# Clinical trial results:
# AN OPEN-LABEL STUDY OF DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS WHO PARTICIPATED IN PREVIOUS DUPILUMAB CLINICAL TRIALS

## Summary

| | |
|---|---|
| EudraCT number | 2013-001449-15 |
| Trial protocol | CZ HU DE PL SE LT EE DK FI ES IT NL AT BE SK |
| Global end of trial date | 27 June 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 July 2023 |
| First version publication date | 12 July 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | R668-AD-1225 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Regeneron |
| Sponsor organisation address | 777 Old Saw Mill River Road, Tarrytown, United States, 10591 |
| Public contact | Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 8447346643, clinicaltrials@regeneron.com |
| Scientific contact | Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 9144093597 18447346643, donell.carey@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 | 27 June 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 June 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the long-term safety of dupilumab administered in adult patients with atopic dermatitis (AD).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 October 2013 |
| 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 | United States: 752 |
| Country: Number of subjects enrolled | Australia: 39 |
| Country: Number of subjects enrolled | Austria: 7 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Canada: 295 |
| Country: Number of subjects enrolled | Czechia: 43 |
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | Estonia: 49 |
| Country: Number of subjects enrolled | Finland: 6 |
| Country: Number of subjects enrolled | France: 35 |
| Country: Number of subjects enrolled | Germany: 431 |
| Country: Number of subjects enrolled | Hong Kong: 6 |
| Country: Number of subjects enrolled | Hungary: 37 |
| Country: Number of subjects enrolled | Ireland: 3 |
| Country: Number of subjects enrolled | Italy: 35 |
| Country: Number of subjects enrolled | Japan: 246 |
| Country: Number of subjects enrolled | Lithuania: 16 |
| Country: Number of subjects enrolled | Netherlands: 50 |
| Country: Number of subjects enrolled | New Zealand: 6 |
| Country: Number of subjects enrolled | Poland: 344 |

| | |
|---|---|
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Singapore: 10 |
| Country: Number of subjects enrolled | Slovakia: 3 |
| Country: Number of subjects enrolled | Spain: 48 |
| Country: Number of subjects enrolled | United Kingdom: 66 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 96 |
| Country: Number of subjects enrolled | Bulgaria: 12 |
| Worldwide total number of subjects | 2677 |
| EEA total number of subjects | 1146 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 2568 |
| From 65 to 84 years | 106 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

1297 participants completed the study and1380 participants withdrawn. Withdrawal from study included study terminated by the Sponsor (708), and withdrawal by the participant (375), Adverse Event (107), Lost to Follow-Up (73), Lack of Efficacy (50), Protocol Deviation (34), Pregnancy (20), Physician Decision (9), and reasons not specified (4)

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Dupilumab |

Arm description:

Participants received repeated doses of dupilumab

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

Dosage and administration details:

200 mg QW, 300 mg QW, or 300 mg Q2W

| **Number of subjects in period 1** | Dupilumab |
|---|---|
| Started | 2677 |
| Completed | 1297 |
| Not completed | 1380 |
| Terminated by Sponsor | 708 |
| Consent withdrawn by subject | 375 |
| Physician decision | 9 |
| Adverse event, non-fatal | 107 |
| Protocol Deviation | 34 |
| Pregnancy | 20 |
| Unknown | 4 |
| Lost to follow-up | 73 |
| Lack of efficacy | 50 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Dupilumab |
| Reporting group description: | |
| Participants received repeated doses of dupilumab | |

| Reporting group values | Dupilumab | Total | |
|---|---|---|---|
| Number of subjects | 2677 | 2677 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 2569 | 2569 | |
| From 65-84 years | 106 | 106 | |
| 85 years and over | 2 | 2 | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 39.2 | | |
| standard deviation | ± 13.42 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 1066 | 1066 | |
| Male | 1611 | 1611 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 94 | 94 | |
| Not Hispanic or Latino | 2532 | 2532 | |
| Unknown or Not Reported | 51 | 51 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 541 | 541 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 147 | 147 | |
| White | 1936 | 1936 | |
| More than one race | 33 | 33 | |
| Unknown or Not Reported | 20 | 20 | |

## End points

### End points reporting groups

| Reporting group title | Dupilumab |
|---|---|
| Reporting group description: | |
| Participants received repeated doses of dupilumab | |

### Primary: OPTIONAL SUB-STUDY: Number of Adverse Events of Special Interest (AESIs) through the last study visit after switching to the new dupilumab drug product

| End point title | OPTIONAL SUB-STUDY: Number of Adverse Events of Special Interest (AESIs) through the last study visit after switching to the new dupilumab drug product[1] |
|---|---|
| End point description: | |
| Adverse events of special interest in this study include: Anaphylactic reactions, Systemic hypersensitivity reactions, Helminthic infections, Any severe type of conjunctivitis or blepharitis, Keratitis, Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) | |
| End point type | Primary |
| End point timeframe: | |
| Up to 24 Weeks | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was reported for this endpoint

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Events | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Treatment Emergent Adverse Events (TEAEs)

| End point title | Number of Treatment Emergent Adverse Events (TEAEs)[2] |
|---|---|
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| Up to 272 weeks | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was reported for this endpoint

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Number of Events | 14717 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with Investigator's Global Assessment (IGA) score = 0-1 at each visit

| End point title | Percentage of participants with Investigator's Global Assessment (IGA) score = 0-1 at each visit |
|---|---|

End point description:

IGA is an assessment scale used to determine severity of hand and foot 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.

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Baseline of study | 12.0 | | | |
| Week 4 | 31.1 | | | |
| Week 16 | 46.7 | | | |
| Week 36 | 46.2 | | | |
| Week 52 | 53.8 | | | |
| Week 100 | 58.2 | | | |
| Week 124 | 59.6 | | | |
| Week 156 | 67.2 | | | |
| Week 172 | 71.1 | | | |
| Week 188 | 56.5 | | | |
| Week 204 | 64.4 | | | |
| Week 220 | 81.2 | | | |
| Week 236 | 50.0 | | | |
| End of Study (Extension) | 67.5 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of AESIs

| End point title | Rate of AESIs |
|---|---|

End point description:

Rate (events per patient-year) of AESIs

Adverse events of special interest in this study include: Anaphylactic reactions, Systemic hypersensitivity reactions, Helminthic infections, Any severe type of conjunctivitis or blepharitis, Keratitis, Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Events per Patient-Year | | | | |
| number (not applicable) | 2.762 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of AESIs

| End point title | Number of AESIs |
|---|---|

End point description:

Adverse events of special interest in this study include: Anaphylactic reactions, Systemic hypersensitivity reactions, Helminthic infections, Any severe type of conjunctivitis or blepharitis, Keratitis, Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Events | 161 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Serious Adverse Events (SAEs) of special interest

| End point title | Number of Serious Adverse Events (SAEs) of special interest |
|---|---|

End point description:

Adverse events of special interest in this study include: Anaphylactic reactions, Systemic hypersensitivity reactions, Helminthic infections, Any severe type of conjunctivitis or blepharitis, Keratitis, Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Events | 9 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Eczema Area and Severity Index (EASI)-75 (≥75% reduction in EASI scores from baseline of the parent study) at each visit

| End point title | Percentage of Participants with Eczema Area and Severity Index (EASI)-75 (≥75% reduction in EASI scores from baseline of the parent study) at each visit |
|---|---|

End point description:

The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, induration, 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.

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Baseline of study | 33.4 | | | |
| Week 4 | 65.3 | | | |
| Week 16 | 82.0 | | | |
| Week 36 | 85.3 | | | |

| | | | | |
|---|---|---|---|---|
| Week 52 | 88.8 | | | |
| Week 100 | 91.4 | | | |
| Week 124 | 92.0 | | | |
| Week 156 | 89.5 | | | |
| Week 172 | 94.1 | | | |
| Week 188 | 96.8 | | | |
| Week 204 | 90.9 | | | |
| Week 220 | 93.5 | | | |
| Week 236 | 100 | | | |
| End of Study (Extension) | 88.9 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with low disease activity state (eg, IGA ≤2) at each visit

| | |
|---|---|
| End point title | Percentage of participants with low disease activity state (eg, IGA ≤2) at each visit |
| End point description: | |
| Low disease activity state is defined as an IGA score of ≤2 [mild = 2, almost clear = 1, or clear = 0] | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 272 weeks | |

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Baseline of study | 34.7 | | | |
| Week 4 | 70.0 | | | |
| Week 16 | 83.0 | | | |
| Week 36 | 84.6 | | | |
| Week 52 | 89.6 | | | |
| Week 100 | 90.9 | | | |
| Week 124 | 93.1 | | | |
| Week 156 | 94.8 | | | |
| Week 172 | 96.3 | | | |
| Week 188 | 96.8 | | | |
| Week 204 | 96.0 | | | |
| Week 220 | 97.1 | | | |
| Week 236 | 90.0 | | | |
| End of Study (Extension) | 92.6 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in EASI score at each visit

| End point title | Change from baseline in EASI score at each visit |
|---|---|

End point description:

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -8.59 (± 10.196) | | | |
| Week 16 | -11.89 (± 12.583) | | | |
| Week 36 | -17.32 (± 13.989) | | | |
| Week 52 | -16.46 (± 13.719) | | | |
| Week 100 | -17.99 (± 14.049) | | | |
| Week 124 | -17.68 (± 13.794) | | | |
| Week 156 | -14.23 (± 14.358) | | | |
| Week 172 | -13.23 (± 13.651) | | | |
| Week 188 | -19.24 (± 11.253) | | | |
| Week 204 | -14.50 (± 15.615) | | | |
| Week 220 | -12.75 (± 14.444) | | | |
| Week 236 | -16.69 (± 9.743) | | | |
| End of Study (Extension) | -13.14 (± 14.614) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent change from baseline in EASI score at each visit

| End point title | Percent change from baseline in EASI score at each visit |
|---|---|

End point description:

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -42.02 (± 88.963) | | | |
| Week 16 | -54.82 (± 316.630) | | | |
| Week 36 | -60.40 (± 603.886) | | | |
| Week 52 | -75.76 (± 73.014) | | | |
| Week 100 | -82.61 (± 29.534) | | | |
| Week 124 | -84.15 (± 27.737) | | | |
| Week 156 | -83.45 (± 32.410) | | | |
| Week 172 | -74.98 (± 78.138) | | | |
| Week 188 | -88.72 (± 15.122) | | | |
| Week 204 | -70.91 (± 74.941) | | | |
| Week 220 | -30.79 (± 370.994) | | | |
| Week 236 | -87.56 (± 10.851) | | | |
| End of Study (Extension) | -55.44 (± 213.819) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with EASI-50 (≥50% reduction in EASI scores from baseline of the parent study) at each visit

| End point title | Percentage of Participants with EASI-50 (≥50% reduction in |
|---|---|

| | |
|---|---|
| | EASI scores from baseline of the parent study) at each visit |
| End point description: | |
| EASI-50 was defined as >=50% reduction in EASI scores from baseline of the parent study | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 272 weeks | |

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Week 4 | 86.0 | | | |
| Week 16 | 95.0 | | | |
| Week 36 | 96.7 | | | |
| Week 52 | 97.4 | | | |
| Week 100 | 98.5 | | | |
| Week 124 | 98.3 | | | |
| Week 156 | 97.4 | | | |
| Week 172 | 98.4 | | | |
| Week 188 | 100 | | | |
| Week 204 | 94.9 | | | |
| Week 220 | 97.8 | | | |
| Week 236 | 100 | | | |
| End of Study (Extension) | 96.9 | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Participants with EASI-90 (≥90% reduction in EASI scores from baseline of the parent study) at each visit**

| | |
|---|---|
| End point title | Percentage of Participants with EASI-90 (≥90% reduction in EASI scores from baseline of the parent study) at each visit |
| End point description: | |
| EASI-90 was defined as >=90% reduction in EASI scores from baseline of the parent study | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 272 weeks | |

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Week 4 | 38.6 | | | |
| Week 16 | 57.7 | | | |
| Week 36 | 59.7 | | | |
| Week 52 | 68.4 | | | |
| Week 100 | 73.0 | | | |
| Week 124 | 74.4 | | | |
| Week 156 | 76.3 | | | |
| Week 172 | 81.8 | | | |
| Week 188 | 72.6 | | | |
| Week 204 | 75.8 | | | |
| Week 220 | 84.1 | | | |
| Week 236 | 70.0 | | | |
| End of Study (Extension) | 76.2 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Pruritus Numerical Rating Scale (NRS) in Parent Study

| End point title | Change from baseline in Pruritus Numerical Rating Scale (NRS) in Parent Study |
|---|---|

End point description:

The Pruritus NRS is an assessment tool for patients to report the intensity of their pruritus (itch), using a scale from 0-10, where 0 is no itch and 10 is the worst itch imaginable.
Daily peak pruritus NRS score is the worst one between morning and evening scores of the day. Baseline Pruritus NRS is determined based on average of daily peak NRS scores during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of 7 days is required to calculate baseline average score.

Weekly worst score is calculated by taking the worst score within the week

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 | -2.86 (± 2.492) | | | |
| Week 4 | -3.81 (± 2.403) | | | |

| | | | | |
|---|---|---|---|---|
| Week 16 | -4.44 (± 2.377) | | | |
| Week 36 | -4.67 (± 2.365) | | | |
| Week 52 | -4.76 (± 2.371) | | | |
| Week 100 | -4.69 (± 2.315) | | | |
| Week 124 | -4.56 (± 2.359) | | | |
| Week 156 | -4.37 (± 2.352) | | | |
| Week 172 | -4.64 (± 2.256) | | | |
| Week 188 | -4.73 (± 2.194) | | | |
| Week 204 | -4.83 (± 2.341) | | | |
| Week 220 | -4.90 (± 2.231) | | | |
| Week 236 | -4.81 (± 2.308) | | | |
| Week 252 | -4.89 (± 2.201) | | | |
| Week 272 | -4.69 (± 2.238) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent change from baseline in Pruritus NRS

| End point title | Percent change from baseline in Pruritus NRS |
|---|---|

End point description:

The Pruritus NRS is an assessment tool for patients to report the intensity of their pruritus (itch), using a scale from 0-10, where 0 is no itch and 10 is the worst itch imaginable.
Daily peak pruritus NRS score is the worst one between morning and evening scores of the day. Baseline Pruritus NRS is determined based on average of daily peak NRS scores during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of 7 days is required to calculate baseline average score.

Weekly worst score is calculated by taking the worst score within the week

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

End point timeframe:

Up to 272 weeks

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Week 1 | -9.55 (± 40.989) | | | |
| Week 4 | -28.88 (± 41.792) | | | |
| Week 16 | -38.96 (± 47.891) | | | |
| Week 36 | -41.38 (± 52.300) | | | |
| Week 52 | -46.41 (± 41.912) | | | |
| Week 100 | -50.62 (± 42.112) | | | |
| Week 124 | -51.47 (± 39.063) | | | |
| Week 156 | -48.16 (± 55.076) | | | |
| Week 172 | -50.30 (± 42.907) | | | |
| Week 188 | -50.56 (± 43.444) | | | |
| Week 204 | -52.53 (± 43.465) | | | |
| Week 220 | -51.18 (± 39.244) | | | |
| Week 236 | -51.67 (± 37.690) | | | |
| Week 252 | -51.01 (± 47.328) | | | |
| Week 272 | -46.23 (± 46.404) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with improvement (reduction) of Pruritus NRS ≥3 from baseline

| End point title | Percentage of Participants with improvement (reduction) of Pruritus NRS ≥3 from baseline |
|---|---|

End point description:

The Pruritus NRS is an assessment tool for patients to report the intensity of their pruritus (itch), using a scale from 0-10, where 0 is no itch and 10 is the worst itch imaginable.
Daily peak pruritus NRS score is the worst one between morning and evening scores of the day. Baseline Pruritus NRS is determined based on average of daily peak NRS scores during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of 7 days is required to calculate baseline average score.

Weekly worst score is calculated by taking the worst score within the week

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Week 1 | 11.9 | | | |
| Week 4 | 28.3 | | | |
| Week 16 | 39.3 | | | |
| Week 36 | 43.8 | | | |
| Week 52 | 45.9 | | | |
| Week 100 | 51.1 | | | |
| Week 124 | 48.8 | | | |
| Week 156 | 46.5 | | | |
| Week 172 | 54.1 | | | |
| Week 188 | 52.5 | | | |
| Week 204 | 56.9 | | | |
| Week 220 | 51.5 | | | |
| Week 236 | 51.3 | | | |
| Week 252 | 56.2 | | | |
| Week 272 | 50.0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with improvement (reduction) of Pruritus NRS ≥4 from baseline

| End point title | Percentage of Participants with improvement (reduction) of Pruritus NRS ≥4 from baseline |
|---|---|

End point description:

The Pruritus NRS is an assessment tool for patients to report the intensity of their pruritus (itch), using a scale from 0-10, where 0 is no itch and 10 is the worst itch imaginable.
Daily peak pruritus NRS score is the worst one between morning and evening scores of the day. Baseline Pruritus NRS is determined based on average of daily peak NRS scores during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of 7 days is required to calculate baseline average score.

Weekly worst score is calculated by taking the worst score within the week

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Week 1 | 7.0 | | | |

| | | | | |
|---|---|---|---|---|
| Week 4 | 18.6 | | | |
| Week 16 | 29.3 | | | |
| Week 36 | 33.3 | | | |
| Week 52 | 35.4 | | | |
| Week 100 | 41.4 | | | |
| Week 124 | 39.4 | | | |
| Week 156 | 35.6 | | | |
| Week 172 | 42.9 | | | |
| Week 188 | 40.9 | | | |
| Week 204 | 44.1 | | | |
| Week 220 | 40.2 | | | |
| Week 236 | 37.2 | | | |
| Week 252 | 42.7 | | | |
| Week 272 | 36.0 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants requiring rescue treatment: Phototherapy

| | |
|---|---|
| End point title | Percentage of Participants requiring rescue treatment: Phototherapy |

End point description:

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0.0747 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants requiring rescue treatment: Systemic treatment

| | |
|---|---|
| End point title | Percentage of Participants requiring rescue treatment: Systemic treatment |

End point description:

| End point type | Secondary |
|---|---|
| End point timeframe: Up to 272 weeks | |

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 1.6 | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Changes from Current Study Baseline to prespecified time points through the end of the study: Dermatology Life Quality Index (DLQI)**

| End point title | Changes from Current Study Baseline to prespecified time points through the end of the study: Dermatology Life Quality Index (DLQI) |
|---|---|

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 format is a simple response to 10 items, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL

| End point type | Secondary |
|---|---|
| End point timeframe: Up to 272 weeks | |

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline of Current Study | 8.5 (± 7.11) | | | |
| Week 12 | -4.9 (± 5.93) | | | |
| Week 24 | -6.0 (± 6.41) | | | |
| Week 36 | -6.5 (± 6.51) | | | |
| Week 48 | -5.6 (± 6.20) | | | |
| Week 76 | -7.2 (± 6.41) | | | |
| Week 100 | -7.3 (± 6.66) | | | |
| Week 124 | -7.9 (± 6.40) | | | |
| Week 148 | -8.3 (± 5.14) | | | |
| End of Study | -3.6 (± 7.37) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants requiring rescue treatment: Overall

| End point title | Percentage of participants requiring rescue treatment: Overall |
|---|---|

End point description:

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 1.7 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from Current Study Baseline to prespecified time points through the end of the study: Patient Oriented Eczema Measure (POEM)

| End point title | Changes from Current Study Baseline to prespecified time points through the end of the study: Patient Oriented Eczema Measure (POEM) |
|---|---|

End point description:

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) with a scoring system of 0 to 28; a high score is indicative of a poor QOL.

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | -7.7 (± 7.32) | | | |
| Week 24 | -9.3 (± 7.44) | | | |
| Week 36 | -10.0 (± 7.46) | | | |
| Week 48 | -8.8 (± 7.46) | | | |
| Week 76 | -11.6 (± 7.79) | | | |
| Week 100 | -11.4 (± 7.30) | | | |
| Week 124 | -12.7 (± 7.11) | | | |
| Week 148 | -10.5 (± 6.06) | | | |
| End of Study | -4.5 (± 10.91) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from Parent Study Baseline to prespecified time points through the end of the study: EuroQol-5D (EQ-5D)

| End point title | Changes from Parent Study Baseline to prespecified time points through the end of the study: EuroQol-5D (EQ-5D) |
|---|---|

End point description:

The EQ-5D as a measure of health-related QOL, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number.

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

End point timeframe:

Up to 272 weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2677 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | 0.2769 (± 0.31571) | | | |
| Week 24 | 0.3001 (± 0.32062) | | | |
| Week 36 | 0.3056 (± 0.33204) | | | |
| Week 48 | 0.2854 (± 0.31017) | | | |
| Week 76 | 0.2965 (± 0.30658) | | | |
| Week 100 | 0.3217 (± 0.33832) | | | |

| | | | | |
|---|---|---|---|---|
| Week 124 | 0.3242 (± 0.28937) | | | |
| Week 148 | 0.3046 (± 0.26337) | | | |
| End of Study | 0.1864 (± 0.32838) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: OPTIONAL SUB-STUDY: Incidence of treatment-emergent anti-drug antibody (ADA) response in patients receiving the new dupilumab drug product

| End point title | OPTIONAL SUB-STUDY: Incidence of treatment-emergent anti-drug antibody (ADA) response in patients receiving the new dupilumab drug product |
|---|---|

End point description:

For participants receiving dupilumab from a new manufacturing process, ADA baseline was defined as the baseline visit in the sub-study, or at the end of the main study, dependent on available data.

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

End point timeframe:

Up to 24 Weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 999[3] | | | |
| Units: Number of Participants | 9999 | | | |

Notes:

[3] - No data was collected

### Statistical analyses

No statistical analyses for this end point

## Secondary: OPTIONAL SUB-STUDY: Ctrough of functional dupilumab in serum before and after switching to the new dupilumab drug product

| End point title | OPTIONAL SUB-STUDY: Ctrough of functional dupilumab in serum before and after switching to the new dupilumab drug product |
|---|---|

End point description:

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

End point timeframe:

Up to 24 Weeks

| End point values | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: mg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0 | 65.9 (± 40.8) | | | |
| Week 12 | 65.4 (± 34.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From first dose to end of study (plus extension), approximately 272 weeks | |
| Adverse event reporting additional description: | |
| Participants received repeated doses of dupilumab | |
| Assessment type | Systematic |

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

| Reporting groups | |
|---|---|
| Reporting group title | Total |
| Reporting group description: | |
| Participants received repeated doses of dupilumab | |

| Serious adverse events | Total | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 283 / 2677 (10.57%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 8 / 2677 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mycosis fungoides | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 2677 (0.11%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Basal cell carcinoma | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hodgkin's disease | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intraductal proliferative breast lesion | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small cell lung cancer | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adenocarcinoma of colon | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder transitional cell carcinoma | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bowen's disease | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast cancer female | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast cancer stage I | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon adenoma | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon cancer | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Granular cell tumour | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hodgkin's disease lymphocyte predominance type stage III | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal cancer stage II | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant melanoma | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ovarian germ cell teratoma benign | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic carcinoma metastatic | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plasma cell myeloma | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plasmacytoma | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate cancer metastatic | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seminoma | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of the tongue | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| T-cell lymphoma | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Uterine cancer | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast cancer | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular disorders | | | | |
| Peripheral arterial occlusive disease | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Deep vein thrombosis | | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aortic aneurysm | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aortic arteriosclerosis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arteriosclerosis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertension | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Female sterilisation | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abortion threatened | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage in pregnancy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Premature separation of placenta | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cyst | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Food allergy | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Sarcoidosis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Serum sickness | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 4 / 2677 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Choking | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasal septum disorder | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Status asthmaticus | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Drug abuse | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 4 / 2677 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Panic attack | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Emotional distress | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| "Schizophrenia, paranoid type" | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suicide attempt | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Major depression | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatobiliary disorders | | | | |
| Cholelithiasis | | | | |
| subjects affected / exposed | 4 / 2677 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute hepatic failure | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bile duct stone | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholecystitis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholestasis of pregnancy | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Drug-induced liver injury | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 5 / 2677 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 4 / 2677 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|
| Meniscus injury | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament injury | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb traumatic amputation | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle injury | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sternal fracture | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thermal burn | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transplant dysfunction | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Traumatic arthrosis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Traumatic intracranial haemorrhage | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound dehiscence | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clavicle fracture | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |
| Atrial septal defect | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital knee deformity | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dolichocolon | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina pectoris | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aortic valve incompetence | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arrhythmia | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial flutter | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bundle branch block left | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chordae tendinae rupture | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial ischaemia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prinzmetal angina | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Syncope | | | | |
| subjects affected / exposed | 5 / 2677 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Migraine | | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoaesthesia | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intracranial aneurysm | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemic cerebral infarction | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Migraine with aura | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nerve compression | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subarachnoid haemorrhage | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thalamic infarction | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Febrile neutropenia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemolytic anaemia | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Meniere's disease | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ectropion | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Entropion | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Trichiasis | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atopic keratoconjunctivitis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chalazion | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corneal erosion | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corneal neovascularisation | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corneal perforation | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eyelid cyst | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Keratoconus | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mydriasis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Optic neuropathy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal artery occlusion | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Retinal detachment | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ulcerative keratitis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorders | | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 5 / 2677 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine polyp | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Umbilical hernia | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ascites | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticular perforation | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hiatus hernia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incarcerated umbilical hernia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal polyp | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis chronic | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematochezia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin and subcutaneous tissue disorders | | | | |
| Dermatitis atopic | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 6 / 2677 (0.22%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erythema nodosum | | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Actinic keratosis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Alopecia areata | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angioedema | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Drug eruption | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Eczema | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pruritus generalised | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin ulcer | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urethral | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| IgA nephropathy | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |

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|---|---|---|---|
| Goitre | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thyroid mass | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 11 / 2677 (0.41%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|
| Foot deformity | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 6 / 2677 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corona virus infection | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 2677 (0.11%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eczema herpeticum | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 2 / 2677 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal abscess | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopneumonia | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic sinusitis | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis bacterial | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hand-foot-and-mouth disease | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis A | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes ophthalmic | | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster disseminated | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impetigo | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infected dermal cyst | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Keratitis bacterial | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parotitis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perirectal abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superinfection bacterial | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral corneal ulcer | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 2677 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Total | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1613 / 2677 (60.25%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 218 / 2677 (8.14%) | | |
| occurrences (all) | 411 | | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 138 / 2677 (5.16%) | | |
| occurrences (all) | 506 | | |
| Eye disorders | | | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 242 / 2677 (9.04%) | | |
| occurrences (all) | 329 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 446 / 2677 (16.66%) | | |
| occurrences (all) | 787 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 774 / 2677 (28.91%) | | |
| occurrences (all) | 1602 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 365 / 2677 (13.63%) | | |
| occurrences (all) | 567 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 277 / 2677 (10.35%) | | |
| occurrences (all) | 417 | | |
| Oral herpes | | | |
| subjects affected / exposed | 200 / 2677 (7.47%) | | |
| occurrences (all) | 463 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 December 2013 | Removed the requirement to administer 400 mg SC dupilumab as a loading dose for participants treated in a previous AD study unless the last dose administered is less than 4 weeks before their first dose in the OLE study.<br>Permanently discontinued participants from the study who received prohibited medications.<br>Removed the key secondary endpoint of "number of disease-free days per participant year" from the protocol. |
| 12 June 2014 | Changed dose from 200 mg QW to 300 mg QW. |
| 12 January 2015 | Allowed participants who failed screening or who failed to complete the baseline visit within 28 days of screening to be rescreened. |
| 26 July 2015 | Extended the study duration for each participant for to up to 3 years or until the product is commercially available in the geographic region of the participant (whichever comes first), and up to 2 years in the UK. |
| 28 June 2016 | Reduced number of visits and assessments |
| 05 June 2017 | Reduce the duration of the end of study visit from 16 weeks to 12 weeks after the last dose of dupilumab. Allowed participants in DE, PL, FR, and JP who had completed 3 years of treatment to resume treatment until 31 Dec 2017. |
| 04 January 2018 | Extended the treatment period to 5 years in PL and FI, and to September 2018 in FR. |
| 12 November 2019 | Aligned the dosing regimen of dupilumab with the dosing regimen approved by various regulatory agencies, globally, for this patient population (300 mg Q2W).<br>Criteria for the events that required accelerated reporting to the sponsor were updated to align with current standards for the dupilumab clinical development program.<br>The Finland country-specific amendments and PL country-specific amendments were merged into one global protocol. |
| 11 May 2021 | Included a substudy to assess the safety, PK, and immunogenicity of dupilumab derived from a new manufacturing process in adults with AD. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported