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
Protocol Deviation	34
Adverse event, non-fatal	107
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 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 Units: Years			
arithmetic mean	39.2		
standard deviation	± 13.42	-	
Sex: Female, Male Units: Participants			
Female	1066	1066	
Male	1611	1611	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	94	94	
Not Hispanic or Latino	2532	2532	
Unknown or Not Reported	51	51	
Race (NIH/OMB) 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"			

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				

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		

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			

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			

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				

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				

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				

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			

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				

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			

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			

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				

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				

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			

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		

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			

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			

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				

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. Permanently discontinued participants from the study who received prohibited medications. 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). Criteria for the events that required accelerated reporting to the sponsor were updated to align with current standards for the dupilumab clinical development program. 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