



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Multi-center, Parallel-group Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Dupilumab Compared to Placebo in Japanese Patients With Atopic Dermatitis Aged 6 Months to <18 Years Whose Disease is not Adequately Controlled With Existing Therapies

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2020-002601-26 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 28 October 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 May 2024 |
| First version publication date | 12 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC16823 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04678882 |
| WHO universal trial number (UTN) | U1111-1301-1257 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi K.K. |
| Sponsor organisation address | 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo, Japan, 163-1488 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 December 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric participants. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 15 January 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 62 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1 |
| Children (2-11 years) | 44 |
| Adolescents (12-17 years) | 17 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |

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

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 19 centers in Japan. A total of 75 participants were screened from 15 February 2021 to 02 August 2021, of which 13 were screen failures. Screen failures were mainly due to not meeting inclusion criteria.

Pre-assignment

Screening details:

62 participants were randomized in 1:1 ratio to receive dupilumab or placebo in randomization treatment period. Randomization was stratified by age categories: ≥ 6 months- < 6 years, ≥ 6 years- < 12 years, ≥ 12 years. For age group of ≥ 6 years- < 12 years, randomization was further stratified by baseline Investigator's Global Assessment (IGA) score (3 versus 4).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Randomization Treatment Period(16 Weeks) |
| 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 (Randomization Treatment Period) |

Arm description:

Participants received placebo matched to dupilumab subcutaneously (SC) every 2 weeks (q2w) with placebo loading dose for ≥ 30 kilograms (kg) body weight at baseline; placebo matched to dupilumab SC every 4 weeks (q4w) for ≥ 5 to < 30 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo was administered SC as an identical formulation to the active 200 or 300 mg formulation without dupilumab to deliver placebo in 1.14 or 2 milliliters (mL) respectively, up to 16 weeks during the randomization treatment period. SC injection sites were alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

| | |
|------------------|--|
| Arm title | Dupilumab (Randomization Treatment Period) |
|------------------|--|

Arm description:

Participants received dupilumab 300 milligrams (mg) SC q2w with 600 mg loading dose for ≥ 60 kg body weight at baseline; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight at baseline; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight at baseline; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab |
| Investigational medicinal product code | SAR231893 |
| Other name | Dupixent |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Dupilumab was supplied as 175 or 150 milligram per milliliter (mg/mL) solution in prefilled syringes to deliver 200 mg in 1.14 mL or 300 mg in 2 mL respectively, and was administered SC up to 16 weeks during the randomization treatment period. SC injection sites were alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

| Number of subjects in period 1 | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) |
|--|---|---|
| Started | 32 | 30 |
| Completed | 32 | 28 |
| Not completed | 0 | 2 |
| Adverse Event: Not Related to COVID-19 | - | 1 |
| Withdrawal by Subject | - | 1 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | Open-label Extension Period(Week 17-EOS) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo/Dupilumab (Open-label Extension Period) |

Arm description:

Participants who received placebo during the randomization treatment period and who entered the open-label extension (OLE) period, received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab |
| Investigational medicinal product code | SAR231893 |
| Other name | Dupixent |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Dupilumab was supplied as 175 or 150 mg/mL solution in prefilled syringes to deliver 200 mg in 1.14 mL or 300 mg in 2 mL respectively, and was administered SC during the OLE period for 3 years or until approval of the indication in Japan. SC injection sites were alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

| | |
|------------------|---|
| Arm title | Dupilumab/Dupilumab (Open-label Extension Period) |
|------------------|---|

Arm description:

Participants who received dupilumab during the randomization treatment period and who entered the

OLE period, received dupilumab 300 mg SC q2w with 300 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 200 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab |
| Investigational medicinal product code | SAR231893 |
| Other name | Dupixent |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Dupilumab was supplied as 175 or 150 mg/mL solution in prefilled syringes to deliver 200 mg in 1.14 mL or 300 mg in 2 mL respectively, and was administered SC during the OLE period for 3 years or until approval of the indication in Japan. SC injection sites were alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

| Number of subjects in period 2 | Placebo/Dupilumab (Open-label Extension Period) | Dupilumab/Dupiluma b (Open-label Extension Period) |
|---------------------------------------|---|--|
| Started | 32 | 28 |
| Completed | 30 | 26 |
| Not completed | 2 | 2 |
| Not Related to COVID-19 | 1 | 1 |
| Withdrawal by Subject | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received placebo matched to dupilumab subcutaneously (SC) every 2 weeks (q2w) with placebo loading dose for ≥ 30 kilograms (kg) body weight at baseline; placebo matched to dupilumab SC every 4 weeks (q4w) for ≥ 5 to < 30 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|-----------------------|--|
| Reporting group title | Dupilumab (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received dupilumab 300 milligrams (mg) SC q2w with 600 mg loading dose for ≥ 60 kg body weight at baseline; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight at baseline; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight at baseline; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| Reporting group values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | Total |
|---|--|--|-------|
| Number of subjects | 32 | 30 | 62 |
| Age Categorical Units: Subjects | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 9.6 ± 4.2 | 10.0 ± 4.1 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 11 | 12 | 23 |
| Male | 21 | 18 | 39 |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received placebo matched to dupilumab subcutaneously (SC) every 2 weeks (q2w) with placebo loading dose for ≥ 30 kilograms (kg) body weight at baseline; placebo matched to dupilumab SC every 4 weeks (q4w) for ≥ 5 to < 30 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|-----------------------|--|
| Reporting group title | Dupilumab (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received dupilumab 300 milligrams (mg) SC q2w with 600 mg loading dose for ≥ 60 kg body weight at baseline; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight at baseline; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight at baseline; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|-----------------------|---|
| Reporting group title | Placebo/Dupilumab (Open-label Extension Period) |
|-----------------------|---|

Reporting group description:

Participants who received placebo during the randomization treatment period and who entered the open-label extension (OLE) period, received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|-----------------------|---|
| Reporting group title | Dupilumab/Dupilumab (Open-label Extension Period) |
|-----------------------|---|

Reporting group description:

Participants who received dupilumab during the randomization treatment period and who entered the OLE period, received dupilumab 300 mg SC q2w with 300 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 200 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|----------------------------|---|
| Subject analysis set title | Placebo/Dupilumab (Dupilumab Exposure Period) |
|----------------------------|---|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Participants received placebo matched to dupilumab SC q2w with placebo loading dose for ≥ 30 kg body weight at baseline; placebo matched to dupilumab SC q4w for ≥ 5 to < 30 kg body weight at baseline, for up to 16 weeks during the randomization treatment period. Participants then entered the OLE period and received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|----------------------------|--|
| Subject analysis set title | Dupilumab /Dupilumab (Dupilumab Exposure Period) |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Participants received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight at baseline; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight at baseline; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight at baseline; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight at baseline, for up to 16 weeks during the randomization treatment period. Participants then entered the OLE period and received dupilumab 300 mg SC q2w with 300 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 200 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

Primary: Percentage of Participants With Eczema Area and Severity Index (EASI)-75 ($\geq 75\%$ Improvement From Baseline EASI) at Week 16

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

End point description:

EASI score was a validated measure used to assess severity and extent of atopic dermatitis (AD). The 4

AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], lichenification) were assessed for severity on scale of 0 (absent) to 3 (severe). Area of AD involvement was assessed as percentage by body area of head, trunk, upper limbs, lower limbs, and converted to score of 0 to 6. In each body region, area was expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). For each body region, EASI score = (sum of the 4 AD disease characteristics scores) multiplied by (area of AD involvement score). Total EASI score ranged from 0 to 72, higher scores indicated increased extent and severity of AD. The Intent-to-treat (ITT) population included all randomized participants analyzed according to treatment group allocated by randomization regardless if the treatment kit was used or not.

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

End point timeframe:

Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 30 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 18.8 | 43.3 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Dupilumab versus Placebo |
| Comparison groups | Placebo (Randomization Treatment Period) v Dupilumab (Randomization Treatment Period) |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.0304 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response rate difference |
| Point estimate | 25.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.26 |
| upper limit | 46.9 |

Notes:

[1] - A hierarchical testing procedure was used to control the overall type-I error. Testing was then performed sequentially in order the outcome measure is reported and continued when previous outcome measure was statistically significant at two-sided 0.05.

[2] - Cochran-Mantel-Haenszel(CMH) test was performed on association between responder status and intervention group, adjusted by randomization strata(≥6 months-<6 years, ≥6 years-<12 years and IGA=3, ≥6 years-<12 years and IGA=4, and ≥12years at baseline).

Secondary: Percent Change in EASI Score From Baseline to Week 16

| | |
|-----------------|---|
| End point title | Percent Change in EASI Score From Baseline to Week 16 |
|-----------------|---|

End point description:

EASI score was validated measure used to assess severity and extent of AD. The 4 AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], lichenification)

were assessed for severity on scale of 0(absent) to 3(severe). Area of AD involvement was assessed as percentage by body area of head,trunk,upper limbs,lower limbs, and converted to score of 0-6. In each body region, area was expressed as 0,1(1%-9%),2(10%-29%),3(30%-49%),4(50%-69%),5(70%-89%), or 6(90%-100%). For each body region, EASI score=(sum of the 4 AD disease characteristics scores) multiplied by (area of AD involvement score). Total EASI score ranged 0-72, higher scores=increased extent and severity of AD. Baseline value=last available value before study drug administration. ITT population=all randomized participants analyzed according to treatment group allocated by randomization regardless if treatment kit was used or not. Only those participants with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 29 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -23.27 (\pm 7.81) | -62.65 (\pm 7.87) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Dupilumab Versus Placebo |
| Comparison groups | Placebo (Randomization Treatment Period) v Dupilumab (Randomization Treatment Period) |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.0003 ^[4] |
| Method | ANCOVA |
| Parameter estimate | Least Square (LS) Mean Difference |
| Point estimate | -39.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -60.57 |
| upper limit | -18.19 |

Notes:

[3] - A hierarchical testing procedure was used to control the overall type-I error. Testing was then performed sequentially in order the outcome measure is reported and continued when previous outcome measure was statistically significant at two-sided 0.05.

[4] - Covariance model with treatment group (placebo vs pooled dupilumab), randomization strata defined as (≥ 6 months to < 6 years, ≥ 6 years to < 12 years and IGA=3, ≥ 6 years to < 12 years and IGA=4, and ≥ 12 years), and baseline EASI score as covariates.

Secondary: Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Itch Numerical Rating Scale (NRS) for Participants Aged ≥ 6 Years to < 12 Years old

| | |
|-----------------|---|
| End point title | Percent Change From Baseline to Week 16 in Weekly Average |
|-----------------|---|

End point description:

The worst itch scale was a simple assessment tool used to report the intensity of their pruritus (itch). This was a 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible, and higher scores indicated greater severity. Participants were asked the following 2 questions: "What was the worst itch you had today?" and "What was the worst itch you had last night?". The daily worst itch score was calculated as the worse of the scores for the 2 questions. Baseline worst itch average score for maximum itch intensity was determined based on the average of daily worst itch scores for maximum itch intensity during the 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥6 years to <12 years old with data available were analyzed.

End point type Secondary

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 14 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -6.16 (± 9.65) | -39.45 (± 10.14) | | |

Statistical analyses

| Statistical analysis title | Dupilumab Versus Placebo |
|---|---|
| Comparison groups | Placebo (Randomization Treatment Period) v Dupilumab (Randomization Treatment Period) |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.0117 ^[6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -33.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -59.15 |
| upper limit | -7.42 |

Notes:

[5] - A hierarchical testing procedure was used to control the overall type-I error. Testing was then performed sequentially in order the outcome measure is reported and continued when previous outcome measure was statistically significant at two-sided 0.05.

[6] - Covariance model with treatment group (placebo vs pooled dupilumab), randomization strata defined as (IGA=3 vs 4), and baseline NRS score as covariates.

Secondary: Percentage of Participants With Investigator's Global Assessment (IGA) 0 or 1 at Week 16

| | |
|--|--|
| End point title | Percentage of Participants With Investigator's Global Assessment (IGA) 0 or 1 at Week 16 |
| End point description: The IGA was a static 5-point assessment instrument used in clinical studies to rate the severity of AD globally. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) were an overall assessment of the skin lesions based on erythema and papulation/infiltration. Higher score indicated more severe disease. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization regardless if the treatment kit was used or not. | |
| End point type | Secondary |
| End point timeframe: Week 16 | |

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 30 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 9.4 | 10.0 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Dupilumab Versus Placebo |
| Comparison groups | Placebo (Randomization Treatment Period) v Dupilumab (Randomization Treatment Period) |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.8476 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response rate difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.73 |
| upper limit | 16.66 |

Notes:

[7] - A hierarchical testing procedure was used to control the overall type-I error. Testing was then performed sequentially in order the outcome measure is reported and continued when previous outcome measure was statistically significant at two-sided 0.05.

[8] - CMH test was performed on association between responder status and intervention group, adjusted by randomization strata (≥6 months to <6 years, ≥6 years to <12 years old and IGA=3, ≥6 years to <12 years old and IGA=4, and ≥12 years at baseline).

Secondary: Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using the Peak Pruritus NRS for Participants Aged ≥12 Years to <18 Years old

| | |
|-----------------|--|
| End point title | Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using the Peak Pruritus NRS for Participants Aged ≥12 Years to <18 Years old |
|-----------------|--|

End point description:

The peak pruritus NRS was a simple assessment tool used report the intensity of their pruritus (itch) during a 24-hour recall period. Participants were asked the following question: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". Participants answered the question on the scale of 0 (no itch) to 10 (worst itch imaginable), where higher scores indicated greater severity. Baseline pruritus NRS average score for maximum itch intensity was determined based on the average of daily NRS scores for maximum itch intensity during the 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥ 12 years to < 18 years old were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 9 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -22.20 (\pm 6.73) | -20.91 (\pm 6.33) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Scratch/Itch NRS for Participants Aged ≥ 6 Months to < 6 Years old

| | |
|-----------------|--|
| End point title | Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Scratch/Itch NRS for Participants Aged ≥ 6 Months to < 6 Years old |
|-----------------|--|

End point description:

The worst scratch/itch scale was an assessment tool that parents/caregivers of children aged ≥ 6 months to < 6 years old used to report intensity of their child pruritus (scratch/itch) on 11-point scale (0-10) in which 0=no scratching/itching while 10=worst scratching/itching possible; higher scores indicated greater severity. Parents/caregivers were asked following instructions: "Answer the question below based on what you observe and what your child tells you (if applicable)", and following question: "How would you rate your child's scratching/itching at its worst in past 24 hours?". Baseline worst itch scratch/itch average score for maximum itch intensity was determined based on average of daily worst scratch/itch scores for maximum itch intensity during 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥ 6 months to < 6 years old were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 4 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -10.88 (\pm 6.38) | -16.53 (\pm 7.93) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using Peak Pruritus NRS (Participants Aged ≥ 12 Years[Yr]-<18Yr), Worst Itch NRS (Participants Aged ≥ 6 Yr-<12Yr), and Worst Scratch/Itch NRS (Participants Aged ≥ 6 Months-<6Yr)

| | |
|-----------------|--|
| End point title | Percent Change From Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using Peak Pruritus NRS (Participants Aged ≥ 12 Years[Yr]-<18Yr), Worst Itch NRS (Participants Aged ≥ 6 Yr-<12Yr), and Worst Scratch/Itch NRS (Participants Aged ≥ 6 Months-<6Yr) |
|-----------------|--|

End point description:

Participants were asked certain questions for each scale that was used to report the intensity of pruritus (scratch/itch): the peak pruritus NRS for participants aged ≥ 12 years to <18 years old, the worst itch scale for participants aged ≥ 6 years to <12 years old, and the worst scratch/itch scale for participants aged ≥ 6 months to <6 years old. Participants or their parents/caregivers answered the questions on the scale of 0 (no itch) to 10 (worst itch imaginable), where higher scores indicated greater severity. The results of worst pruritus NRS across 3 age categories were pooled as a single indicator. The baseline value was defined as the last available value before study drug administration. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization regardless if the treatment kit was used or not. Only those participants with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 27 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -10.38 (\pm 5.83) | -31.85 (\pm 6.25) | | |

Statistical analyses

Secondary: Percentage of Participants With EASI-50 ($\geq 50\%$ Improvement From Baseline) and EASI-90 ($\geq 90\%$ Improvement From Baseline) at Week 16

| | |
|-----------------|--|
| End point title | Percentage of Participants With EASI-50 ($\geq 50\%$ Improvement From Baseline) and EASI-90 ($\geq 90\%$ Improvement From Baseline) at Week 16 |
|-----------------|--|

End point description:

EASI score was a validated measure used to assess severity and extent of AD. The 4 AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], lichenification) were assessed for severity on scale of 0 (absent) to 3 (severe). Area of AD involvement was assessed as percentage by body area of head, trunk, upper limbs, lower limbs, and converted to score of 0 to 6. In each body region, area was expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). For each body region, EASI score = (sum of the 4 AD disease characteristics scores) multiplied by (area of AD involvement score). Total EASI score ranged from 0 to 72, higher scores indicated increased extent and severity of AD. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization regardless if the treatment kit was used or not.

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

End point timeframe:

Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 30 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| EASI-50 | 31.3 | 73.3 | | |
| EASI-90 | 12.5 | 6.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis

| | |
|-----------------|--|
| End point title | Change from Baseline to Week 16 in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis |
|-----------------|--|

End point description:

Body surface area affected by AD was assessed for each section of the body using the rule of nines. The possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%] and was reported as a percentage of all major body sections combined. The baseline value was defined as the last available value before study drug administration. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization regardless if the treatment kit was used or not. Only those participants with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 29 | | |
| Units: percent BSA | | | | |
| least squares mean (standard error) | -8.56 (\pm 3.85) | -27.28 (\pm 3.84) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Children's Dermatology Life Quality Index (CDLQI) (≥ 4 years)

| | |
|-----------------|--|
| End point title | Change from Baseline to Week 16 in Children's Dermatology Life Quality Index (CDLQI) (≥ 4 years) |
|-----------------|--|

End point description:

CDLQI was a validated questionnaire designed to measure impact of skin disease on Quality of Life (QOL) in children aged ≥ 4 years of age. To complete the questionnaire, participants provided responses to 10 questions that focused on domains such as symptoms feelings associated with disease, impact of disease on leisure, school or holidays, personal relationships, sleep, and side effects of treatment for the skin disease. 9 questions were scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 had an added possible response, which was scored as 3. CDLQI for a participant is sum of score of each question with maximum of 30 and minimum of 0. Higher score indicated greater impact on the QOL. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥ 4 years old with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 25 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 0.44 (\pm 0.77) | -2.81 (\pm 0.76) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Infants' Dermatitis Quality of Life Index (IDQOL) (<4 years)

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 16 in Infants' Dermatitis Quality of Life Index (IDQOL) (<4 years) |
|-----------------|---|

End point description:

IDQOL was a validated questionnaire developed to measure the impact of skin disease on QOL of infants and preschool children <4 years of age. IDQOL was completed by child's parent or caregiver. The questionnaire consisted of 10 questions related to itching and scratching; mood of the child; how long it took for the child to get to sleep; whether the eczema had interfered with the child's playing, swimming or participation in other family activities; problems during mealtimes; problems caused by treatment; level of comfort while dressing or undressing the child; and problems during bathing. Each question asked about the impact over the previous week and was scored on a scale of 0 (minimum impact) to 3 (maximum impact). The higher the score, the greater was the impact on QOL. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged <4 years old were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 0.27 (± 3.46) | -9.27 (± 3.46) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The POEM was a 7-item, validated PRO questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults. The format was a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflected disease-related morbidity. Higher scores indicated more severe disease. The baseline value was defined as the last available value before study drug administration. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization regardless if the treatment kit was used or not. Only those participants with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 29 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.89 (± 1.29) | -8.45 (± 1.36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using the Peak Pruritus NRS for Participants Aged ≥12 Years to <18 Years old

| | |
|-----------------|--|
| End point title | Change from Baseline to Week 16 in Weekly Average of Daily Worst Pruritus Using the Peak Pruritus NRS for Participants Aged ≥12 Years to <18 Years old |
|-----------------|--|

End point description:

The peak pruritus NRS was a simple assessment tool used report the intensity of their pruritus (itch) during a 24-hour recall period. Participants were asked the following question: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". Participants answered the question on the scale of 0 (no itch) to 10 (worst itch imaginable), where higher scores indicated greater severity. Baseline pruritus NRS average score for maximum itch intensity was determined based on the average of daily NRS scores for maximum itch intensity during the 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥12 years to <18 years old were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 9 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.38 (± 0.46) | -1.32 (± 0.43) | | |

Statistical analyses

Secondary: Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch NRS for Participants Aged ≥6 Years to <12 Years old

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch NRS for Participants Aged ≥6 Years to <12 Years old |
|-----------------|---|

End point description:

The worst itch scale was a simple assessment tool used to report the intensity of their pruritus (itch). This was a 11-point scale (0 to 10) in which 0 indicated no itching while 10 indicated worst itching possible, and higher scores indicated greater severity. Participants were asked the following 2 questions: "What was the worst itch you had today?" and "What was the worst itch you had last night?". The daily worst itch score was calculated as the worse of the scores for the 2 questions. Baseline worst itch average score for maximum itch intensity was determined based on the average of daily worst itch scores for maximum itch intensity during the 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥6 years to <12 years old with data available were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 14 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.77 (± 0.68) | -2.95 (± 0.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Weekly Average of Daily Worst Scratch/Itch NRS for Participants Aged ≥6 Months to <6 Years old

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 16 in Weekly Average of Daily Worst Scratch/Itch NRS for Participants Aged ≥6 Months to <6 Years old |
|-----------------|---|

End point description:

The worst scratch/itch scale was an assessment tool that parents/caregivers of children aged ≥6 months to <6 years old used to report intensity of their child pruritus (scratch/itch) on 11-point scale (0-10) in which 0=no scratching/itching while 10=worst scratching/itching possible; higher scores indicated greater severity. Parents/caregivers were asked following instructions: "Answer the question below based on what you observe and what your child tells you (if applicable)", and following question: "How would you rate your child's scratching/itching at its worst in past 24 hours?". Baseline worst itch scratch/itch average score for maximum itch intensity was determined based on average of daily worst scratch/itch scores for maximum itch intensity during 7 days immediately preceding randomization. The baseline value was defined as the last available value before study drug administration. Only participants from ITT population aged ≥6 months to <6 years old were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 4 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.80 (± 0.49) | -1.24 (± 0.61) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Skin-Infection TEAEs (Excluding Herpetic Infections) From Baseline to 16 Weeks of Treatment

| | |
|-----------------|---|
| End point title | Number of Participants With Skin-Infection TEAEs (Excluding Herpetic Infections) From Baseline to 16 Weeks of Treatment |
|-----------------|---|

End point description:

AE: Any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period. The baseline value was defined as the last available value before study drug administration. Safety population included all participants randomly assigned to study intervention and who received at least 1 dose of study intervention.

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

End point timeframe:

Baseline (Day 1) to Week 16

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 30 | | |
| Units: participants | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), Serious Adverse Events (SAEs), and Adverse Event of Special Interest (AESI) From Baseline to 16 Weeks of Treatment

| | |
|---|---|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), Serious Adverse Events (SAEs), and Adverse Event of Special Interest (AESI) From Baseline to 16 Weeks of Treatment |
| End point description: Adverse event(AE): Any untoward medical occurrence in participant or clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. SAE: Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was congenital anomaly/birth defect, was medically important event. TEAEs: AEs that developed, worsened or became serious during treatment-emergent period. AESI: an AE(serious or nonserious) of scientific and medical concern specific to Sponsor's product or program, for which ongoing monitoring and immediate notification by Investigator to Sponsor was required. Baseline value=as last available value before study drug administration. Safety population=all participants randomly assigned to study intervention and who received at least 1 dose of study intervention. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1) to Week 16 | |

| End point values | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 30 | | |
| Units: participants | | | | |
| Any TEAE | 19 | 19 | | |
| Any TESAE | 1 | 1 | | |
| Any SAE | 1 | 1 | | |
| Any AESI | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Anti-drug Antibody (ADA) to Dupilumab Over Time in Pediatric Participants with AD (Aged ≥6 Months to <18 Years old)

| | |
|---|--|
| End point title | Number of Participants With Treatment-emergent Anti-drug Antibody (ADA) to Dupilumab Over Time in Pediatric Participants with AD (Aged ≥6 Months to <18 Years old) |
| End point description: Treatment-emergent ADA were defined as a positive response in the ADA assay post first dose, when baseline results are negative or missing. ADA population included all participants in the safety population who had at least 1 non-missing result in the ADA assay after first dose of the study treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1) to Week 116 | |

| End point values | Placebo (Randomization Treatment Period) | Placebo/Dupilu mab (Open- label Extension Period) | Dupilumab (Randomization Treatment Period) | Dupilumab/Dup ilumab (Open- label Extension Period) |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 32 | 30 | 28 |
| Units: participants | 2 | 1 | 2 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With TEAEs, SAEs, and AESI From Baseline of OLE Through the Last Study Visit

| | |
|--|---|
| End point title | Number of Participants With TEAEs, SAEs, and AESI From Baseline of OLE Through the Last Study Visit |
| End point description: | |
| <p>AE: Any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. SAE: Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period. AESI: an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required. Safety population included all participants randomly assigned to study intervention and who received at least 1 dose of study intervention.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Week 16 to Week 116 | |

| End point values | Placebo/Dupilu mab (Open- label Extension Period) | Dupilumab/Dup ilumab (Open- label Extension Period) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 28 | | |
| Units: participants | | | | |
| Any TEAE | 30 | 25 | | |
| Any SAE | 1 | 2 | | |
| Any AESI | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Dupilumab up to Week 116

| | |
|-----------------|---|
| End point title | Serum Concentration of Dupilumab up to Week 116 |
|-----------------|---|

End point description:

Serum samples were collected at specified timepoints. The PK population included all participants in the safety population with at least 1 non-missing result for functional dupilumab concentration in serum after first dose of the study treatment. Participants were analyzed according to the intervention actually received. Only those participants with data available were analyzed. Here, n=number of participants analyzed at the specified timepoint. 9999=parameter was not estimable as no participants were analyzed.

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

End point timeframe:

Pre-dose at Baseline (Day 1), and Weeks 4, 12, 16, 24, 32, 52, 68, 92, and 116

| End point values | Placebo/Dupilumab (Dupilumab Exposure Period) | Dupilumab /Dupilumab (Dupilumab Exposure Period) | | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=0, 30) | 9999 (± 9999) | 0.000 (± 0.000) | | |
| Week 4 (n=0, 29) | 9999 (± 9999) | 52439.45 (± 24687.36) | | |
| Week 12 (n=0, 25) | 9999 (± 9999) | 70160.00 (± 28052.67) | | |
| Week 16 (n=0, 27) | 9999 (± 9999) | 75525.93 (± 31785.13) | | |
| Week 24 (n=30, 23) | 47883.33 (± 15953.99) | 86665.22 (± 45997.76) | | |
| Week 32 (n=29, 20) | 58496.55 (± 25001.72) | 84075.00 (± 49956.25) | | |
| Week 52 (n=23, 22) | 61856.52 (± 20717.49) | 78286.36 (± 42318.32) | | |
| Week 68 (n=27, 24) | 62133.33 (± 18267.44) | 77916.67 (± 41003.26) | | |
| Week 92 (n=26, 25) | 57373.08 (± 19790.96) | 70153.56 (± 31250.06) | | |
| Week 116 (n=17, 17) | 51405.88 (± 16209.85) | 64294.12 (± 24337.07) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 16 (randomization treatment period) and Week 16 to end of study (EOS) (OLE period), up to approximately 140 weeks

Adverse event reporting additional description:

Analysis was performed on safety population.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received placebo matched to dupilumab SC q2w with placebo loading dose for ≥ 30 kg body weight at baseline; placebo matched to dupilumab SC q4w for ≥ 5 to < 30 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|-----------------------|--|
| Reporting group title | Dupilumab (Randomization Treatment Period) |
|-----------------------|--|

Reporting group description:

Participants received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight at baseline; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight at baseline; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight at baseline; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight at baseline, for up to 16 weeks during the randomization treatment period.

| | |
|-----------------------|---|
| Reporting group title | Placebo/Dupilumab (Open-label Extension Period) |
|-----------------------|---|

Reporting group description:

Participants who received placebo during the randomization treatment period and who entered the OLE period, received dupilumab 300 mg SC q2w with 600 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 400 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| | |
|-----------------------|---|
| Reporting group title | Dupilumab/Dupilumab (Open-label Extension Period) |
|-----------------------|---|

Reporting group description:

Participants who received dupilumab during the randomization treatment period and who entered the OLE period, received dupilumab 300 mg SC q2w with 300 mg loading dose for ≥ 60 kg body weight; dupilumab 200 mg SC q2w with 200 mg loading dose for ≥ 30 to < 60 kg body weight; dupilumab 300 mg SC q4w for ≥ 15 to < 30 kg body weight; and dupilumab 200 mg SC q4w for ≥ 5 to < 15 kg body weight, for 3 years or until approval of the indication in Japan.

| Serious adverse events | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | Placebo/Dupilumab (Open-label Extension Period) |
|---|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 30 (3.33%) | 1 / 32 (3.13%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Skin Laceration | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Febrile Convulsion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Terminal Ileitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 32 (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 |
| Psychiatric disorders | | | |
| Attention Deficit Hyperactivity Disorder | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Covid-19 | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | 0 / 32 (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 |
| Serious adverse events | | | |
| Dupilumab/Dupilumab (Open-label Extension Period) | | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|----------------|--|--|
| Skin Laceration | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Febrile Convulsion | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Terminal Ileitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Attention Deficit Hyperactivity Disorder | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Covid-19 | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo (Randomization Treatment Period) | Dupilumab (Randomization Treatment Period) | Placebo/Dupilumab (Open-label Extension Period) |
|---|--|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 32 (37.50%) | 14 / 30 (46.67%) | 28 / 32 (87.50%) |

| | | | |
|--|----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| Wound | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Ligament Sprain | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | 3 / 32 (9.38%) |
| occurrences (all) | 1 | 0 | 3 |
| Hand Fracture | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 1 | 1 |
| Foot Fracture | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Arthropod Bite | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 2 | 0 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 30 (3.33%) | 1 / 32 (3.13%) |
| occurrences (all) | 1 | 1 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 30 (6.67%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 3 / 30 (10.00%) | 6 / 32 (18.75%) |
| occurrences (all) | 0 | 3 | 7 |
| Injection Site Reaction | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |

| | | | |
|--|---------------------|----------------------|----------------------|
| Conjunctivitis Allergic subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 4 / 30 (13.33%) 4 | 6 / 32 (18.75%) 9 |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 2 / 30 (6.67%) 5 | 0 / 32 (0.00%) 0 |
| Enteritis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Dental Caries subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 1 / 30 (3.33%) 1 | 4 / 32 (12.50%) 8 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis Contact subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | 4 / 32 (12.50%) 4 |
| Dermatitis Atopic subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 30 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Acne subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 30 (3.33%) 1 | 4 / 32 (12.50%) 7 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | 2 / 32 (6.25%) 2 |
| Psychiatric disorders | | | |
| Autism Spectrum Disorder subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|-----------------|------------------|
| Myalgia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 3 |
| Back Pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 0 | 2 |
| Infections and infestations | | | |
| Impetigo | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 1 | 0 | 3 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 30 (3.33%) | 5 / 32 (15.63%) |
| occurrences (all) | 4 | 1 | 5 |
| Covid-19 | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 14 / 32 (43.75%) |
| occurrences (all) | 0 | 0 | 15 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral Herpes | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 30 (6.67%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 32 (21.88%) | 3 / 30 (10.00%) | 19 / 32 (59.38%) |
| occurrences (all) | 7 | 3 | 49 |
| Influenza | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|---|---|--|--|
| Non-serious adverse events | Dupilumab/Dupilumab (Open-label Extension Period) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 28 (82.14%) | | |
| Injury, poisoning and procedural complications | | | |
| Wound | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Ligament Sprain | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Hand Fracture | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Foot Fracture | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | | |
| occurrences (all) | 3 | | |
| Arthropod Bite | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------------|--|--|
| Pyrexia subjects affected / exposed occurrences (all) | 11 / 28 (39.29%) 15 | | |
| Injection Site Reaction subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | | |
| Eye disorders Conjunctivitis Allergic subjects affected / exposed occurrences (all) | 4 / 28 (14.29%) 5 | | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | | |
| Enteritis subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |
| Dental Caries subjects affected / exposed occurrences (all) | 3 / 28 (10.71%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |
| Skin and subcutaneous tissue disorders Dermatitis Contact subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | | |
| Dermatitis Atopic subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | | |
| Acne subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |
| Urticaria | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 3 / 28 (10.71%) 4 | | |
| Psychiatric disorders Autism Spectrum Disorder subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | | |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Back Pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 2 / 28 (7.14%) 3 2 / 28 (7.14%) 2 | | |
| Infections and infestations Impetigo subjects affected / exposed occurrences (all) Hordeolum subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Covid-19 subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Oral Herpes | 1 / 28 (3.57%) 1 2 / 28 (7.14%) 2 1 / 28 (3.57%) 1 15 / 28 (53.57%) 17 2 / 28 (7.14%) 2 3 / 28 (10.71%) 5 | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 3 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 28 (39.29%) | | |
| occurrences (all) | 18 | | |
| Influenza | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported