



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 | 2014-001198-15 |
| Trial protocol | EE DE ES FI DK BG |
| Global end of trial date | 12 February 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 08 March 2017 |
| First version publication date | 08 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | R668-AD-1334 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02277743 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study Name: SOLO 1 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Regeneron Pharmaceuticals, Inc. |
| Sponsor organisation address | 777 Old Saw Mill River Rd., Tarrytown, United States, |
| Public contact | Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |
| Scientific contact | Clinical Trials information, 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 | 16 March 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2016 |
| 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 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 | 28 October 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 | Japan: 106 |
| Country: Number of subjects enrolled | Singapore: 14 |
| Country: Number of subjects enrolled | United States: 238 |
| Country: Number of subjects enrolled | Canada: 48 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | Estonia: 54 |
| Country: Number of subjects enrolled | Finland: 8 |
| Country: Number of subjects enrolled | Germany: 124 |
| Worldwide total number of subjects | 671 |
| EEA total number of subjects | 265 |

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) | 639 |
| From 65 to 84 years | 31 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 countries between 28 Oct 2014 and 12 Feb 2016. A total of 917 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 917 subjects, 671 were randomized and 669 were treated in the study. Subjects were randomized in 1:1:1 ratio to receive dupilumab 300 mg once weekly (qw), dupilumab 300 mg every 2 weeks (q2w) or placebo qw.

Period 1

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

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 q 2w | Dupilumab 300 mg qw |
|---------------------------------------|---------|--------------------------|------------------------|
| Started | 224 | 224 | 223 |
| Treated | 223 | 223 | 223 |
| Completed | 184 | 208 | 197 |
| Not completed | 40 | 16 | 26 |
| Adverse event | 10 | 6 | 6 |
| Other than specified | 18 | 5 | 16 |
| Protocol deviation | 1 | 1 | 1 |
| Lack of efficacy | 11 | 4 | 3 |

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 | 224 | 224 | 223 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------------|---------|---------|---------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.5 | 39.8 | 39.3 |
| standard deviation | ± 13.91 | ± 14.68 | ± 14.39 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 106 | 94 | 81 |
| Male | 118 | 130 | 142 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 212 | 215 | 212 |
| Hispanic or Latino | 11 | 6 | 8 |
| Not reported or missing | 1 | 3 | 3 |
| Race | | | |
| Units: Subjects | | | |
| White | 146 | 155 | 149 |
| Black or African American | 16 | 10 | 20 |
| Asian | 56 | 54 | 51 |
| Other | 6 | 5 | 3 |
| Region | | | |
| Units: Subjects | | | |
| North and South America | 95 | 95 | 96 |
| Asia Pacific | 40 | 42 | 38 |
| Eastern Europe | 23 | 22 | 24 |
| Western Europe | 66 | 65 | 65 |

| | | | |
|--|-----------------|-----------------|-----------------|
| 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. Data for EASI score was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 34.5 ± 14.47 | 33 ± 13.57 | 33.2 ± 13.98 |
| 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). Data for IGA score was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 3.5 ± 0.5 | 3.5 ± 0.5 | 3.5 ± 0.5 |
| Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) | | | |
| 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]). Weekly average obtained in the 7-day period prior to the baseline visit. Data for pruritus NRS score was reported for 669 subjects (n=224, 224 and 221). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 7.4 ± 1.77 | 7.2 ± 1.89 | 7.2 ± 2.06 |
| 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. Data for Body surface area was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Percentage of body surface area arithmetic mean standard deviation | 57.5 ± 23.38 | 54.7 ± 23.19 | 56.1 ± 22.96 |
| 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]). Data for SCORAD score was reported for 669 subjects (n=223, 223 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 68.3 ± 13.96 | 66.9 ± 13.97 | 67.5 ± 13.61 |
| 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 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Data for DLQI score was reported for 670 subjects (n=223, 224 and 223). | | | |

| | | | |
|---|----------------|----------------|----------------|
| Units: Units on a scale arithmetic mean standard deviation | 14.8 ± 7.23 | 13.9 ± 7.37 | 14.1 ± 7.51 |
| 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 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Data for POEM score was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 20.3 ± 5.9 | 19.8 ± 6.37 | 20.4 ± 6.25 |
| 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. Data for GISS was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 9 ± 1.85 | 8.9 ± 1.81 | 8.9 ± 1.74 |
| 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. Data for HADS score was reported for 615 subjects (n=204, 207 and 204). | | | |
| Units: Units on a scale arithmetic mean standard deviation | 12.6 ± 8.33 | 12.2 ± 7.26 | 12.6 ± 7.95 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 671 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|-------------------------|-----|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 281 | | |
| Male | 390 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 639 | | |
| Hispanic or Latino | 25 | | |
| Not reported or missing | 7 | | |
| Race | | | |

| | | | |
|--|-----|--|--|
| Units: Subjects | | | |
| White | 450 | | |
| Black or African American | 46 | | |
| Asian | 161 | | |
| Other | 14 | | |
| Region | | | |
| Units: Subjects | | | |
| North and South America | 286 | | |
| Asia Pacific | 120 | | |
| Eastern Europe | 69 | | |
| Western Europe | 196 | | |
| 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. Data for EASI score was reported for 670 subjects (n=223, 224 and 223). | | | |
| 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). Data for IGA score was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | - | | |
| Weekly Average of Peak Daily Pruritus Numerical Rating Scale (NRS) | | | |
| 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]). Weekly average obtained in the 7-day period prior to the baseline visit. Data for pruritus NRS score was reported for 669 subjects (n=224, 224 and 221). | | | |
| 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. Data for Body surface area was reported for 670 subjects (n=223, 224 and 223). | | | |
| 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]). Data for SCORAD score was reported for 669 subjects (n=223, 223 and 223).

| | | | |
|---|---|--|--|
| 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 (absent disease) to 30 (severe disease); a high score was indicative of a poor QOL. Data for DLQI score was reported for 670 subjects (n=223, 224 and 223). | | | |
| 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 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). Data for POEM score was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | - | | |
| 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. Data for GISS was reported for 670 subjects (n=223, 224 and 223). | | | |
| Units: Units on a scale arithmetic mean standard deviation | - | | |
| 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. Data for HADS score was reported for 615 subjects (n=204, 207 and 204). | | | |
| Units: Units on a scale arithmetic mean standard deviation | - | | |

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 qw from Week 1 to Week 15. One subject randomized to placebo but received Dupilumab, analyzed in Dupilumab 300 mg q2w arm. | |
| 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 from Week 1 to Week 15. One subject randomized to placebo and 5 subjects randomized to Dupilumab 300 mg qw arm, received Dupilumab 300 mg q2w and analyzed in Dupilumab 300 mg q2w arm. | |
| 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 from Week 1 to Week 15. Five subjects randomized to Dupilumab qw arm, analyzed in Dupilumab 300 mg q2w arm. | |

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. Values after first rescue treatment use were set to missing and subjects with missing EASI score at Week 16 were considered 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 | 224 | 224 | 223 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 14.7 | 51.3 | 52.5 | |

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 | 448 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 36.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.58 |
| upper limit | 44.63 |

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 | 447 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 37.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 29.7 |
| upper limit | 45.77 |

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 | 224 | 224 | 223 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 10.3 | 37.9 | 37.2 | |

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 | 448 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 27.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.18 |
| upper limit | 35.17 |

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 | 447 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.47 |
| upper limit | 34.44 |

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 | 212 | 213 | 201 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 12.3 | 40.8 | 40.3 | |

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 the previous endpoint was statistically significant at 0.025 level.

| | |
|---|--------------------------------|
| Comparison groups | Dupilumab 300 mg q2w v Placebo |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 28.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.64 |
| upper limit | 36.52 |

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 | 413 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.94 |
| upper limit | 36.13 |

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 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 q2w | Dupilumab 300 mg qw | |
|-------------------------------|-----------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 221 | 220 | 211 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 17.2 | 46.8 | 51.7 | |

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 | 441 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 29.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.36 |
| upper limit | 37.88 |

Notes:

[7] - 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 | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 34.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 26.08 |
| upper limit | 42.84 |

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 | 96 | 169 | 162 | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -26.8 (± 28.38) | -51.1 (± 28.81) | -49 (± 33.45) | |

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 | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[9] |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -24.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.26 |
| upper limit | -17.52 |

Notes:

[9] - 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 | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[10] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -22.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.33 |
| upper limit | -15.33 |

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 | 212 | 213 | 201 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 6.1 | 16 | 23.4 | |

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 | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 ^[11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 9.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.95 |
| upper limit | 15.71 |

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 | 413 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 17.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.57 |
| upper limit | 23.93 |

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 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 | 212 | 213 | 201 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 3.3 | 9.4 | 9.5 | |

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 | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0097 ^[13] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 6.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.49 |
| upper limit | 10.68 |

Notes:

[13] - 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 | 413 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0094 ^[14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 6.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.45 |
| upper limit | 10.86 |

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:

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 | 96 | 169 | 162 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -2.13 (\pm 2.044) | -3.78 (\pm 2.325) | -3.72 (\pm 2.186) | |

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 | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[15] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.236 |
| upper limit | -1.26 |

Notes:

[15] - 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 | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[16] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.189 |
| upper limit | -1.186 |

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 | 97 | 173 | 162 | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -39.5 (± 33.66) | -73.9 (± 26.28) | -73.8 (± 26.41) | |

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 | 270 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[17] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -34.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.35 |
| upper limit | -26.88 |

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 | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[18] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -34.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.17 |
| upper limit | -26.56 |

Notes:

[18] - Threshold for significance at 0.025 level.

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

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Eczema Area and Severity Index--50 (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 | 224 | 224 | 223 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 24.6 | 68.8 | 61 | |

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 | 448 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[19] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 44.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 35.91 |
| upper limit | 52.48 |

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 | 447 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[20] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 36.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 27.9 |
| upper limit | 44.96 |

Notes:

[20] - Threshold for significance at 0.025 level.

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

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Eczema Area and Severity Index--90 (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 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 | 224 | 224 | 223 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 7.6 | 35.7 | 33.2 | |

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 | 448 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[21] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 28.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.96 |
| upper limit | 35.29 |

Notes:

[21] - 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 qw v Placebo |
|-------------------|-------------------------------|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 447 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[22] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentage |
| Point estimate | 25.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.51 |
| upper limit | 32.68 |

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 | 97 | 173 | 162 | |
| Units: Percentage of body surface area | | | | |
| arithmetic mean (standard deviation) | -17.2 (± 17.381) | -33.72 (± 19.619) | -35.42 (± 19.926) | |

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 | 270 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[23] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -17.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.487 |
| upper limit | -13.353 |

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 | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[24] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -18.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.125 |
| upper limit | -14.65 |

Notes:

[24] - Threshold for significance at 0.025 level.

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

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in the 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 | 97 | 172 | 161 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -28.9 (± 24.25) | -57.2 (± 24.03) | -56.7 (± 24.27) | |

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 | 269 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[25] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -28.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.79 |
| upper limit | -21.54 |

Notes:

[25] - 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 | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[26] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.09 |
| upper limit | -20.87 |

Notes:

[26] - Threshold for significance at 0.025 level.

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 (absent disease) to 30 (severe disease); 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 | 97 | 173 | 162 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -5.6 (\pm 5.86) | -9 (\pm 6.61) | -8.8 (\pm 6.79) | |

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 | 270 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[27] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.16 |
| upper limit | -2.8 |

Notes:

[27] - 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 | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[28] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.87 |
| upper limit | -2.49 |

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 (absent disease) to 28 (severe disease) (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 | 96 | 173 | 162 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -5.3 (± 6.24) | -11.5 (± 7.07) | -11.3 (± 6.36) | |

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 | 269 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[29] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -6.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.02 |
| upper limit | -5.01 |

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 | 258 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[30] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -5.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.44 |
| upper limit | -4.32 |

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 | 82 | 159 | 146 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -2.7 (\pm 4.4) | -4.8 (\pm 5.5) | -4.9 (\pm 5.36) | |

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 | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 ^[31] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.44 |
| upper limit | -0.95 |

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 | 228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 ^[32] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.46 |
| upper limit | -1.03 |

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 | 97 | 173 | 162 | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -26.2 (± 25.7) | -52.5 (± 27.33) | -51.1 (± 26.58) | |

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 | 270 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[33] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.04 |
| upper limit | -18.91 |

Notes:

[33] - 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 | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[34] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -25.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.06 |
| upper limit | -18.12 |

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 | 194 | 214 | 212 | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -4.2 (± 22.77) | -20.4 (± 21.4) | -18.9 (± 28.4) | |

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 | 408 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[35] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -16.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.08 |
| upper limit | -11.9 |

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 | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[36] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -15.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.62 |
| upper limit | -10.5 |

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 was analyzed as treated. 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 | 222 | 229 | 218 | |
| 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 was analyzed as treated. Here, number of subjects analyzed = subjects with available data for this endpoint.

| | |
|----------------|-----------|
| 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 | 224 | 224 | 223 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 5 | 3.1 | 0.9 | |

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 was analyzed as treated. Here, number of subjects analyzed = subjects with available data for this endpoint.

| | |
|----------------|-----------|
| 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 | 224 | 224 | 223 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 0.9 | 1.7 | 1.8 | |

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 (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 | 12 / 222 (5.41%) | 2 / 218 (0.92%) | 7 / 229 (3.06%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lipoma | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laceration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 218 (0.46%) | 0 / 229 (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 |
| Surgical and medical procedures | | | |
| Limb operation | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| 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 | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 222 (1.35%) | 0 / 218 (0.00%) | 2 / 229 (0.87%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 | 2 / 222 (0.90%) | 0 / 218 (0.00%) | 0 / 229 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 218 (0.46%) | 0 / 229 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 | | | |
| Abscess sweat gland | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 0 / 218 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 |
| Kidney infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 218 (0.46%) | 0 / 229 (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 |
| Mastitis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 218 (0.00%) | 0 / 229 (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 | 97 / 222 (43.69%) | 90 / 218 (41.28%) | 92 / 229 (40.17%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 222 (5.86%) | 11 / 218 (5.05%) | 21 / 229 (9.17%) |
| occurrences (all) | 16 | 15 | 33 |

| | | | |
|---|--|---|---|
| General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all) | 13 / 222 (5.86%) 18 | 41 / 218 (18.81%) 111 | 19 / 229 (8.30%) 63 |
| Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all) | 3 / 222 (1.35%) 3 | 8 / 218 (3.67%) 11 | 12 / 229 (5.24%) 13 |
| Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all) | 66 / 222 (29.73%) 77 | 21 / 218 (9.63%) 26 | 35 / 229 (15.28%) 44 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 22 / 222 (9.91%) 30 7 / 222 (3.15%) 7 | 26 / 218 (11.93%) 34 12 / 218 (5.50%) 14 | 27 / 229 (11.79%) 32 7 / 229 (3.06%) 7 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 October 2014 | -Clarified 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 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. |
| 05 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 and indicated that Japan had been added to the countries that would use co-primary endpoint. - 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 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 was conducted at selected sites. -Added a potential use for research samples: to study biomarkers that had predictive utility for response to dupilumab treatment. -Clarified that samples for exploratory biomarker testing had been banked. -Clarified the assessment of "Other" endpoints through week 16 that 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