



Clinical trial results:

Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Dupilumab Monotherapy in Patients 12 to <18 Years of Age, With Moderate-to-severe Atopic Dermatitis

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004458-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 05 June 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 19 December 2018 |
| First version publication date | 06 February 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | R668-AD-1526 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03054428 |
| WHO universal trial number (UTN) | - |

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 Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |
| Scientific contact | Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | 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? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 July 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the efficacy of dupilumab as a monotherapy in subjects ≥ 12 years to < 18 years of age with moderate-to-severe atopic dermatitis (AD). The secondary objective of the study was to assess the safety of dupilumab as a monotherapy in subjects ≥ 12 years to < 18 years of age with moderate-to-severe AD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 21 March 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 | United States: 220 |
| Country: Number of subjects enrolled | Canada: 31 |
| Worldwide total number of subjects | 251 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 251 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 50 sites in the United States and Canada between 21 March 2017 and 04 Jun 2018. A total of 295 subjects were screened in the study. The most common causes for screening failures were lack of adequate disease severity and lack of willingness to comply with study visits and procedures.

Pre-assignment

Screening details:

Out of 295 subjects, 251 were enrolled and randomized in an approximate 1:1:1 ratio to 1 of 3 treatment groups: Dupilumab once every 2 weeks (Q2W), Dupilumab once every 4 weeks (Q4W) and Placebo.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (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 | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

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

| | |
|------------------|----------------------|
| Arm title | Dupilumab 300 mg Q4W |
|------------------|----------------------|

Arm description:

Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given.

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

Dosage and administration details:

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

| | |
|------------------|--------------------------------|
| Arm title | Dupilumab 200 mg or 300 mg Q2W |
|------------------|--------------------------------|

Arm description:

Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.

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

Dosage and administration details:

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

| Number of subjects in period 1 | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W |
|---|---------|----------------------|--------------------------------|
| Started | 85 | 84 | 82 |
| Completed Week 16 | 80 | 81 | 79 |
| Completed | 2 | 4 | 3 |
| Not completed | 83 | 80 | 79 |
| Consent withdrawn by subject | 3 | 2 | 3 |
| Physician decision | - | 1 | 1 |
| Discontinued for R668-AD-1434, but did not enroll | 1 | - | - |
| Transitioned to R668-AD-1434 (open-label) | - | - | 73 |
| Discontinued to enroll in R668-AD-1434 | - | - | 1 |
| Lost to follow-up | - | - | 1 |
| Transitioned to R668-AD-1434 open-label study | 76 | 76 | - |
| Lack of efficacy | 3 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

| | |
|-----------------------|----------------------|
| Reporting group title | Dupilumab 300 mg Q4W |
|-----------------------|----------------------|

Reporting group description:

Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given.

| | |
|-----------------------|--------------------------------|
| Reporting group title | Dupilumab 200 mg or 300 mg Q2W |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1.

| Reporting group values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W |
|---------------------------|---------|----------------------|--------------------------------|
| Number of subjects | 85 | 84 | 82 |
| Age categorical | | | |
| Units: Subjects | | | |
| ≥12-<15 | 41 | 45 | 43 |
| ≥15-<18 | 44 | 39 | 39 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 14.5 | 14.4 | 14.5 |
| standard deviation | ± 1.78 | ± 1.59 | ± 1.74 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 32 | 32 | 39 |
| Male | 53 | 52 | 43 |
| Race | | | |
| Units: Subjects | | | |
| White | 48 | 55 | 54 |
| Black or African American | 15 | 8 | 7 |
| Asian | 13 | 13 | 12 |
| Other | 6 | 8 | 7 |
| Not Reported/Missing | 3 | 0 | 2 |
| Ethnicity | | | |
| Units: Subjects | | | |
| NOT HISPANIC OR LATINO | 72 | 64 | 69 |
| HISPANIC OR LATINO | 13 | 20 | 13 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Investigator's Global Assessment (IGA) Score | | | |
| IGA is an assessment scale used to determine severity of atopic dermatitis (AD) and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear). | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 3.5 ± 0.50 | 3.5 ± 0.50 | 3.5 ± 0.50 |
| Eczema Area and Severity Index (EASI) Score | | | |
| The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 35.5 ± 13.97 | 35.8 ± 14.82 | 35.3 ± 13.84 |
| Peak weekly averaged pruritus Numerical Rating Scale (NRS) Score | | | |
| Peak Pruritus NRS is an assessment tool used by subjects to report intensity of pruritus (itch) during a 24-hour recall period. Subjects were asked the following questions: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your itch at the worst moment during the previous 24 hours?" Baseline NRS was the prorated average of NRSs reported continuously for 7 days right before and on the baseline visit (ie, study day -6 to day 1). | | | |
| Units: Peak weekly average score arithmetic mean standard deviation | 7.7 ± 1.62 | 7.5 ± 1.84 | 7.5 ± 1.52 |
| Body Surface Area (BSA) of AD | | | |
| BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. | | | |
| Units: Percentage of BSA arithmetic mean standard deviation | 56.4 ± 24.13 | 56.9 ± 23.51 | 56.0 ± 21.40 |
| Scoring Atopic Dermatitis (SCORAD) Score | | | |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 70.4 ± 13.25 | 69.8 ± 14.12 | 70.6 ± 13.89 |
| Children's Dermatology Life Quality Index (CDLQI) Total Score | | | |
| The CDLQI is a 10-item questionnaire used to measure how much a subject's skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant 1 = Only a little 2 = Quite a lot 3 = Very much = yes = prevent school | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 13.1 ± 6.72 | 14.8 ± 7.38 | 13.0 ± 6.21 |

| | | | |
|---|--------|--------|--------|
| Patient Oriented Eczema Measure (POEM) | | | |
| <p>The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4= 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor QOL.</p> | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 21.1 | 21.1 | 21.0 |
| standard deviation | ± 5.38 | ± 5.47 | ± 5.01 |
| Total Hospital Anxiety and Depression Scale (HADS) | | | |
| <p>The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.'</p> | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 11.6 | 13.3 | 12.6 |
| standard deviation | ± 7.76 | ± 8.17 | ± 8.04 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 251 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| ≥12-<15 | 129 | | |
| ≥15-<18 | 122 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 103 | | |
| Male | 148 | | |
| Race | | | |
| Units: Subjects | | | |
| White | 157 | | |
| Black or African American | 30 | | |
| Asian | 38 | | |
| Other | 21 | | |
| Not Reported/Missing | 5 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| NOT HISPANIC OR LATINO | 205 | | |
| HISPANIC OR LATINO | 46 | | |
| Investigator's Global Assessment (IGA) Score | | | |
| <p>IGA is an assessment scale used to determine severity of atopic dermatitis (AD) and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear).</p> | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |

| | | | |
|--|---|--|--|
| standard deviation | - | | |
| Eczema Area and Severity Index (EASI) Score | | | |
| The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. | | | |
| Units: Scores on a scale arithmetic mean standard deviation | - | | |
| Peak weekly averaged pruritus Numerical Rating Scale (NRS) Score | | | |
| Peak Pruritus NRS is an assessment tool used by subjects to report intensity of pruritus (itch) during a 24-hour recall period. Subjects were asked the following questions: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your itch at the worst moment during the previous 24 hours?" Baseline NRS was the prorated average of NRSs reported continuously for 7 days right before and on the baseline visit (ie, study day -6 to day 1). | | | |
| Units: Peak weekly average score arithmetic mean standard deviation | - | | |
| Body Surface Area (BSA) of AD | | | |
| BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. | | | |
| Units: Percentage of BSA arithmetic mean standard deviation | - | | |
| Scoring Atopic Dermatitis (SCORAD) Score | | | |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). | | | |
| Units: Scores on a scale arithmetic mean standard deviation | - | | |
| Children's Dermatology Life Quality Index (CDLQI) Total Score | | | |
| The CDLQI is a 10-item questionnaire used to measure how much a subject's skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant 1 = Only a little 2 = Quite a lot 3 = Very much = yes = prevent school | | | |
| Units: Scores on a scale arithmetic mean standard deviation | - | | |
| Patient Oriented Eczema Measure (POEM) | | | |
| The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 = 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor QOL. | | | |
| Units: Scores on a scale | | | |

| | | | |
|--|---|--|--|
| arithmetic mean | | | |
| standard deviation | - | | |
| Total Hospital Anxiety and Depression Scale (HADS) | | | |
| The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.' | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo matching dupilumab once every 2 weeks (Q2W) (including doubling the amount of placebo on day 1 to match the loading dose). In order to maintain blinding for the study, subjects in the <60 kilogram (kg) weight stratum received, in a 1:1 ratio, either placebo matching 200 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 milligram (mg) dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). In the ≥60 kg weight stratum, the subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). | |
| Reporting group title | Dupilumab 300 mg Q4W |
| Reporting group description: Subjects received once every 4 weeks (Q4W) subcutaneous (SC) injections of 300 milligrams (mg) dupilumab following a loading dose of 600 mg on day 1. In order to maintain blinding, all subjects received an injection once every 2 weeks (Q2W) from day 1 to week 14. Subjects received placebo 2 millilitre (mL) injection at the weeks dupilumab was not given. | |
| Reporting group title | Dupilumab 200 mg or 300 mg Q2W |
| Reporting group description: Subjects with baseline weight <60 kg received once every 2 weeks (Q2W) subcutaneous (SC) injections of 200 milligram (mg) dupilumab following a loading dose of 400 mg on day 1. Subjects with baseline weight ≥60 kg received Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1. | |

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

| | |
|---|---|
| End point title | Percentage of Subjects with Investigator's Global Assessment (IGA) 0 or 1 (and Reduction from Baseline of ≥2 Points) at Week 16 |
| End point description: IGA is an assessment scale used to determine severity of atopic dermatitis (AD) and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear). Subjects with IGA "0" or "1" and a reduction from baseline of ≥2 points at Week 16 were reported. Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Subject considered non-responder after rescue treatment use – Full analysis set (FAS). FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized). | |
| End point type | Primary |
| End point timeframe: At Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 2.4 | 17.9 | 24.4 | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
| Statistical analysis description: | |
| A hierarchical testing procedure was used to control type I error. Analysis was performed using Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (less than [$<$] 60 kilogram [kg] vs greater than or equal to [\geq] 60 kg). | |
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | percentage difference |
| Point estimate | 22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.2 |
| upper limit | 31.87 |

Notes:

[1] - Threshold for significance at 0.05 level.

| | |
|--|---------------------------------|
| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
| Statistical analysis description: | |
| A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (<60 kg vs ≥ 60 kg). | |
| Comparison groups | Placebo v Dupilumab 300 mg Q4W |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | $= 0.0007$ ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | percentage difference |
| Point estimate | 15.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.7 |
| upper limit | 24.31 |

Notes:

[2] - Threshold for significance at 0.05 level.

Primary: Percentage of Subjects with Eczema Area and Severity Index (EASI)-75

(≥75% Improvement from Baseline) at Week 16

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

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16.

Values after first rescue treatment used were set to missing. Subjects with missing score at week 16 were considered as a non-responder. Subject considered nonresponder after rescue treatment use – Full analysis set (FAS). FAS included all randomized subjects. Efficacy analyses were based on the treatment allocated at randomization (as randomized).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 8.2 | 38.1 | 41.5 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (< 60 kg vs ≥ 60 kg).

| | |
|---|--|
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | percentage difference |
| Point estimate | 33.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.07 |
| upper limit | 45.39 |

Notes:

[3] - Threshold for significance at 0.05 level.

| | |
|--|---------------------------------|
| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
| Statistical analysis description: A hierarchical testing procedure was used to control type I error. Analysis was performed using CMH test stratified by baseline disease severity (IGA=3 vs IGA=4) and baseline weight group (< 60 kg vs >=60 kg). | |
| Comparison groups | Dupilumab 300 mg Q4W v Placebo |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | percentage difference |
| Point estimate | 29.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.94 |
| upper limit | 41.78 |

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in EASI Score at Week 16

| | |
|---|---|
| End point title | Percent Change from Baseline in EASI Score at Week 16 |
| End point description: The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. | |
| [Multiple imputation (MI) Method with Data Set to Missing after Rescue Treatment Use – Full analysis set (FAS). FAS included all randomized subjects. Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered as non-responders.] | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -23.6 (± 5.49) | -64.8 (± 4.51) | -65.9 (± 3.99) | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
|-----------------------------------|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs. Placebo) of the LS mean percent change using analysis of covariance (ANCOVA) model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

| | |
|---|--|
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Least Square (LS) Mean difference |
| Point estimate | -42.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -55.6 |
| upper limit | -29.04 |

Notes:

[5] - Threshold for significance at 0.05 level.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is 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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

| | |
|---|--------------------------------|
| Comparison groups | Dupilumab 300 mg Q4W v Placebo |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -41.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.44 |
| upper limit | -28.02 |

Notes:

[6] - Threshold for significance at 0.05 level.

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

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

End point description:

revise to weekly average post-baseline

[MI Method with Data Set to Missing after Rescue Treatment Use – FAS. Values after first rescue

treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: percent change | | | | |
| least squares mean (standard error) | -19.0 (± 4.09) | -45.5 (± 3.54) | -47.9 (± 3.43) | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
|-----------------------------------|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is 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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

| | |
|---|--|
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[7] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.54 |
| upper limit | -18.38 |

Notes:

[7] - Threshold for significance at 0.05 level.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. The confidence interval (CI) with p-value is 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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.

| | |
|-------------------|--------------------------------|
| Comparison groups | Dupilumab 300 mg Q4W v Placebo |
|-------------------|--------------------------------|

| | |
|---|--------------------|
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -26.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.45 |
| upper limit | 15.63 |

Notes:

[8] - Threshold for significance at 0.05 level.

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

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Improvement (Reduction ≥ 3 Points) of Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 16 |
|-----------------|---|

End point description:

Pruritus NRS is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥ 4 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported.

[Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥ 3 .]

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 83 | 82 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 9.4 | 38.6 | 48.8 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by

CMH test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

| | |
|---|--|
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | percentage difference |
| Point estimate | 39.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 26.9 |
| upper limit | 51.84 |

Notes:

[9] - Threshold for significance at 0.05 level.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

| | |
|---|--------------------------------|
| Comparison groups | Dupilumab 300 mg Q4W v Placebo |
| Number of subjects included in analysis | 168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage difference |
| Point estimate | 29.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.97 |
| upper limit | 41.32 |

Notes:

[10] - Threshold for significance at 0.05 level.

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

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

End point description:

revise

[Values after first rescue treatment were set to missing and subjects with missing peak NRS at Week 16 were counted as non-responders. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with baseline peak pruritus NRS ≥ 4.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 83 | 82 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 4.8 | 26.5 | 36.6 | |

Statistical analyses

| Statistical analysis title | Dupilumab 200 mg or 300 mg Q2W vs Placebo |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

| | |
|---|--|
| Comparison groups | Dupilumab 200 mg or 300 mg Q2W v Placebo |
| Number of subjects included in analysis | 166 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage difference |
| Point estimate | 31.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.45 |
| upper limit | 43.2 |

Notes:

[11] - Threshold for significance at 0.05 level.

| Statistical analysis title | Dupilumab 300 mg Q4W vs Placebo |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error. Difference is Dupilumab minus Placebo. C.I. = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].

| | |
|-------------------|--------------------------------|
| Comparison groups | Dupilumab 300 mg Q4W v Placebo |
|-------------------|--------------------------------|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 ^[12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage difference |
| Point estimate | 21.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.21 |
| upper limit | 32.28 |

Notes:

[12] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with EASI-50 at Week 16

| | |
|--|--|
| End point title | Percentage of Subjects with EASI-50 at Week 16 |
| End point description: | |
| <p>The EASI score was used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-50 responders were the subjects who achieved $\geq 50\%$ overall improvement in EASI score at Week 16. Values after first rescue treatment used were set to missing. Subjects with missing value at week 16 were considered as a non-responder. FAS included all randomized subjects.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 12.9 | 54.8 | 61.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With EASI-90 at Week 16

| | |
|--|--|
| End point title | Percentage of Subjects With EASI-90 at Week 16 |
| End point description: | |
| <p>The EASI score was used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-90 responders were the subjects who achieved $\geq 90\%$ overall improvement in EASI score at Week 16. Values after first rescue treatment used were set to</p> | |

missing. Subjects with missing value at week 16 were considered as a non-responder. FAS included all randomized subjects.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 2.4 | 19.0 | 23.2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS ≥ 3 From Baseline

| | |
|-----------------|--|
| End point title | Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS ≥ 3 From Baseline |
|-----------------|--|

End point description:

It was measured by percentage of subjects with improvement of weekly average of daily peak pruritus numerical rating scale (NRS) score increased by 3 or more points from baseline. Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). FAS included all randomized subjects. Here, number of subjects analyzed=subjects with available data for specified endpoint.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|--------------------------------------|--------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 83 | 82 | |
| Units: weeks | | | | |
| arithmetic mean (standard deviation) | 11.4 (\pm 5.63) | 8.4 (\pm 5.92) | 7.7 (\pm 5.57) | |

Statistical analyses

Secondary: Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS ≥ 4 From Baseline

| | |
|-----------------|--|
| End point title | Time to Onset of Effect on Pruritus as Measured by Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS ≥ 4 From Baseline |
|-----------------|--|

End point description:

It was measured by percentage of subjects with improvement of weekly average of daily peak pruritus numerical rating scale (NRS) score increased by 4 or more points from baseline. Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). FAS included all randomized subjects. Here, number of subjects analyzed=subjects with available data for specified endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|--------------------------------------|--------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 83 | 82 | |
| Units: weeks | | | | |
| arithmetic mean (standard deviation) | 12.8 (\pm 4.90) | 9.9 (\pm 5.87) | 10.6 (\pm 5.50) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Body Surface Area (BSA) at week 16

| | |
|-----------------|--|
| End point title | Change From Baseline in Percent Body Surface Area (BSA) at week 16 |
|-----------------|--|

End point description:

BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. FAS included all randomized subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|--|-----------------------|-----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: percentage of body surface area | | | | |
| least squares mean (standard error) | -11.66 (\pm 2.720) | -33.41 (\pm 2.330) | -30.11 (\pm 2.337) | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Percent Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Score at Week 16 |
| End point description: | |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). FAS included all randomized subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|---------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -17.6 (\pm 3.76) | -47.5 (\pm 3.21) | -51.6 (\pm 3.23) | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--|
| End point title | Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) Total Score at Week 16 |
| End point description: | |
| The CDLQI is a 10-item questionnaire used to measure how much a subject's skin problem had affected the subject's quality of life (QOL) over a recall period of the past week. The questionnaire consists of 10 items. For each item the scale is rated as follows: 0 = Not at all = Not relevant, 1 = Only a little, 2 = Quite a lot, 3 = Very much = yes = prevent school. FAS included all randomized subjects. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|--------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -5.1 (\pm 0.62) | -8.8 (\pm 0.53) | -8.5 (\pm 0.50) | |

Statistical analyses

No statistical analyses for this end point

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:

The POEM is a 7-item questionnaire used to assess disease symptoms in children and adults with atopic eczema. Subjects respond to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4= 'every day'). The total score is the sum of the 7 items which is ranged from 0 to 28; a high score is indicative of a poor quality of life (QOL). FAS included all randomized subjects.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|--------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -3.8 (\pm 0.96) | -9.5 (\pm 0.86) | -10.1 (\pm 0.76) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at

Week 16

| | |
|-----------------|--|
| End point title | Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 16 |
|-----------------|--|

End point description:
revise

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
Baseline, Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|----------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -1.54 (\pm 0.303) | -3.44 (\pm 0.260) | -3.70 (\pm 0.250) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 4

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS at Week 4 |
|-----------------|---|

End point description:

Pruritus NRS scale is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0= no itch; 10= worst itch imaginable]). FAS included all randomized subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
Baseline, Week 4

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|---------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -12.5 (\pm 3.06) | -33.1 (\pm 3.05) | -34.7 (\pm 2.99) | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The HADS is an instrument for screening anxiety and depression. The 14 items on the questionnaire, assessing how the subject was feeling in the past week, include 7 items related to anxiety and 7 items related to depression. A subject could score between 0 and 21 for each sub-scale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either sub-scale are considered to be a 'definite case' of psychological morbidity, while scores of 8 to 10 represents 'probable case' and 0 to 7 'not a case.' FAS included all randomized subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------------|--------------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -2.5 (\pm 0.80) | -5.2 (\pm 0.73) | -3.8 (\pm 0.68) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS \geq 4 From Baseline at Week 4

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Improvement of Weekly Average of Daily Peak Pruritus NRS \geq 4 From Baseline at Week 4 |
|-----------------|---|

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). FAS included all randomized subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
From baseline to Week 4

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 84 | 82 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 4.8 | 20.5 | 22.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Skin-infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) Through Week 16

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Skin-infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) Through Week 16 |
|-----------------|--|

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 16]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. FAS included all randomized subjects. Here, number of subjects analysed=subjects with available data for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline through Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 83 | 82 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 18.8 | 9.6 | 9.8 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Serious TEAEs Through Week 16

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Serious TEAEs Through Week 16 |
|-----------------|---|

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 28]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. FAS population was used.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline through Week 16

| End point values | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg Q2W | |
|-------------------------------|-----------------|----------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 85 | 83 | 82 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 1.2 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Day 197) regardless of seriousness or relationship to investigational product (IP).

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs (TEAEs) that developed/worsened during 'on treatment period' (from 1st dose of IP up to Day 113). TEAEs were collected for the 16-week treatment & follow-up period up to 12 weeks. After completing the treatment period, all were offered an opportunity to enroll in open-label extension (OLE) study R668-AD-1434.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|----------------------|
| Reporting group title | Dupilumab 300 mg Q4W |
|-----------------------|----------------------|

Reporting group description:

Dupilumab 300 mg Q4W

| | |
|-----------------------|----------------------------|
| Reporting group title | Dupilumab 200 mg or 300 mg |
|-----------------------|----------------------------|

Reporting group description:

Dupilumab 200 mg or 300 mg

| Serious adverse events | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg |
|---|----------------|----------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 83 (0.00%) | 0 / 82 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 83 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | Dupilumab 300 mg Q4W | Dupilumab 200 mg or 300 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 40 / 85 (47.06%) | 34 / 83 (40.96%) | 39 / 82 (47.56%) |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 9 / 85 (10.59%) 14 | 4 / 83 (4.82%) 5 | 9 / 82 (10.98%) 11 |
| Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all) | 21 / 85 (24.71%) 29 | 16 / 83 (19.28%) 27 | 15 / 82 (18.29%) 21 |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis streptococcal subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 85 (4.71%) 4 4 / 85 (4.71%) 5 0 / 85 (0.00%) 0 15 / 85 (17.65%) 23 | 0 / 83 (0.00%) 0 10 / 83 (12.05%) 16 5 / 83 (6.02%) 5 7 / 83 (8.43%) 9 | 5 / 82 (6.10%) 6 5 / 82 (6.10%) 8 2 / 82 (2.44%) 2 10 / 82 (12.20%) 13 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 October 2015 | Following changes were made: - Added a 200 mg Q2W regimen (with a loading dose of 400 mg on day 1) to the Q2W treatment group. Subjects below 60 kg received 200 mg Q2W, while subjects ≥ 60 kg received 300 mg Q2W (with a loading dose of 600 mg on day 1). This weight-adjusted dosing better fulfilled the conventional therapeutic objective to utilize the minimum effective dose. - Changed duration of treatment period from 12 weeks to 16 weeks. - Revised inclusion and exclusion criteria. - Added a clarifying note that subjects who had a positive drug test due to a prescription drug being used for medical reasons, would still be eligible for enrollment into the study. - Removed the endpoint hierarchy under Multiplicity Considerations; details were specified in the SAP. - Removed the endpoint hierarchy under Multiplicity Considerations; details were specified in the SAP. - Updated all endpoints previously being assessed at 12 weeks to be assessed at 16 weeks (to align with increase in duration of treatment period from 12 weeks to 16 weeks). - Revised the number of imputations used to generate a complete data set for missing data from the FAS from 50 times to multiple times. - Corrected the IND number. - Added that "Regulatory approvals were also obtained where required by local legislation." - Updated the Introduction to include more current information about completed and ongoing trials in the dupilumab program. - Revised the Biomarker Procedures section to align with the new procedures for collection, use, and storage of biomarker serum and plasma samples and DNA/RNA samples for the optional genomics sub-study. - Revised the definition of concomitant medications and procedures. - Deleted the section on Cytochrome P450. - Clarified the definition of the ADA analysis set. - Included that ADA positive samples would be further characterized for the presence of neutralizing antibody response. |
| 05 July 2017 | - Added an exclusion criterion. - Corrected the expellable volume for 200 mg to 1.14 mL instead of 1.0 mL. - Clarified the text indicating where moisturizers should be applied by the deletion of the following text in the third sentence "on the area(s) of nonlesional skin designated for such assessments". - Added the medication crisaborole to the list of prohibited agents because it is a treatment for atopic dermatitis and would interfere with the efficacy evaluation. - Added crisaborole to the list of prohibited medications to prevent any confounding of efficacy assessment for the study drug. - Added the medication crisaborole to the list of prohibited agents because it is a treatment for atopic dermatitis and would interfere with the efficacy evaluation. - Added crisaborole to the list of prohibited medications to prevent any confounding of efficacy assessment for the study drug. - Removed hematology and chemistry assessments at week 2 and week 12. - Removed the Pain Assessment with VAS from phone visit 16 for accuracy. - Added the IGA scale to the protocol. - The scale was already included in the efficacy procedures and in the Study Manual and was added to Appendix 2 for further clarification. - As per FDA request, provided further details on the methodology for multiple imputation of the continuous endpoints and deleted text related to missing data from the FAS. - For continuous endpoints, added that the MI with ANCOVA model would be used "as the primary analysis method." |
| 23 February 2018 | - Key secondary endpoints were added. - Revision was made in Inclusion Criterion. - The biomarker sample type was changed from "serum/plasma" to "serum" based on clarification letter previously sent to investigators, regulatory authorities, ethic committees and independent review boards. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported