

**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) | EMA-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 (\geq) 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 standard deviation | 8.3 ± 1.76 | 8.5 ± 1.74 | 8.5 ± 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 standard deviation | 39.0 ± 12.01 | 37.4 ± 12.45 | 37.3 ± 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 standard deviation | 4.0 ± 0.00 | 4.0 ± 0.09 | 4.0 ± 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 standard deviation | 7.7 ± 1.54 | 7.8 ± 1.58 | 7.8 ± 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 standard deviation | 60.2 ± 21.46 | 54.8 ± 21.58 | 57.8 ± 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 standard deviation | 72.9 ± 12.01 | 75.6 ± 11.71 | 72.3 ± 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 standard deviation | 20.7 ± 5.48 | 21.3 ± 5.51 | 20.5 ± 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 standard deviation | 14.6 ± 7.41 | 16.2 ± 7.85 | 14.5 ± 6.78 |

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|---|---------|---------|---------|
| 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) ($\geq 50\%$ Improvement from Baseline) at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving Eczema Area and Severity Index - 50 (EASI-50) ($\geq 50\%$ 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) ($\geq 90\%$ Improvement from Baseline) at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving Eczema Area and Severity Index - 90 (EASI - 90) ($\geq 90\%$ 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 (\pm 1.721) | -40.53 (\pm 1.648) | -39.37 (\pm 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 (\pm 0.497) | -10.75 (\pm 0.476) | -10.89 (\pm 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 (\pm 0.912) | -13.19 (\pm 0.861) | -13.54 (\pm 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 (\pm 0.848) | -12.84 (\pm 0.793) | -11.92 (\pm 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 Difference |
| 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 Difference |
| 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 (\pm 1.37) | 15.0 (\pm 1.36) | 14.4 (\pm 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 occurrences (all) | 8 / 120 (6.67%) 9 | 6 / 120 (5.00%) 7 | 6 / 122 (4.92%) 8 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma subjects affected / exposed occurrences (all) | 11 / 120 (9.17%) 12 | 2 / 120 (1.67%) 2 | 4 / 122 (3.28%) 4 |
| Cough subjects affected / exposed occurrences (all) | 9 / 120 (7.50%) 13 | 3 / 120 (2.50%) 3 | 5 / 122 (4.10%) 5 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic subjects affected / exposed occurrences (all) | 17 / 120 (14.17%) 25 | 8 / 120 (6.67%) 12 | 10 / 122 (8.20%) 10 |
| Infections and infestations | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 120 (2.50%) 3 | 5 / 120 (4.17%) 5 | 7 / 122 (5.74%) 8 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 120 (6.67%) 11 | 15 / 120 (12.50%) 16 | 8 / 122 (6.56%) 10 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 12 / 120 (10.00%) 12 | 14 / 120 (11.67%) 19 | 12 / 122 (9.84%) 16 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 120 (5.00%) 6 | 2 / 120 (1.67%) 2 | 1 / 122 (0.82%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 31 August 2017 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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