TCS v Placebo + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	47.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.77
upper limit	58.01

Notes:

[14] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Percentage of Subjects Achieving Eczema Area and Severity Index - 90 (EASI - 90) (≥ 90% Improvement from Baseline) at Week 16

End point title	Percentage of Subjects Achieving Eczema Area and Severity Index - 90 (EASI - 90) (≥ 90% Improvement from Baseline) at Week 16

End point description:

The EASI assessed the severity and extent of atopic dermatitis (AD). Scores range from 0-72. Four AD disease characteristics (erythema, thickness, scratching, and lichenification) were assessed for severity on a scale of "0" (absent) through "3" (severe). Area of involvement assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	7.3	41.8	30.3	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.65
upper limit	32.38

Notes:

[15] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	34.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	24.6
upper limit	44.37

Notes:

[16] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Time to Achieve ≥ 4 Point Reduction of Weekly Average of Daily Worst Itch Score from Baseline during the 16-week Treatment Period

End point title	Time to Achieve ≥ 4 Point Reduction of Weekly Average of Daily Worst Itch Score from Baseline during the 16-week Treatment Period

End point description:

The worst itch scale: a simple assessment tool that subjects used to report intensity of their pruritus (itch). This was an 11-point scale (0 to 10) where 0 (no itching) and 10 (worst itching) possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as worse of scores for 2 questions. FAS was used. Time to event is calculated in weeks as (date of first event - date of first dose)/7. The event of NRS reduction ≥ 4 was based on observed data without setting data to be non-responder after rescue treatment use. Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint and "99999" represents "Not computable" as only 12.3% of subjects achieved NRS reduction during 16-week treatment period & hence median time to achieve ≥ 4-point reduction of NRS for placebo +TCS treated subjects could not be reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	120	120	
Units: Weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	10.0 (7 to 13)	10.0 (8 to 12)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Cox model
Parameter estimate	Hazard ratios
Point estimate	3.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.097
upper limit	4.624

Notes:

[17] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Cox model
Parameter estimate	Hazard ratios
Point estimate	2.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.957
upper limit	4.36

Notes:

[18] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Time to Achieve ≥ 3 Point Reduction of Weekly Average of Daily Worst Itch Score from Baseline during the 16-week Treatment Period

End point title	Time to Achieve ≥ 3 Point Reduction of Weekly Average of Daily Worst Itch Score from Baseline during the 16-week Treatment Period

End point description:

The worst itch scale: a simple assessment tool that subjects used to report intensity of their pruritus (itch). This was an 11-point scale (0 to 10) where 0 (no itching) and 10 (worst itching) possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as worse of scores for 2 questions. FAS was used. Time to event is calculated in weeks as (date of first event - date of first dose)/7. The event of NRS reduction ≥ 3 was based on observed data without setting data to be non-responder after rescue treatment use. Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint and "99999" represents "Not computable" as only 21.1% of subjects achieved NRS reduction during 16-week treatment period & hence median time to achieve ≥ 3-point reduction of NRS for placebo +TCS treated subjects could not be reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	121	120	
Units: Weeks				
median (confidence interval 95%)	99999 (11 to 99999)	6.0 (5 to 9)	5.0 (5 to 7)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cox model
Parameter estimate	Hazard ratios
Point estimate	2.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.631
upper limit	3.182

Notes:

[19] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cox model
Parameter estimate	Hazard ratios
Point estimate	2.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.481
upper limit	2.908

Notes:

[20] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Change from Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis (AD) at Week 16

End point title	Change from Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis (AD) at Week 16

End point description:

BSA affected by AD was assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and were reported as a percentage of all major body sections combined. The proportion assigned to different body regions were different in younger children as compared to older children (head and neck area is assigned a higher proportion in younger children as compared to older children). The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of BSA				
least squares mean (standard error)	-21.65 (± 1.721)	-40.53 (± 1.648)	-39.37 (± 1.629)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Dupilumab 100 mg or 200 mg Q2W + TCS v Placebo + TCS

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-17.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.272
upper limit	-13.161

Notes:

[21] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-18.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.479
upper limit	-14.289

Notes:

[22] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

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

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

End point description:

SCORAD was used to assess the extent and severity of AD. Extent and severity of eczema as well as subjective symptoms (insomnia, etc) were assessed and scored. SCORAD total score ranges from 0 (absent disease) to 103 (severe disease). The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percent change				
least squares mean (standard error)	-29.8 (± 2.26)	-62.4 (± 2.13)	-60.2 (± 2.11)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-30.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-24.48

Notes:

[23] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-32.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.57
upper limit	-26.59

Notes:

[24] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Change from Baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16

End point title	Change from Baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16

End point description:

CDLQI was a validated 10 question tool to measure the impact of skin disease on the quality of life (QOL) in children by assessing how much the skin problem has affected the subject over the past week. Nine questions were scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 has an added possible response, which was scored as 3. CDLQI equals the sum of the score of each question (maximum = 30, minimum = 0). Higher the score, the greater the impact on QOL. It can also be expressed as a percentage of the maximum possible score of 30. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-6.4 (± 0.51)	-10.6 (± 0.47)	-10.7 (± 0.46)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.62
upper limit	-2.99

Notes:

[25] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.57
upper limit	-2.89

Notes:

[26] - The confidence interval (CI) with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

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

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

End point description:

POEM was a 7-item, validated questionnaire used to assess disease symptoms in children and adults. The format was a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflected the disease-related morbidity. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-5.3 (± 0.69)	-13.6 (± 0.65)	-13.4 (± 0.65)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.96
upper limit	-6.31

Notes:

[27] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-8.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.13
upper limit	-6.43

Notes:

[28] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Change from Baseline in Weekly Average of Daily Worst Itch Score at Week 16

End point title	Change from Baseline in Weekly Average of Daily Worst Itch Score at Week 16

End point description:

The worst itch scale was a simple assessment tool that subjects used to report the intensity of their pruritus (itch). This was an 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible. Subjects were asked to answer 2 questions daily throughout the entire study (screening period, treatment period, and follow-up period). The daily worst itch score was calculated as the worse of the scores for the 2 questions. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-2.05 (± 0.215)	-4.22 (± 0.207)	-4.45 (± 0.206)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-2.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.984
upper limit	-1.831

Notes:

[29] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.754
upper limit	-1.599

Notes:

[30] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Change from Baseline in Dermatitis Family Index (DFI) at Week 16

End point title	Change from Baseline in Dermatitis Family Index (DFI) at Week 16

End point description:

DFI was a 10-item questionnaire with items inquiring about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships and the impact of helping with treatment on the primary caregiver’s life. The DFI questions were scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. Timeframe of reference was the past week. A higher DFI score indicated greater impairment in family Quality of life (QOL) as affected by atopic dermatitis. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1) , Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-6.77 (± 0.497)	-10.75 (± 0.476)	-10.89 (± 0.469)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.434
upper limit	-2.796

Notes:

[31] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-3.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.298
upper limit	-2.657

Notes:

[32] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Change from Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pediatric Anxiety Short Form Scale Total Score at Week 16

End point title	Change from Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pediatric Anxiety Short Form Scale Total Score at Week 16

End point description:

The PROMIS Anxiety instrument measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-10.17 (± 0.912)	-13.19 (± 0.861)	-13.54 (± 0.860)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061 [33]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-3.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.779
upper limit	-0.962

Notes:

[33] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0133 [34]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.414
upper limit	-0.629

Notes:

[34] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Change from Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pediatric Depressive Symptoms Short Form Scale Score at Week 16

End point title	Change from Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pediatric Depressive Symptoms Short Form Scale Score at Week 16

End point description:

The PROMIS Depression instrument assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Score on a Scale				
least squares mean (standard error)	-7.42 (± 0.848)	-12.84 (± 0.793)	-11.92 (± 0.790)	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.734
upper limit	-2.272

Notes:

[35] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-5.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.641
upper limit	-3.207

Notes:

[36] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata as fixed factors.

Secondary: Percentage of Subjects Having at Least One Skin Infection Treatment Emergent Adverse Event (TEAE) (Excluding Herpetic Infections) through Week 16

End point title	Percentage of Subjects Having at Least One Skin Infection Treatment Emergent Adverse Event (TEAE) (Excluding Herpetic Infections) through Week 16

End point description:

Treatment-emergent adverse events (TEAEs) were defined as adverse events (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. 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-subjects 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. Percentage of subjects having at least one skin infection TEAE (Excluding Herpetic Infections) through Week 16 were reported. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	13.0	5.7	8.2	

Statistical analyses

Statistical analysis title	Dupilumab 100 mg/200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222 [37]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Differenece
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.49
upper limit	2.87

Notes:

[37] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0508 [38]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Differenece
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.51
upper limit	-0.03

Notes:

[38] - P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe] and baseline weight group [< 30 kg vs ≥ 30 kg].

Secondary: Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) through Week 16

End point title	Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) through Week 16

End point description:

Treatment-emergent adverse events (TEAEs) were defined as adverse events (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. 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-subjects 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. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	122	
Units: Percentage of Subjects				
number (not applicable)	1.6	1.6	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Topical Corticosteroid (TCS) Medication-free Days from Baseline to Week 16

End point title	Percentage of Topical Corticosteroid (TCS) Medication-free Days from Baseline to Week 16

End point description:

Percentage of TCS medication-free days is calculated as the number of days that a patient used neither TCS/TCI nor system rescue therapy divided by the study days of each period. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	122	121	
Units: Days				
arithmetic mean (standard deviation)	0.11 (± 0.185)	0.20 (± 0.230)	0.19 (± 0.207)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Weekly Dose of Topical Corticosteroid (TCS) in Grams for Low or Medium Potency TCS from Baseline to Week 16

End point title	Mean Weekly Dose of Topical Corticosteroid (TCS) in Grams for Low or Medium Potency TCS from Baseline to Week 16

End point description:

Mean weekly dose of TCS in grams for low or medium potency TCS from baseline to Week 16 were reported. The FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 16

End point values	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: Grams				
least squares mean (standard error)	20.1 (± 1.37)	15.0 (± 1.36)	14.4 (± 1.38)	

Statistical analyses

Statistical analysis title	Dupilumab100 mg/ 200 mg Q2W + TCS vs Placebo + TCS

Statistical analysis description:

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

Comparison groups	Placebo + TCS v Dupilumab 100 mg or 200 mg Q2W + TCS
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [39]
Method	ANOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.49
upper limit	-1.96

Notes:

[39] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANOVA model with the treatment, randomization strata as fixed factors.

Statistical analysis title	Dupilumab 300 mg Q4W + TCS vs Placebo + TCS
Comparison groups	Placebo + TCS v Dupilumab 300 mg Q4W + TCS

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0082 [41]
Method	ANOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	-1.31

Notes:

[40] - A 2-sided hierarchical testing procedure was used for the primary and secondary endpoints in a pre-specified order. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level

[41] - The confidence interval (CI) with p-value was based on treatment difference (Dupilumab group vs placebo) of the LS mean percent change using ANOVA model with the treatment, randomization strata as fixed factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event information was collected from the time the informed consent was signed until the subject's last study visit (Week 28). Serious adverse event information was collected until the event was considered chronic and/or stable.

Adverse event reporting additional description:

The safety analysis set (SAF) includes all randomized subjects who received at least one injection of study drug and were analyzed as treated. Treatment compliance/administration and all clinical safety variables were summarized based on the SAF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo + TCS

Reporting group description:

Subjects received matching placebo every 2 weeks (Q2W) or every 4 weeks (Q4W) during the 16-week double-blind treatment phase. Matching placebo was administered concomitantly with topical corticosteroids (TCS), including doubling the amount of placebo on Day 1 to match the loading dose.

Reporting group title	Dupilumab 300 mg Q4W + TCS

Reporting group description:

Subjects received subcutaneous injections of 600 milligrams (mg) loading dose on Day 1, then 300 mg of Dupilumab every 4 weeks (Q4W) from Week 4 to Week 12. Topical corticosteroids (TCS) were administered concomitantly during the 16-week double-blind treatment phase.

Reporting group title	Dupilumab 100 mg or 200 mg Q2W + TCS

Reporting group description:

Subjects received subcutaneous injections of 100 milligrams (mg) or 200 mg of Dupilumab every 2 weeks (Q2W). For 100 mg Q2W treatment group, subjects received a 200 mg loading dose on Day 1, then 100 mg Q2W from Week 2 to Week 14. For 200 mg Q2W treatment group, subjects received a 400 mg loading dose on Day 1, then 200 mg Q2W from Week 2 to Week 14. Topical corticosteroids (TCS) were administered concomitantly in all groups during the 16-week double-blind treatment phase.

Serious adverse events	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 120 (1.67%)	3 / 120 (2.50%)	0 / 122 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 120 (0.00%)	1 / 120 (0.83%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Food allergy			
subjects affected / exposed	0 / 120 (0.00%)	1 / 120 (0.83%)	0 / 122 (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			
Asthma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 120 (0.00%)	0 / 122 (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	1 / 120 (0.83%)	0 / 120 (0.00%)	0 / 122 (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			
Urinary tract infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 120 (0.83%)	0 / 122 (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

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

Non-serious adverse events	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Dupilumab 100 mg or 200 mg Q2W + TCS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 120 (47.50%)	47 / 120 (39.17%)	50 / 122 (40.98%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 120 (8.33%)	6 / 120 (5.00%)	7 / 122 (5.74%)
occurrences (all)	11	7	10
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	2 / 120 (1.67%)	5 / 120 (4.17%)	7 / 122 (5.74%)
occurrences (all)	3	5	9
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	8 / 120 (6.67%)	6 / 120 (5.00%)	6 / 122 (4.92%)
occurrences (all)	9	7	8
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	11 / 120 (9.17%)	2 / 120 (1.67%)	4 / 122 (3.28%)
occurrences (all)	12	2	4
Cough			
subjects affected / exposed	9 / 120 (7.50%)	3 / 120 (2.50%)	5 / 122 (4.10%)
occurrences (all)	13	3	5
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	17 / 120 (14.17%)	8 / 120 (6.67%)	10 / 122 (8.20%)
occurrences (all)	25	12	10
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 120 (2.50%)	5 / 120 (4.17%)	7 / 122 (5.74%)
occurrences (all)	3	5	8
Nasopharyngitis			
subjects affected / exposed	8 / 120 (6.67%)	15 / 120 (12.50%)	8 / 122 (6.56%)
occurrences (all)	11	16	10
Upper respiratory tract infection			
subjects affected / exposed	12 / 120 (10.00%)	14 / 120 (11.67%)	12 / 122 (9.84%)
occurrences (all)	12	19	16
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 120 (5.00%)	2 / 120 (1.67%)	1 / 122 (0.82%)
occurrences (all)	6	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2017	• Children who are engaging in heavy exercise can have transient increases in CPK that are not clinically relevant • Added an Ophthalmological Examination section for subjects who have history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within the last 12 months and subjects who experience adverse events of special interest related to eye disorders • Modified the reporting schedule for subjects assessment of pruritus. Subjects will answer both questions in the evening
20 November 2018	• Included introduction of the modified full analysis set (mFAS), which excludes potentially unblinded subjects, and will be used for sensitivity analysis • Extended the duration of the visit window between Visit 1 and Visit 2 from 21 days to 63 days (ie, changed start of Visit 1 from -35 days to -77 days) and removed the limit of rescreen once to allow for the seamless screening/enrolment of all new subjects into the study • Added rationale for the inclusion of a placebo treatment group in the study design and a description of the risks and benefits to subjects assigned to the placebo treatment group • Corrected the description of age limit of the study population from "aged ≥ 6 to < 12 years at the time of baseline" to "aged ≥ 6 to < 12 years at the time of screening" to be consistent with the wording in the Inclusion Criteria and other sections of the protocol. • Revised language for accelerated reporting of pregnancy to sponsor and the duration subjects who are female of childbearing potential and sexually active are required to use highly effective methods of contraception after the last dose of study drug, to align with the current dupilumab label • Revised text to emphasize that the use of very-highpotency topical corticosteroids (TCS) is prohibited during the study, as their use is not recommended in subjects under 12 years of age. Also included examples of very-high-potency TCS • Included "injection observation" for the every 4 week regimen in the Schedule of Events table, to identify the visits at which the observation occurs • Revised the adverse events of special interest definition for conjunctivitis, keratitis, and blepharitis • Specified the list of potential major protocol violation types for the PPS, per request from the United States Food and Drug Administration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported