



Clinical trial results:

A phase 3 study investigating the efficacy, safety, and tolerability of Dupilumab administered to adult patients with severe atopic dermatitis who are not adequately controlled with or are intolerant to oral cyclosporine A, or when this treatment is not medically advisable

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2015-002653-35 |
| Trial protocol | DE PL BE GB NL SK AT IE ES |
| Global end of trial date | 30 March 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 17 April 2018 |
| First version publication date | 06 February 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | R668-AD-1424 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02755649 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | 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 | 26 April 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult subjects with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable.

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 January 2016 |
| 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 | Netherlands: 16 |
| Country: Number of subjects enrolled | Poland: 107 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Austria: 7 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Germany: 142 |
| Country: Number of subjects enrolled | Ireland: 2 |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Spain: 3 |
| Worldwide total number of subjects | 325 |
| EEA total number of subjects | 309 |

Notes:

Subjects enrolled per age group

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

| | |
|--|-----|
| wk | |
| 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) | 316 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 73 sites in Europe. A total of 390 subjects were screened between 28 Jan 2016 and 14 Sep 2016. Of those, 325 subjects were enrolled into the study and randomized. Sixty subjects were considered screen failures, mostly due to unmet eligibility criteria.

Pre-assignment

Screening details:

After providing informed consent, subjects were assessed for study eligibility. Screening assessments were performed between day -28 & day -15, prior to randomization. Subjects who met eligibility criteria at baseline (day 1) were randomized in a 1:1:1 ratio to receive dupilumab (weekly[QW] or every 2 weeks[Q2W]) or placebo.

Period 1

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo QW + TCS |

Arm description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo (Matched to Dupilumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received SC injection of placebo matching to dupilumab QW following a loading dose on Day 1 from Week 1 to Week 15.

| | |
|--|-------------------------|
| Investigational medicinal product name | Topical corticosteroids |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Subjects received topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

| | |
|------------------|----------------------------|
| Arm title | Dupilumab 300 mg Q2W + TCS |
|------------------|----------------------------|

Arm description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label

extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period])).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab 300 mg |
| Investigational medicinal product code | REGN668 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received one SC injection of Dupilumab every 2 weeks (Q2W) (following two SC injections on day 1) from Week 1 to Week 15.

| | |
|--|-------------------------------|
| Investigational medicinal product name | Topical corticosteroids (TCS) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Subjects received treatment with topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

| | |
|------------------|---------------------------|
| Arm title | Dupilumab 300 mg QW + TCS |
|------------------|---------------------------|

Arm description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period])).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab 300 mg |
| Investigational medicinal product code | REGN668 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received one SC injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15.

| | |
|--|-------------------------------|
| Investigational medicinal product name | Topical corticosteroids (TCS) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Subjects received treatment with topical corticosteroids (TCS) using a standardized regimen through the end of the treatment period (Week 16).

| Number of subjects in period 1 | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS |
|---|------------------|-------------------------------|------------------------------|
| Started | 108 | 107 | 110 |
| Completed (Week 16 - Treatment Period) | 107 | 106 | 109 |
| Completed | 7 | 8 | 8 |
| Not completed | 101 | 99 | 102 |
| Consent withdrawn by subject | - | 1 | - |
| Physician decision | - | - | 2 |
| Rolled over into OLE study | 99 | 98 | 100 |
| Currently undecided | 1 | - | - |
| Did not complete follow-up visits | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Placebo QW + TCS |
|-----------------------|------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|----------------------------|
| Reporting group title | Dupilumab 300 mg Q2W + TCS |
|-----------------------|----------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|---------------------------|
| Reporting group title | Dupilumab 300 mg QW + TCS |
|-----------------------|---------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| Reporting group values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS |
|------------------------------------|------------------|----------------------------|---------------------------|
| Number of subjects | 108 | 107 | 110 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Age continuous Units: years arithmetic mean standard deviation | 38.9 ± 13.35 | 37.5 ± 12.89 | 38.7 ± 13.21 |
| Gender categorical Units: Subjects | | | |
| Female | 40 | 42 | 44 |
| Male | 68 | 65 | 66 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 3 | 1 | 5 |
| Not Hispanic or Latino | 101 | 99 | 101 |
| Unknown or Not Reported | 4 | 7 | 4 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 2 | 2 | 2 |

| | | | |
|--|---------|---------|---------|
| Native Hawaiian or Other pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 2 |
| White | 104 | 104 | 105 |
| More than one race | 2 | 0 | 1 |
| Unknown is Not Reported | 0 | 1 | 0 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Austria | 2 | 2 | 3 |
| Belgium | 4 | 4 | 3 |
| Germany | 51 | 48 | 43 |
| Ireland | 0 | 1 | 1 |
| Netherlands | 4 | 6 | 6 |
| Poland | 33 | 39 | 35 |
| Russia | 7 | 0 | 9 |
| Slovakia | 1 | 2 | 1 |
| Spain | 2 | 1 | 0 |
| United Kingdom | 4 | 4 | 9 |
| Investigator's Global Assessment (IGA) score | | | |
| Units: Subjects | | | |
| IGA score = 3 | 56 | 57 | 58 |
| IGA score = 4 | 52 | 50 | 52 |
| Eczema Area and Severity Index (EASI) Score | | | |
| Units: units on a scale | | | |
| arithmetic mean | 32.9 | 33.3 | 33.1 |
| standard deviation | ± 10.80 | ± 9.93 | ± 11.02 |
| Peak weekly averaged pruritus Numerical Rating Scale (NRS) score | | | |
| Units: subjects | | | |
| arithmetic mean | 6.4 | 6.6 | 6.2 |
| standard deviation | ± 2.23 | ± 2.10 | ± 2.01 |
| Body Surface Area (BSA) involvement of atopic dermatitis | | | |
| Units: units on a scale | | | |
| arithmetic mean | 55.0 | 56.1 | 56.0 |
| standard deviation | ± 20.51 | ± 17.83 | ± 19.26 |
| SCORing Atopic Dermatitis (SCORAD) score | | | |
| Units: units on a scale | | | |
| arithmetic mean | 67.0 | 68.6 | 66.0 |
| standard deviation | ± 12.20 | ± 11.91 | ± 12.70 |
| Global Individual Signs Score (GISS) | | | |
| Units: Units on a scale | | | |
| arithmetic mean | 9.4 | 9.3 | 9.1 |
| standard deviation | ± 1.63 | ± 1.64 | ± 1.63 |
| Dermatology Life Quality Index (DLQI) Total Score | | | |
| Units: units on a scale | | | |
| arithmetic mean | 13.2 | 14.5 | 13.8 |
| standard deviation | ± 7.60 | ± 7.63 | ± 8.03 |
| Patient Oriented Eczema Measure (POEM) | | | |

| | | | |
|--|--------|--------|--------|
| Units: units on a scale | | | |
| arithmetic mean | 19.1 | 19.3 | 18.6 |
| standard deviation | ± 5.99 | ± 6.21 | ± 6.97 |
| Total Hospital Anxiety Depression Scale (HADS) | | | |
| Units: units on a scale | | | |
| arithmetic mean | 13.0 | 12.8 | 13.3 |
| standard deviation | ± 7.85 | ± 8.01 | ± 8.15 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 325 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-----|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 126 | | |
| Male | 199 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 9 | | |
| Not Hispanic or Latino | 301 | | |
| Unknown or Not Reported | 15 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 6 | | |
| Native Hawaiian or Other pacific Islander | 0 | | |
| Black or African American | 2 | | |
| White | 313 | | |
| More than one race | 3 | | |
| Unknown is Not Reported | 1 | | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Austria | 7 | | |
| Belgium | 11 | | |
| Germany | 142 | | |
| Ireland | 2 | | |
| Netherlands | 16 | | |
| Poland | 107 | | |
| Russia | 16 | | |
| Slovakia | 4 | | |
| Spain | 3 | | |
| United Kingdom | 17 | | |
| Investigator's Global Assessment (IGA) score | | | |
| Units: Subjects | | | |

| | | | |
|---------------|-----|--|--|
| IGA score = 3 | 171 | | |
| IGA score = 4 | 154 | | |

| | | | |
|---|---|--|--|
| <p>Eczema Area and Severity Index (EASI) Score</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Peak weekly averaged pruritus Numerical Rating Scale (NRS) score</p> <p>Units: subjects</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Body Surface Area (BSA) involvement of atopic dermatitis</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>SCORing Atopic Dermatitis (SCORAD) score</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Global Individual Signs Score (GISS)</p> <p>Units: Units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Dermatology Life Quality Index (DLQI) Total Score</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Patient Oriented Eczema Measure (POEM)</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |
| <p>Total Hospital Anxiety Depression Scale (HADS)</p> <p>Units: units on a scale</p> <p>arithmetic mean</p> <p>standard deviation</p> | - | | |

End points

End points reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Placebo QW + TCS |
|-----------------------|------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|----------------------------|
| Reporting group title | Dupilumab 300 mg Q2W + TCS |
|-----------------------|----------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|---------------------------|
| Reporting group title | Dupilumab 300 mg QW + TCS |
|-----------------------|---------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

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

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

End point description:

The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16. The analysis population for efficacy analyses is the Full Analysis Set (FAS) which included all randomized subjects. Efficacy analyses were based on the treatment allocated (as randomized).

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 29.6 | 62.6 | 59.1 | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across 2 dose regimens. Difference is Dupilumab minus placebo. Confidence Interval (CI) calculated using normal approximation. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated.

| | |
|---|--|
| Comparison groups | Dupilumab 300 mg QW + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 29.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.87 |
| upper limit | 42.5 |

Notes:

[1] - Threshold for significance at 0.05 level. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by disease severity (IGA 3 vs IGA 4) and prior Cyclosporine A (CSA) use (Yes, No).

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across 2 dose regimens. Difference is Dupilumab minus placebo. Confidence Interval (CI) calculated using normal approximation. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated.

| | |
|---|---|
| Comparison groups | Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.41 |
| upper limit | 45.57 |

Notes:

[2] - Threshold for significance at 0.05 level. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by disease severity (IGA 3 vs IGA 4) and prior Cyclosporine A (CSA) use (Yes, No).

Secondary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score at Week 16

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score at Week 16 |
|-----------------|--|

End point description:

The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. The analysis population for efficacy analyses is the FAS which included all randomized subjects. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 105 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -46.6 (± 2.76) | -79.8 (± 2.59) | -78.2 (± 2.55) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

Hierarchical testing approach to control Type-1 error rate at 0.05 across 2 dose regimens. CI w/p-value is based on treatment difference (dupilumab vs placebo) of LS mean percent change using multiple imputation (MI) w/ANCOVA model w/baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by MI

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 194 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -31.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.85 |
| upper limit | -24.3 |

Notes:

[3] - Threshold for significance at 0.05 level

| | |
|---|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by | |
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -33.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.42 |
| upper limit | -25.88 |

Notes:

[4] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects With Eczema Area and Severity Index (EASI) Score ($\geq 75\%$ Improvement From Baseline) at Week 16 for subjects With Prior CSA Use

| | |
|--|---|
| End point title | Percentage of Subjects With Eczema Area and Severity Index (EASI) Score (≥75% Improvement From Baseline) at Week 16 for subjects With Prior CSA Use |
| End point description: The EASI score is used to measure the severity and extent of atopic dermatitis (AD) and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline to Week 16. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint. | |
| End point type | Secondary |
| End point timeframe: Week 16 | |

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 69 | 69 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 26.4 | 58.0 | 56.5 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Dupilumab 300 mg QW + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 30.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.63 |
| upper limit | 45.64 |

Notes:

[5] - Threshold for significance at 0.05 level.

| | |
|---|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 31.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.11 |
| upper limit | 47.05 |

Notes:

[6] - Threshold for significance at 0.05 level.

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

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

End point description:

The Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 102 | 103 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -25.4 (± 3.39) | 53.9 (± 3.14) | -51.7 (± 3.09) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Dupilumab 300 mg QW + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -26.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.07 |
| upper limit | -17.41 |

Notes:

[7] - Threshold for significance at 0.05 level.

| | |
|---|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by | |
| Comparison groups | Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 191 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference] |
| Point estimate | -28.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.34 |
| upper limit | -19.68 |

Notes:

[8] - Threshold for significance at 0.05 level

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

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

End point description:

Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Subjects achieving a reduction of ≥ 4 points from baseline in weekly average of peak daily pruritus NRS score at Week 16 were reported. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 91 | 94 | 94 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 14.3 | 45.7 | 40.4 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Dupilumab 300 mg QW + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 26.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.89 |
| upper limit | 38.39 |

Notes:

[9] - Threshold for significance at 0.05 level.

| | |
|---|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 31.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.08 |
| upper limit | 43.83 |

Notes:

[10] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Weekly Average of Peak Pruritus Numerical Rating Scale (NRS) at Week 2

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Weekly Average of Peak Pruritus Numerical Rating Scale (NRS) at Week 2 |
|-----------------|--|

End point description:

Pruritus NRS is an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject's 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]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint. Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

End point timeframe:

Week 2

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 105 | 105 | 110 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -10.0 (± 2.24) | -17.2 (± 2.25) | -19.7 (± 2.21) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0017 ^[11] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.8 |
| upper limit | -3.66 |

Notes:

[11] - Threshold for significance at 0.05 level

| | |
|---|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by | |
| Comparison groups | Dupilumab 300 mg Q2W + TCS v Placebo QW + TCS |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0214 ^[12] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.31 |
| upper limit | -1.06 |

Notes:

[12] - Threshold for significance at 0.05 level

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

| | |
|---|---|
| End point title | Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 16 |
| End point description: The SCORAD is a clinical tool for assessing the severity of AD 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). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint. | |
| End point type | Secondary |
| End point timeframe: Week 16 | |

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 104 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -29.5 (± 2.55) | -62.4 (± 2.48) | -58.3 (± 2.45) | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|---|---|
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by | |
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[13] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -28.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.56 |
| upper limit | -21.93 |

Notes:

[13] - Threshold for significance at 0.05 level

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|---|--|
| Statistical analysis description: A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens.CI with p-value is based on treatment difference(dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata(disease severity[IGA 3 vs IGA 4] & prior CSA use [Yes,No]) as fixed factors.Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by | |
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[14] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -32.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.7 |
| upper limit | -26.06 |

Notes:

[14] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects Achieving SCORAD 50 (≥50% Improvement From Baseline) at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving SCORAD 50 (≥50% Improvement From Baseline) at Week 16 |
|-----------------|--|

End point description:

The SCORAD is a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). 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). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized).

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 25.9 | 66.4 | 55.5 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[15] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 29.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.1 |
| upper limit | 41.96 |

Notes:

[15] - Threshold for significance at 0.05 level.

| | |
|----------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|-------------------|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
|-------------------|---|

| | |
|---|---------------------------|
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[16] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 40.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.24 |
| upper limit | 52.61 |

Notes:

[16] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Percent Body Surface Area (BSA) Involvement With Atopic Dermatitis (AD) at Week 16

| | |
|-----------------|--|
| End point title | Change From Baseline in Percent Body Surface Area (BSA) Involvement With Atopic Dermatitis (AD) at Week 16 |
|-----------------|--|

End point description:

BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 104 | |
| Units: Percent BSA | | | | |
| least squares mean (standard error) | -19.57 (± 1.798) | -39.23 (± 1.715) | -37.52 (± 1.690) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|-------------------|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
|-------------------|--|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[17] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -17.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.706 |
| upper limit | -13.197 |

Notes:

[17] - Threshold for significance at 0.05 level

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[18] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -19.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.431 |
| upper limit | -14.895 |

Notes:

[18] - Threshold for significance at 0.05 level

Secondary: Percentage of Subjects With Investigator Global Assessment (IGA) 0 or 1 (on the 0 to 4 IGA Scale) and a Reduction From Baseline of ≥ 2 Points at Week 16

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Investigator Global Assessment (IGA) 0 or 1 (on the 0 to 4 IGA Scale) and a 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 score of "0" or "1" and a reduction from baseline of ≥ 2 points at Week 16 were reported. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized).

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 13.9 | 40.2 | 39.1 | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|--|---|
| Statistical analysis description: | |
| A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[19] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.99 |
| upper limit | 36.41 |

Notes:

[19] - Threshold for significance at 0.05 level

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|--|--|
| Statistical analysis description: | |
| A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16. | |
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[20] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 26.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.95 |
| upper limit | 37.65 |

Notes:

[20] - Threshold for significance at 0.05 level

Secondary: Change From Baseline in the Dermatology Life Quality Index (DLQI) at Week 16

| | |
|-----------------|--|
| End point title | Change From Baseline in the Dermatology Life Quality Index (DLQI) at 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 is indicative of a poor QOL. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 104 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -4.5 (± 0.49) | -9.5 (± 0.46) | -8.8 (± 0.45) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[21] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.6 |
| upper limit | -3.04 |

Notes:

[21] - Threshold for significance at 0.05 level

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[22] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.31 |
| upper limit | -3.74 |

Notes:

[22] - Threshold for significance at 0.05 level

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

| | |
|-----------------|---|
| End point title | Change From Baseline in the Patient Oriented Eczema Measure (POEM) at 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]). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "number of subjects analyzed" = subjects who were evaluable for this endpoint.

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

End point timeframe:

Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 88 | 103 | 104 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -4.3 (± 0.62) | -11.9 (± 0.60) | -11.4 (± 0.59) | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[23] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.78 |
| upper limit | -5.47 |

Notes:

[23] - Threshold for significance at 0.05 level

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 191 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[24] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.29 |
| upper limit | -5.97 |

Notes:

[24] - Threshold for significance at 0.05 level

Secondary: Change From Baseline in Mean Weekly Dose of Topical Corticosteroid (TCS) Use During Treatment Period

| | |
|-----------------|--|
| End point title | Change From Baseline in Mean Weekly Dose of Topical Corticosteroid (TCS) Use During Treatment Period |
|-----------------|--|

End point description:

The type, amount, frequency, and potency of topical products used during the study were recorded at home by subjects in a medication diary. Subjects returned TCS tubes at each clinic visit up until week 16, and these tubes were weighed by the site staff to determine the actual amount of TCS used. During the 16-week placebo-controlled study treatment period, medium-potency TCS dosing frequency was symptom-based (IGA score) adjusted every 4 weeks per the protocol-specified tapering algorithm. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline to week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Grams | | | | |
| least squares mean (standard error) | 25.1 (± 1.48) | 15.0 (± 1.51) | 17.5 (± 1.49) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 [25] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.64 |
| upper limit | -3.51 |

Notes:

[25] - Threshold for significance at 0.05 level

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[26] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -10.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.15 |
| upper limit | -5.95 |

Notes:

[26] - Threshold for significance at 0.05 level

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

| | |
|-----------------|---|
| End point title | Change From Baseline in Total Hospital Anxiety and Depression Scale (HADS) Score at 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. The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

End point timeframe:

At week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 104 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -2.3 (± 0.56) | -6.1 (± 0.54) | -5.2 (± 0.53) | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 ^[27] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.41 |
| upper limit | -1.43 |

Notes:

[27] - Threshold for significance at 0.05 level

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[28] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.38 |
| upper limit | -2.4 |

Notes:

[28] - Threshold for significance at 0.05 level

Secondary: Percent Change From Baseline in the Total Global Individual Signs Score (GISS) at Week 16 (Erythema, Infiltration/ Papulation, Excoriations, Lichenification)

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in the Total Global Individual Signs Score (GISS) at Week 16 (Erythema, Infiltration/ Papulation, Excoriations, Lichenification) |
|-----------------|---|

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. Total score ranges from 0 (absent disease) to 12 (severe disease). The analysis population for efficacy analyses is the FAS. Efficacy analyses were based on the treatment allocated (as randomized). Full Analysis Set (FAS) included all randomized. Here "Number of Subjects analyzed" = Subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 16

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 103 | 104 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -29.0 (± 2.75) | -55.2 (± 2.66) | -53.3 (± 2.65) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab group vs. placebo) of LS mean percent change using MI with ANCOVA with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [29] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -24.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.63 |
| upper limit | -16.88 |

Notes:

[29] - Threshold for significance at 0.05 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error rate at 0.05 across 2 dose regimens. CI with p-value is based on treatment difference (dupilumab vs. placebo) of LS mean percent change using MI with ANCOVA model with baseline measurement as covariate & treatment, randomization strata (disease severity [IGA 3 vs IGA 4] & prior CSA use [Yes, No]) as fixed factors. Efficacy data from subjects who received rescue treatment were set to missing after timepoint of rescue & then imputed by

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[30] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -26.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.49 |
| upper limit | -18.86 |

Notes:

[30] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) From Baseline Through Week 28

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Skin Infection Treatment Emergent Adverse Events (TEAEs) (Excluding Herpetic Infections) From Baseline Through Week 28 |
|-----------------|--|

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 16]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Safety analysis set (SAF) included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

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

End point timeframe:

Baseline to Week 28

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 8.3 | 1.9 | 3.6 | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1486 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | -4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.97 |
| upper limit | 1.58 |

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0319 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | -6.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.27 |
| upper limit | -0.65 |

Secondary: Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) Through Week 28

| | |
|-----------------|--|
| End point title | Percentage of Subjects Having at Least One Serious Treatment Emergent Adverse Event (TEAE) Through Week 28 |
|-----------------|--|

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 16]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

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

End point timeframe:

Baseline to week 28

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 1.9 | 1.9 | 1.8 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9829 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 3.53 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 3.63 |

Secondary: Percentage of Subjects Having at Least One Treatment-Emergent Adverse Event (TEAE) Leading to Treatment Discontinuation Through Week 28

| | |
|-----------------|---|
| End point title | Percentage of Subjects Having at Least One Treatment-Emergent Adverse Event (TEAE) Leading to Treatment Discontinuation Through Week 28 |
|-----------------|---|

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 28]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

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

End point timeframe:

Baseline to week 28

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 0.9 | 0 | 1.8 | |

Statistical analyses

| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5619 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.19 |
| upper limit | 3.97 |

| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3241 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | -0.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.73 |
| upper limit | 0.88 |

Secondary: Percentage of Subjects With Treatment-Emergent Adverse Events Through Week 28

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Treatment-Emergent Adverse Events Through Week 28 |
|-----------------|---|

End point description:

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (time from the first dose of study drug up to the end of study [Week 28]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. SAF included all randomized subjects who received any study drug; it was based on the treatment received (as treated).

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

End point timeframe:

Baseline to week 28

| End point values | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS | |
|-------------------------------|------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 108 | 107 | 110 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 69.4 | 72.0 | 69.1 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Dupilumab 300 mg QW + TCS vs Placebo QW + TCS |
|----------------------------|---|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|--|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg QW + TCS |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9518 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.6 |
| upper limit | 11.9 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Dupilumab 300 mg Q2W + TCS vs Placebo QW + TCS |
|-----------------------------------|--|

Statistical analysis description:

A hierarchical testing approach was used to control Type-1 error at 0.05 across the 2 dose regimens. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by CMH test stratified by disease severity (IGA 3 vs IGA 4) and prior CSA use (Yes,No). Subjects who used rescue treatment were categorized as non-responders from time rescue treatment was initiated. Subjects with missing values at Week 16 were categorized as non-responders at Week 16.

| | |
|---|---|
| Comparison groups | Placebo QW + TCS v Dupilumab 300 mg Q2W + TCS |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6833 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | difference in percentages |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.64 |
| upper limit | 14.68 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of informed consent form up to end of study (EOS), Week 28, regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Pre-treatment AEs were AEs that developed/worsened in severity during pre-treatment period (from informed consent to first dose of study drug); All AEs collected during treatment and follow-up period were considered TEAEs. TEAEs were AEs that developed or worsened in severity compared to baseline during treatment and follow-up period.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Placebo QW + TCS |
|-----------------------|------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of matching placebo once per week (QW) (following two SC injections on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|----------------------------|
| Reporting group title | Dupilumab 300 mg Q2W + TCS |
|-----------------------|----------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg every 2 weeks (Q2W) from Week 1 to Week 15 (following a SC loading dose of 600 mg on day 1). During weeks in which dupilumab was not administered, subjects received matching placebo. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| | |
|-----------------------|---------------------------|
| Reporting group title | Dupilumab 300 mg QW + TCS |
|-----------------------|---------------------------|

Reporting group description:

Subjects received one subcutaneous (SC) injection of dupilumab 300 mg once per week (QW) (following an SC loading dose of 600 mg on day 1) from Week 1 to Week 15. All subjects were required to undergo treatment with topical corticosteroids (TCS) using a standardized regimen that continued through the end of the treatment period (Week 16). Starting at week 16, subjects could roll over into an open-label extension (OLE) study (R668-AD-1225), if they were considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

| Serious adverse events | Placebo QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS |
|---|------------------|----------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 2 / 107 (1.87%) | 3 / 110 (2.73%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 107 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 107 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 107 (0.93%) | 0 / 110 (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 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 107 (0.93%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Emphysema | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 107 (0.00%) | 0 / 110 (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 | 0 / 108 (0.00%) | 0 / 107 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 107 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 QW + TCS | Dupilumab 300 mg Q2W + TCS | Dupilumab 300 mg QW + TCS |
|---|-------------------|-------------------------------|------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 108 (41.67%) | 54 / 107 (50.47%) | 51 / 110 (46.36%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | 10 / 107 (9.35%) | 11 / 110 (10.00%) |
| occurrences (all) | 17 | 20 | 13 |
| Eye disorders | | | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | 16 / 107 (14.95%) | 10 / 110 (9.09%) |
| occurrences (all) | 9 | 18 | 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 7 / 107 (6.54%) | 4 / 110 (3.64%) |
| occurrences (all) | 2 | 8 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 18 / 108 (16.67%) | 8 / 107 (7.48%) | 10 / 110 (9.09%) |
| occurrences (all) | 25 | 10 | 15 |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 12 / 107 (11.21%) | 8 / 110 (7.27%) |
| occurrences (all) | 4 | 14 | 8 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 108 (16.67%) | 22 / 107 (20.56%) | 18 / 110 (16.36%) |
| occurrences (all) | 26 | 29 | 24 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 12 May 2016 | <ol style="list-style-type: none">1. Extended the treatment period from 16 weeks to 24 weeks and add week 24 endpoints to meet the criteria for dupilumab to be considered for chronic use in the treatment of AD.2. The introduction was modified to provide support for the safety of a 24-week treatment period.3. As a result, endpoints for week 24 corresponding to those for week 16 have been added and the hierarchy modified accordingly.4. As the treatment period is extended from 16 weeks to 24 weeks and there is a 1-step analysis after the last patient completes 16 weeks of treatment, planned interim analysis section has been modified to state that the results of the 1-step analysis will not be used to change the conduct and integrity of the study. 1-step analysis has also been modified to accommodate the extension of the treatment period and the addition of week 24 endpoints.5. Removed the endpoint "Percent change from baseline to week 16 in the GISS".6. Exclusion criterion #4 was changed from "within 8 weeks prior to the screening visit" to "within 4 weeks of the baseline visit". The original wording would have resulted in automatic exclusion of all patients on systemic treatments (which is common in a population with severe AD) who present for screening. The revised criterion is now also consistent with all other AD protocols.7. The secondary endpoint "Topical treatment for AD – medication-free days" was added |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported