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

## Summary

| | |
|---|---|
| EudraCT number | 2014-002619-40 |
| Trial protocol | DE LT IT GB SE PL FR |
| Global end of trial date | 20 January 2016 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 06 June 2020 |
| First version publication date | 23 February 2017 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | R668-AD-1416 |

### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 24 February 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 676 |
| From 65 to 84 years | 30 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

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

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Dupilumab 300 mg q2w |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Dupilumab 300 mg qw |

Arm description:

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

| | |
|---|---|
| Arm type | Experimental |

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

Dosage and administration details:

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

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

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) from Week 1 to Week 15. | |
| Reporting group title | Dupilumab 300 mg q2w |
| Reporting group description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15. | |
| Reporting group title | Dupilumab 300 mg qw |
| Reporting group description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15. | |

| Reporting group values | Placebo | Dupilumab 300 mg q2w | Dupilumab 300 mg qw |
|---|---|---|---|
| Number of subjects | 236 | 233 | 239 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 37.4 | 36.9 | 37.1 |
| standard deviation | ± 14.09 | ± 13.96 | ± 14.51 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 104 | 96 | 100 |
| Male | 132 | 137 | 139 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 219 | 218 | 220 |
| Hispanic or Latino | 8 | 7 | 12 |
| Not reported/missing | 9 | 8 | 7 |

| | | | |
|---|---|---|---|
| Asia Pacific | 28 | 28 | 29 |

| | | | |
|---|---|---|---|
| Eczema Area and Severity Index (EASI) score | | | |
| The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 33.6 | 31.8 | 31.9 |
| standard deviation | ± 14.31 | ± 13.08 | ± 12.7 |
| Investigator's Global Assessment (IGA) score | | | |
| IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 3.5 | 3.5 | 3.5 |
| standard deviation | ± 0.5 | ± 0.5 | ± 0.5 |
| Weekly average of peak daily pruritus numerical rating scale (NRS) | | | |
| Pruritus NRS is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Weekly average obtained in the 7-day period prior to the baseline visit. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 7.5 | 7.6 | 7.5 |
| standard deviation | ± 1.85 | ± 1.6 | ± 1.81 |
| Body surface area (BSA) involvement with atopic dermatitis | | | |
| Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. | | | |
| Units: Percentage of Body Surface Area | | | |
| arithmetic mean | 54.3 | 52.7 | 52.2 |
| standard deviation | ± 23.06 | ± 21.23 | ± 21.51 |
| SCORing Atopic Dermatitis (SCORAD) score | | | |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 69.2 | 67.2 | 67.5 |
| standard deviation | ± 14.91 | ± 13.48 | ± 13.1 |
| Dermatology Life Quality Index (DLQI) score | | | |
| The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 to 30; a high score was indicative of a poor QOL. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 15.4 | 15.4 | 16 |
| standard deviation | ± 7.69 | ± 7.07 | ± 7.33 |
| Patient Oriented Eczema Measure (POEM) | | | |
| The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, | | | |

| | | | |
|---|---|---|---|
| sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 21 | 20.8 | 20.9 |
| standard deviation | ± 5.94 | ± 5.49 | ± 5.59 |
| Global Individual Signs Score (GISS) | | | |
| Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 9.2 | 9 | 9 |
| standard deviation | ± 1.78 | ± 1.8 | ± 1.75 |
| Total Hospital Anxiety Depression Scale (HADS) | | | |
| The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 13.7 | 13.7 | 14.6 |
| standard deviation | ± 8.32 | ± 7.52 | ± 8.24 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 708 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 300 | | |
| Male | 408 | | |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 657 | | |
| Hispanic or Latino | 27 | | |
| Not reported/missing | 24 | | |
| Race<br>Units: Subjects | | | |
| White | 489 | | |
| Asian | 139 | | |
| Black or African American | 48 | | |
| More than one race | 15 | | |
| Not reported/missing | 17 | | |
| American Indian or Alaska Native | 0 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Region<br>Units: Subjects | | | |
| North and South America | 346 | | |

| | | | |
|---|---|---|---|
| Western Europe | 163 | | |
| Eastern Europe | 114 | | |
| Asia Pacific | 85 | | |
| Eczema Area and Severity Index (EASI) score | | | |
| The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 to 72 points, with the higher scores reflecting the worse severity of AD. | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Investigator's Global Assessment (IGA) score | | | |
| IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weekly average of peak daily pruritus numerical rating scale (NRS) | | | |
| Pruritus NRS is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Weekly average obtained in the 7-day period prior to the baseline visit. | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Body surface area (BSA) involvement with atopic dermatitis | | | |
| Body surface area affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. | | | |
| Units: Percentage of Body Surface Area | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| SCORing Atopic Dermatitis (SCORAD) score | | | |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Dermatology Life Quality Index (DLQI) score | | | |
| The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 to 30; a high score was indicative of a poor QOL. | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Patient Oriented Eczema Measure (POEM) | | | |
| The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, | | | |

| | | | |
|---|---|---|---|
| sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]). | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -<br><br>- | | |
| Global Individual Signs Score (GISS) | | | |
| Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (each assessed for the whole body, not by anatomical region) on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) using the EASI severity grading criteria. | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -<br><br>- | | |
| Total Hospital Anxiety Depression Scale (HADS) | | | |
| The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | -<br><br>- | | |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) from Week 1 to Week 15. | |
| Reporting group title | Dupilumab 300 mg q2w |
| Reporting group description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw from Week 1 to Week 15. | |
| Reporting group title | Dupilumab 300 mg qw |
| Reporting group description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw from Week 1 to Week 15. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Two subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection once weekly (qw) for 16 weeks | |
| Subject analysis set title | Dupilumab 300 mg q2w |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a placebo alternating with single 300 mg injection of Dupilumab qw for 16 weeks. | |
| Subject analysis set title | Dupilumab 300 mg qw |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Two subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection of Dupilumab qw for 16 weeks. | |

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

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

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

## Statistical analyses

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

Notes:

[1] - Threshold for significance at 0.025 level.

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

Notes:

[2] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Week 16

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

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

Notes:

[3] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

severity.

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

Notes:

[4] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

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

Notes:

[5] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

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

Notes:

[6] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 16

| (QG SRLQW YDOXHV | Placebo | Dupilumab 300 mg q2w | Dupilumab 300 mg qw | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 226 | 231 | 234 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 12.8 | 50.6 | 49.1 | |

6WDWLVWLFDO DQDO\VHV

| 6WDWLVWLFDO DQDO\VLV WLWOH | Dupilumab 300 mg qw vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg qw v Placebo |
| Number of subjects included in analysis | 460 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 36.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.56 |
| upper limit | 44.06 |

Notes:

[7] - Threshold for significance at 0.025 level.

| 6WDWLVWLFDO DQDO\VLV WLWOH | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 457 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 37.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 30.03 |
| upper limit | 45.6 |

Notes:

[8] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

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

Statistical analysis description:

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

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

Notes:

[9] - Threshold for significance at 0.025 level.

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was

statistically significant).

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 300 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [10] |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -28.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.04 |
| upper limit | -21.83 |

Notes:

[10] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 4

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |

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

Notes:

[11] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

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

Notes:

[12] - Threshold for significance at 0.025 level.

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

| | |
|---|---|
| End point title | Percentage of Subjects with Improvement (Reduction ≥4 Points) of Pruritus NRS Score from Baseline to Week 2 |

End point description:

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

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

End point timeframe:

Baseline to Week 2

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

## Statistical analyses

| Statistical analysis title | Dupilumab 300 mg qw vs Placebo |
|---|---|
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). | |
| Comparison groups | Dupilumab 300 mg qw v Placebo |
| Number of subjects included in analysis | 449 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [13] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.31 |
| upper limit | 16.32 |

Notes:

[13] - Threshold for significance at 0.025 level.

| Statistical analysis title | Dupilumab 300 mg q2w vs Placebo |
|---|---|
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). | |
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 446 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 9.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.54 |
| upper limit | 13.98 |

Notes:

[14] - Threshold for significance at 0.025 level.

| Secondary: Change From Baseline in Peak Daily Pruritus NRS Score to Week 16 | |
|---|---|
| End point title | Change From Baseline in Peak Daily Pruritus NRS Score to Week 16 |
| End point description:<br>Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint. | |
| End point type | Secondary |
| End point timeframe:<br>Baseline to Week 16 | |

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

**Statistical analyses**

| Statistical analysis title | Dupilumab 300 mg q2w vs Placebo |
|---|---|
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). | |
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 300 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [15] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.605 |
| upper limit | -1.587 |

Notes:

[15] - Threshold for significance at 0.025 level.

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

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

Notes:

[16] - Threshold for significance at 0.025 level.

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

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

**Statistical analyses**

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

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

Notes:

[17] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

| Comparison groups | Dupilumab 300 mg qw v Placebo |
|---|---|
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [18] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -38.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -45.55 |
| upper limit | -30.88 |

Notes:

[18] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Week 16

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

### Statistical analyses

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

Notes:

[19] - Threshold for significance at 0.025 level.

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

Notes:

[20] - Threshold for significance at 0.025 level.

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

| End point title | Percentage of Subjects with EASI-90 (≥90% Improvement |
|---|---|

| | |
|---|---|
| | from Baseline) at Week 16 |

End point description:

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

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

End point timeframe:

Week 16

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

**Statistical analyses**

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 469 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [21] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 22.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.09 |
| upper limit | 29.59 |

Notes:

[21] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

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

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

Notes:

[22] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |

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

Notes:

[23] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

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

Notes:

[24] - Threshold for significance at 0.025 level.

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

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

End point description:

SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 [absent disease] to 103 [severe disease]). Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline to Week 16

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

## Statistical analyses

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

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg qw v Placebo |
| Number of subjects included in analysis | 283 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [25] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -33.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.75 |
| upper limit | -27.8 |

Notes:

[25] - Threshold for significance at 0.025 level.

| Statistical analysis title |
|---|

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

| End point title | Change From Baseline in Dermatology Life Quality Index (DLQI) to Week 16 |
|---|---|

End point description:

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL). The 10 questions assessed QOL over the past week, with an overall scoring of 0 to 30; a high score was indicative of a poor QOL. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

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

Statistical analysis description:

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

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

Notes:

[27] - Threshold for significance at 0.025 level.

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| Comparison groups | Dupilumab 300 mg q2w v Placebo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [28] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -5.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.86 |
| upper limit | -4.47 |

Notes:

[28] - Threshold for significance at 0.025 level.

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

| | |
|---|---|
| End point title | Change From Baseline in Patient Oriented Eczema Measure (POEM) to Week 16 |

End point description:

The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 to 28 (high score indicative of poor quality of life [QOL]). Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |

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

Notes:

[29] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg qw v Placebo |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [30] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.36 |
| upper limit | -6.64 |

Notes:

[30] - Threshold for significance at 0.025 level.

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

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

End point description:

The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 (no symptoms) and 21 (severe symptoms) for either anxiety or depression. Cut-offs for identifying psychiatric distress has been reported as 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. Analysis was performed on FAS population. Here, number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline to Week 16

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

## Statistical analyses

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

Notes:

[31] - Threshold for significance at 0.025 level.

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

Notes:

[32] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 16

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

### Statistical analyses

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

Statistical analysis description:

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

| Comparison groups | Dupilumab 300 mg qw v Placebo |
|---|---|
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [33] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -28.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.03 |
| upper limit | -22.74 |

Notes:

[33] - Threshold for significance at 0.025 level.

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [34] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -27.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.73 |
| upper limit | -21.7 |

Notes:

[34] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline to Week 2

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

### Statistical analyses

| **Statistical analysis title** | Dupilumab 300 mg q2w vs Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |

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

Notes:

[35] - Threshold for significance at 0.025 level.

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

Statistical analysis description:

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

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

Notes:

[36] - Threshold for significance at 0.025 level.

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

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

End point description:

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

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

End point timeframe:

Baseline up to Week 16

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

### Statistical analyses

No statistical analyses for this end point

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

| End point title | Percentage of Subjects With Treatment-Emergent Serious Adverse Events (TESAEs) From Baseline Through Week 16 |
|---|---|

End point description:

Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug and analyzed based on the treatment received.

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

End point timeframe:

Baseline up to Week 16

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

### Statistical analyses

No statistical analyses for this end point

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

| End point title | Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation from Baseline Through Week 16 |
|---|---|

End point description:

Analysis was performed on safety analysis set (SAF) which included all randomized subjects who received any study drug and analyzed based on the treatment received.

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

End point timeframe:

Baseline up to Week 16

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 28) regardless of seriousness or relationship to investigational product | |
| Adverse event reporting additional description: | |
| Reported adverse events are treatment emergent adverse events that developed/worsened during the 'on-treatment period' (including the 16 week treatment period). | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects exposed to Placebo (for Dupilumab) for 16 weeks (mean exposure of 14 weeks). | |
| Reporting group title | Dupilumab 300 mg qw |
| Reporting group description: | |
| Subjects exposed to Dupilumab 300 mg qw for 16 weeks (mean exposure of 15 weeks). | |
| Reporting group title | Dupilumab 300 mg q2w |
| Reporting group description: | |
| Subjects exposed to Dupilumab 300 mg alternating with placebo qw for 16 weeks (mean exposure of 15 weeks). | |

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

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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 October 2014 | -Clarified that the required period for application of emollients prior to randomization was at least the 7 consecutive days immediately before randomization. -Added positive hepatitis B core antibody as an exclusion criterion in response to a health authority request. -Clarified that the first step of rescue treatment should be limited to topical medications if possible. -Modified the list of medications leading to temporary or permanent discontinuation of study drug, and added possible resumption of study drug treatment after the medication leading to discontinuation was stopped. -Revised the list of prohibited medications, and the study periods in which they were prohibited. -Modified the frequency for subject self-assessment of pruritus. -Specified that fasting was recommended but not mandatory prior to collecting samples for laboratory testing. -Allowed retesting for bilirubin and creatine phosphokinase. |
| 01 February 2015 | -Clarified that emollients should not be applied to areas of non-lesional designated for assessment of skin dryness for at least 8 hours before each clinic visit. -Changed the terminology for the European reference market. -Reorganized the secondary endpoints into “Key” and “Other” categories. -Revised the definition of the Full Analysis Set, and added the Per Protocol Set. -Added description of methods for missing data imputation, and for data analysis for continuous secondary endpoints to be used in US and US reference market countries. -Added an inclusion criterion requiring a subject to have a baseline Pruritus Numerical Rating Scale (NRS) score ≥3 for weekly average of peak daily pruritus to be eligible to enroll in the study. -Clarified that non-invasive skin swabs were included in a sub-study that might be conducted at selected sites. -Added a potential use for research samples: to study biomarkers that might had predictive utility for response to dupilumab treatment. -Clarified that samples for exploratory biomarker testing might had been banked. -Clarified that assessment of “Other” endpoints through Week 16 would include both absolute and percent changes. -For the primary efficacy analysis, added a sensitivity analysis using the Cochran-Mantel Haenszel adjusted by randomization strata on observed values, regardless of rescue medication use or missing values. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

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