Clinical trial results:
A Randomized, Double Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Persistent Asthma

Summary

EudraCT number	2014-004940-36
Trial protocol	GB Outside EU/EEA IT DE ES PL HU
Global end of trial date	23 November 2017

Results information

Result version number	v2 (current)
This version publication date	10 April 2019
First version publication date	07 June 2018
Version creation reason	• Correction of full data set Subject Disposition corrected. Baseline Characteristics corrected.

Trial information

Trial identification

Sponsor protocol code	EFC13579

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02414854
WHO universal trial number (UTN)	U1111-1163-1293
Other trial identifiers	Study Name: LIBERTY ASTHMA QUEST

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001501-PIP02-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab (SAR231893 [REGN668]) in subjects with persistent asthma.

Protection of trial subjects:

Paediatric Subjects: The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimize distress and discomfort.
Adult Subjects: Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. The following applies to both Paediatric and Adult Subjects: During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Stable dose of medium to high dose inhaled corticosteroid (ICS) in combination with a second controller medication (for example; long-acting beta agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA] and methylxanthines) for at least 1 month prior to screening and continued throughout the study. Use of a third controller medication was also allowed. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Evidence for comparator: -

Actual start date of recruitment	27 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 156
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Brazil: 72
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Chile: 162
Country: Number of subjects enrolled	Colombia: 25

Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Japan: 114
Country: Number of subjects enrolled	Korea, Republic of: 74
Country: Number of subjects enrolled	Mexico: 115
Country: Number of subjects enrolled	Poland: 96
Country: Number of subjects enrolled	Russian Federation: 123
Country: Number of subjects enrolled	South Africa: 61
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Turkey: 74
Country: Number of subjects enrolled	Ukraine: 181
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 423
Worldwide total number of subjects	1902
EEA total number of subjects	251

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)	107
Adults (18-64 years)	1544
From 65 to 84 years	251
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

4148 subjects were screened from Apr 2015-Sep 2016. 1902 were randomized at 321 centers/22 countries. 2246 were screen failures. 1897 subjects were treated; some received a different treatment than that assigned at randomization and for adverse event (AE) analysis were allocated to treatment actually received.

Pre-assignment

Screening details:

Randomization was stratified by age (<18 years, ≥18 years), blood eosinophil count (<0.3 Giga/L, ≥0.3 Giga/L), ICS dose level (medium, high), and country. Assignment to arms was done centrally using Interactive Voice/Web Response System in 2:2:1:1 ratio to Dupilumab 200 mg q2w, Dupilumab 300 mg q2w, Placebo (for 200 mg)q2w, Placebo (for 300 mg)q2w

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (for Dupilumab 200 mg) q2w

Arm description:

2 subcutaneous injections of matched Placebo (for Dupilumab 200 mg) as a loading dose on Day 1 (Week 0), followed by a single injection every 2 weeks (q2w) from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Dupilumab 200 mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection (1.14 mL) in the abdomen, upper thigh or upper arm.

Arm title	Dupilumab 200 mg q2w

Arm description:

2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 (Week 0), followed by a single 200 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	SAR231893, REGN668
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection 200 mg (1.14 mL of 175 mg/mL solution) in the abdomen, upper thigh or upper arm.

Arm title	Placebo (for Dupilumab 300 mg) q2w

Arm description:

2 subcutaneous injections of matched Placebo (for Dupilumab 300 mg) as a loading dose on Day 1 (Week 0), followed by a single injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Dupilumab 300 mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection (2.0 mL) in the abdomen, upper thigh or upper arm.

Arm title	Dupilumab 300 mg q2w

Arm description:

2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 (Week 0), followed by a single 300 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	SAR231893, REGN668
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection 300 mg (2.0 mL of 150 mg/mL solution) in the abdomen, upper thigh or upper arm.

Number of subjects in period 1	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w
Started	317	631	321
Treated	315	629	321
Completed	295	586	301
Not completed	22	45	20
Other than specified above	12	37	17
Adverse event	9	7	1
Poor compliance to protocol	1	1	2

Number of subjects in period 1	Dupilumab 300 mg q2w
Started	633
Treated	632
Completed	582
Not completed	51
Other than specified above	37
Adverse event	12
Poor compliance to protocol	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (for Dupilumab 200 mg) q2w
Reporting group description:	
2 subcutaneous injections of matched Placebo (for Dupilumab 200 mg) as a loading dose on Day 1 (Week 0), followed by a single injection every 2 weeks (q2w) from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Dupilumab 200 mg q2w
Reporting group description:	
2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 (Week 0), followed by a single 200 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Placebo (for Dupilumab 300 mg) q2w
Reporting group description:	
2 subcutaneous injections of matched Placebo (for Dupilumab 300 mg) as a loading dose on Day 1 (Week 0), followed by a single injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 (Week 0), followed by a single 300 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	

Reporting group values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w
Number of subjects	317	631	321
Age categorical Units: Subjects			
Adolescents (12-17 years)	21	34	18
Adults (18-64 years)	253	512	263
From 65-84 years	43	85	40
Age continuous Units: years			
arithmetic mean	48.2	47.9	48.2
standard deviation	± 15.6	± 15.3	± 14.7
Gender categorical Units: Subjects			
Female	198	387	218
Male	119	244	103
Race Units: Subjects			
Caucasian/White	265	510	273
Black/of African descent	14	33	12
Asian/Oriental	33	78	33
American Indian or Alaska Native	1	0	0
Native Hawaiian or Other Pacific Islander	0	1	0
Other	4	9	3

Ethnicity Units: Subjects			
Hispanic	81	171	79
Not Hispanic	236	460	242
Blood Eosinophil Group Units: Subjects			
<0.15 Giga/L	85	193	83
≥0.15 - <0.3 Giga/L	84	173	95
≥0.3 Giga/L	148	264	142
Missing	0	1	1
ICS Dose Level Units: Subjects			
High	172	317	167
Medium	144	310	151
Low	1	4	3

Reporting group values	Dupilumab 300 mg q2w	Total	
Number of subjects	633	1902	
Age categorical Units: Subjects			
Adolescents (12-17 years)	34	107	
Adults (18-64 years)	516	1544	
From 65-84 years	83	251	
Age continuous Units: years			
arithmetic mean	47.7		
standard deviation	± 15.6	-	
Gender categorical Units: Subjects			
Female	394	1197	
Male	239	705	
Race Units: Subjects			
Caucasian/White	529	1577	
Black/of African descent	21	80	
Asian/Oriental	79	223	
American Indian or Alaska Native	0	1	
Native Hawaiian or Other Pacific Islander	0	1	
Other	4	20	
Ethnicity Units: Subjects			
Hispanic	159	490	
Not Hispanic	474	1412	
Blood Eosinophil Group Units: Subjects			
<0.15 Giga/L	181	542	
≥0.15 - <0.3 Giga/L	175	527	
≥0.3 Giga/L	277	831	
Missing	0	2	
ICS Dose Level			

Units: Subjects			
High	323	979	
Medium	303	908	
Low	7	15	

End points

End points reporting groups

Reporting group title	Placebo (for Dupilumab 200 mg) q2w
Reporting group description:	
2 subcutaneous injections of matched Placebo (for Dupilumab 200 mg) as a loading dose on Day 1 (Week 0), followed by a single injection every 2 weeks (q2w) from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Dupilumab 200 mg q2w
Reporting group description:	
2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 (Week 0), followed by a single 200 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Placebo (for Dupilumab 300 mg) q2w
Reporting group description:	
2 subcutaneous injections of matched Placebo (for Dupilumab 300 mg) as a loading dose on Day 1 (Week 0), followed by a single injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 (Week 0), followed by a single 300 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.	

Primary: Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: Intent-to-Treat (ITT) Population

End point title	Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: Intent-to-Treat (ITT) Population
End point description:	
A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population that included all randomized population analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe:	
Baseline to Week 52	

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: Exacerbation per subject-year				
number (confidence interval 95%)	0.871 (0.724 to 1.048)	0.456 (0.389 to 0.534)	0.970 (0.810 to 1.160)	0.524 (0.450 to 0.611)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using negative binomial model with total number of events onset from randomization up to Week 52 or last contact date (whichever comes earlier) as response variable; with 4 treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to study as covariates; and log transformed standardized observation duration as an offset variable. Here, it is test no. 1 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	954
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Negative binomial regression model
Parameter estimate	Relative risk
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.68

Notes:

[1] - Hierarchical testing procedure was used to control type I error rate at 0.05 level. The procedure included the 2 primary endpoints and the first 13 secondary endpoints reported and considered 2 pair-wise comparisons: Dupilumab 200 mg q2w vs Placebo (for Dupilumab 200 mg) q2w and Dupilumab 300 mg q2w vs Placebo (for Dupilumab 300 mg) q2w. Testing order is specified in analysis description.

[2] - Hierarchical testing sequence performed continued only when previous endpoint was statistically significant at 0.05. Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 200 mg q2w vs Placebo (for 200 mg) q2w

Statistical analysis description:

Analysis was performed using negative binomial model with total number of events onset from randomization up to Week 52 or last contact date (whichever comes earlier) as response variable; with 4 treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to study as covariates; and log transformed standardized observation duration as an offset variable. Here, it is test no. 3 of testing order.

Comparison groups	Dupilumab 200 mg q2w v Placebo (for Dupilumab 200 mg) q2w
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Negative binomial regression model
Parameter estimate	Relative risk
Point estimate	0.523

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.413
upper limit	0.662

Notes:

[3] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[4] - Threshold for significance at 0.05 level.

Primary: Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 12: ITT Population

End point title	Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 12: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liter				
arithmetic mean (standard deviation)				
Baseline (n=317,631,321,633)	1.76 (± 0.61)	1.78 (± 0.62)	1.75 (± 0.57)	1.78 (± 0.60)
Week 12 (n=307,611,313,610)	1.92 (± 0.70)	2.07 (± 0.76)	1.93 (± 0.68)	2.09 (± 0.70)
Change at Week 12 (n=307,611,313,610)	0.15 (± 0.36)	0.28 (± 0.45)	0.18 (± 0.39)	0.31 (± 0.43)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using mixed-effect model with repeated measures (MMRM) model with change from baseline in FEV1 values up to Week 12 as response variable; and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1 value and baseline-by-visit interaction as covariates. Here, it is test no. 2 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w

Number of subjects included in analysis	954
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.18

Notes:

[5] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[6] - Threshold for significance at 0.05 level.

Statistical analysis title	Dupilumab 200 mg q2w vs Placebo (for 200 mg) q2w

Statistical analysis description:

Analysis was performed using MMRM model with change from baseline in FEV1 values up to Week 12 as response variable; and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1 value and baseline-by-visit interaction as covariates. Here, it is test no. 4 of testing order.

Comparison groups	Dupilumab 200 mg q2w v Placebo (for Dupilumab 200 mg) q2w
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.19

Notes:

[7] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[8] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population

End point title	Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population. Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	307	611	313	610
Units: percent change				
arithmetic mean (standard deviation)	10.16 (± 23.88)	18.74 (± 30.86)	11.87 (± 26.40)	20.89 (± 34.14)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis performed using MMRM model(n=954 for 300 vs placebo)with percent change from baseline in FEV1 values up to Week 12 as response variable; & treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1 value & baseline-by-visit interaction as covariates. Hierarchical testing procedure used to control type I error & handle multiple secondary endpoint analyses. Here, it is test no. 5 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	923
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	9.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.74
upper limit	13.07

Notes:

[9] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[10] - Threshold for significance at 0.05 level.

Secondary: Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point title	Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point description:

A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed ITT population with baseline eosinophil ≥0.15 Giga/L.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	232	437	237	452
Units: Exacerbation per subject-year				
number (confidence interval 95%)	1.007 (0.814 to 1.245)	0.445 (0.368 to 0.538)	1.081 (0.879 to 1.329)	0.434 (0.359 to 0.525)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using negative binomial model with total number of events onset from randomization up to Week 52 or last contact date (whichever comes earlier) as response variable; with 4 treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to study as covariates; and log transformed standardized observation duration as an offset variable. Here, it is test no. 6 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Negative binomial regression model
Parameter estimate	Relative risk
Point estimate	0.402
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.307
upper limit	0.526

Notes:

[11] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[12] - Threshold for significance at 0.05 level.

Secondary: Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point title	Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed ITT population with baseline eosinophil ≥0.15 Giga/L. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	232	437	237	452
Units: liter				
arithmetic mean (standard deviation)				
Baseline (n=232,437,237,452)	1.77 (± 0.63)	1.81 (± 0.63)	1.75 (± 0.55)	1.79 (± 0.59)
Change at Week 12 (n=224,425,229,434)	0.17 (± 0.36)	0.34 (± 0.46)	0.21 (± 0.38)	0.35 (± 0.45)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using MMRM model with change from baseline in FEV1 values up to Week 12 as response variable; and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1 value and baseline-by-visit interaction as covariates. Here, it is test no. 7 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.21

Notes:

[13] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[14] - Threshold for significance at 0.05 level.

Secondary: Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point title	Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point description:

A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population with baseline eosinophil ≥0.3 Giga/L.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	264	142	277
Units: Exacerbation per subject-year				
number (confidence interval 95%)	1.081 (0.846 to 1.382)	0.370 (0.289 to 0.475)	1.236 (0.972 to 1.571)	0.403 (0.317 to 0.512)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using negative binomial model with total number of events onset from randomization up to Week 52 or last contact date (whichever comes earlier) as response variable; with 4 treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to study as covariates; and log transformed standardized observation duration as an offset variable. Here, it is test no. 8 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Negative binomial regression model
Parameter estimate	Relative risk
Point estimate	0.326
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.234
upper limit	0.454

Notes:

[15] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).

[16] - Threshold for significance at 0.05 level.

Secondary: Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point title	Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed ITT population with baseline eosinophil ≥0.3 Giga/L. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	264	142	277
Units: liter				
arithmetic mean (standard deviation)				
Baseline (n=148,264,142,277)	1.78 (± 0.66)	1.81 (± 0.64)	1.73 (± 0.54)	1.75 (± 0.59)
Change at Week 12 (n=144,256,139,266)	0.19 (± 0.39)	0.39 (± 0.45)	0.20 (± 0.40)	0.43 (± 0.43)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using MMRM model with change from baseline in FEV1 values up to Week 12 as response variable; and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1 value and baseline-by-visit interaction as covariates. Here, it is test no. 9 of testing order.

Comparison groups	Dupilumab 300 mg q2w v Placebo (for Dupilumab 300 mg) q2w
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.32

Notes:

[17] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).
[18] - Threshold for significance at 0.05 level.

Secondary: Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil <0.3 Giga/L

End point title	Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil <0.3 Giga/L

End point description:

A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population with baseline eosinophil <0.3 Giga/L.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	169	366	178	356
Units: Exacerbation per subject-year				
number (confidence interval 95%)	0.675 (0.515 to 0.884)	0.512 (0.418 to 0.628)	0.732 (0.562 to 0.954)	0.610 (0.502 to 0.742)

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo (for 300 mg) q2w

Statistical analysis description:

Analysis was performed using negative binomial model with total number of events onset from randomization up to Week 52 or last contact date (whichever comes earlier) as response variable; with 4 treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to study as covariates; and log transformed standardized observation duration as an offset variable. Here, it is test no. 10 of testing order.

Comparison groups	Placebo (for Dupilumab 300 mg) q2w v Dupilumab 300 mg q2w
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.2599 [20]
Method	Negative binomial regression model
Parameter estimate	Relative risk
Point estimate	0.834
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.144

Notes:

[19] - Testing according to the hierarchical testing procedure (performed only if previous endpoints were statistically significant).

[20] - Threshold for significance at 0.05 level.

Secondary: Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With High Dose ICS at Baseline

End point title	Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With High Dose ICS at Baseline

End point description:

A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population with high dose ICS at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	172	317	167	323
Units: Exacerbation per subject-year				
number (confidence interval 95%)	1.040 (0.824 to 1.314)	0.560 (0.455 to 0.690)	1.038 (0.818 to 1.317)	0.639 (0.523 to 0.780)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline

End point title	Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population with high dose ICS at baseline. Number of subjects analysed=subjects evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	310	162	309
Units: liter				
arithmetic mean (standard deviation)	0.14 (± 0.34)	0.27 (± 0.42)	0.20 (± 0.40)	0.32 (± 0.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ [S]) Self- Administered Global Score at Week 24: ITT Population

End point title	Change From Baseline in Asthma Quality of Life Questionnaire

	With Standardized Activities (AQLQ [S]) Self- Administered Global Score at Week 24: ITT Population

End point description:

The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to subjects with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n=299,591,314,603)	4.26 (± 1.02)	4.31 (± 1.08)	4.30 (± 1.03)	4.28 (± 1.05)
Week 24 (n=298,592,302,596)	5.23 (± 1.07)	5.46 (± 1.12)	5.30 (± 1.15)	5.47 (± 1.09)
Change at Week 24 (n=281,560,295,569)	0.95 (± 1.03)	1.13 (± 1.14)	1.02 (± 1.10)	1.17 (± 1.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in AQLQ (S) Self- Administered Global Score at Week 24: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point title	Change From Baseline in AQLQ (S) Self- Administered Global Score at Week 24: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point description:

The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to subjects with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life. Analysis was performed on ITT population with baseline eosinophil ≥0.3 Giga/L. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	264	142	277
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n=136,254,138,263)	4.24 (± 0.98)	4.24 (± 1.11)	4.21 (± 0.97)	4.36 (± 1.05)
Change at Week 24 (n=129,241,130,244)	0.97 (± 1.01)	1.39 (± 1.15)	1.02 (± 1.25)	1.30 (± 1.15)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire 5-item Version (ACQ-5) Score at Week 24: ITT Population

End point title	Change From Baseline in Asthma Control Questionnaire 5-item Version (ACQ-5) Score at Week 24: ITT Population

End point description:

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Subjects were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n=317,631,321,633)	2.71 (± 0.73)	2.76 (± 0.80)	2.77 (± 0.77)	2.77 (± 0.76)
Week 24 (n=296,590,297,585)	1.67 (± 1.06)	1.33 (± 1.05)	1.58 (± 1.08)	1.37 (± 1.10)
Change at Week 24 (n=296,590,297,585)	-1.06 (± 1.01)	-1.43 (± 1.05)	-1.19 (± 1.10)	-1.38 (± 1.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Severe Exacerbation Events Resulting in Hospitalization or Emergency Room Visit During The 52-Week Treatment Period: ITT Population

End point title	Annualized Rate of Severe Exacerbation Events Resulting in Hospitalization or Emergency Room Visit During The 52-Week Treatment Period: ITT Population

End point description:

A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for ≥3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations (resulted hospitalization or emergency room visit) that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: Exacerbation per subject-year				
number (confidence interval 95%)	0.081 (0.049 to 0.135)	0.043 (0.027 to 0.068)	0.034 (0.017 to 0.066)	0.025 (0.014 to 0.043)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil <0.3 Giga/L

End point title	Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil <0.3 Giga/L

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed ITT population with baseline eosinophil <0.3 Giga/L. Number of subjects analysed=subjects evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	163	354	173	344
Units: liter				
arithmetic mean (standard deviation)	0.12 (± 0.32)	0.21 (± 0.43)	0.17 (± 0.39)	0.21 (± 0.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point title	Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.3 Giga/L

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population with baseline eosinophil ≥0.3 Giga/L. Number of subjects analyzed=subjects evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	144	256	139	266
Units: percent change				
arithmetic mean (standard deviation)	13.40 (± 27.01)	26.41 (± 33.69)	13.05 (± 25.27)	30.58 (± 38.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline

End point title	Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population with high dose ICS at baseline. Number of subjects analysed=subjects evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	310	162	309
Units: percent change				
arithmetic mean (standard deviation)	8.47 (± 20.94)	17.99 (± 28.43)	13.22 (± 26.52)	23.41 (± 37.26)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point title	Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil ≥0.15 Giga/L

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population with baseline eosinophil ≥0.15 Giga/L. Number of subjects analyzed=subjects evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	425	229	434
Units: percent change				
arithmetic mean (standard deviation)	11.43 (± 24.71)	22.04 (± 31.96)	13.49 (± 25.18)	24.04 (± 35.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population

End point title	Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liter				
arithmetic mean (standard deviation)				
Change at Week 2 (n=315,610,313,625)	0.08 (± 0.35)	0.22 (± 0.38)	0.10 (± 0.34)	0.25 (± 0.40)
Change at Week 4 (n=307,613,311,614)	0.13 (± 0.35)	0.24 (± 0.40)	0.13 (± 0.34)	0.27 (± 0.41)
Change at Week 8 (n=305,604,311,609)	0.15 (± 0.38)	0.28 (± 0.42)	0.19 (± 0.40)	0.29 (± 0.43)
Change at Week 24 (n=300,599,296,596)	0.13 (± 0.40)	0.31 (± 0.45)	0.19 (± 0.44)	0.30 (± 0.44)
Change at Week 36 (n=289,590,301,584)	0.14 (± 0.41)	0.31 (± 0.48)	0.21 (± 0.42)	0.32 (± 0.45)
Change at Week 52 (n=240,477,250,488)	0.12 (± 0.38)	0.31 (± 0.50)	0.20 (± 0.42)	0.32 (± 0.44)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population

End point title	Percent Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: percent change				
arithmetic mean (standard deviation)				
Change at Week 2 (n=315,610,313,625)	5.78 (± 23.36)	14.32 (± 26.55)	6.60 (± 21.84)	17.38 (± 30.82)
Change at Week 4 (n=307,613,311,614)	9.61 (± 25.54)	16.11 (± 28.12)	8.67 (± 23.55)	18.77 (± 32.73)
Change at Week 8 (n=305,604,311,609)	10.27 (± 25.60)	18.81 (± 29.80)	12.24 (± 25.78)	19.85 (± 33.63)
Change at Week 24 (n=300,599,296,596)	9.42 (± 26.76)	19.76 (± 30.64)	12.86 (± 28.14)	20.75 (± 35.35)
Change at Week 36 (n=289,590,301,584)	10.57 (± 26.41)	19.92 (± 32.26)	13.45 (± 27.69)	22.08 (± 35.93)
Change at Week 52 (n=240,477,250,488)	8.37 (± 23.59)	19.96 (± 33.35)	12.89 (± 27.70)	21.57 (± 34.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Predicted FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Percent Predicted FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: percent predicted of FEV1				
arithmetic mean (standard deviation)				
Change at Week 2 (n=315,610,313,625)	2.58 (± 11.36)	7.10 (± 12.28)	3.32 (± 10.98)	8.44 (± 13.20)
Change at Week 4 (n=307,613,311,614)	4.55 (± 11.69)	7.92 (± 12.81)	4.13 (± 11.41)	9.20 (± 14.10)
Change at Week 8 (n=305,604,311,609)	4.93 (± 12.30)	9.27 (± 13.13)	6.08 (± 12.55)	9.70 (± 14.15)
Change at Week 12 (n=307,611,313,610)	5.02 (± 12.10)	9.22 (± 13.87)	5.90 (± 13.02)	10.28 (± 14.44)

Change at Week 24 (n=300,599,296,596)	4.38 (± 12.85)	9.98 (± 13.94)	6.41 (± 14.02)	10.14 (± 14.75)
Change at Week 36 (n=289,590,301,584)	5.09 (± 12.99)	10.12 (± 14.61)	6.82 (± 13.54)	10.94 (± 15.06)
Change at Week 52 (n=240,477,250,488)	4.25 (± 12.06)	10.08 (± 14.79)	6.68 (± 13.56)	11.02 (± 14.59)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning (AM)/Evening (PM) Peak Expiratory Flow (PEF) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Morning (AM)/Evening (PM) Peak Expiratory Flow (PEF) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

The PEF is a subject’s maximum speed of expiration, as measured with a peak flow meter. Peak flow testing for PEF was performed at home (morning and evening) while sitting or standing prior to using any medication (if needed) for asthma. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liters/min				
arithmetic mean (standard deviation)				
AM: Change at Week 2 (n=314,620,320,630)	4.19 (± 31.30)	15.21 (± 39.45)	3.45 (± 28.95)	14.46 (± 36.29)
AM: Change at Week 4 (n=313,619,319,625)	6.23 (± 42.42)	21.81 (± 53.85)	5.55 (± 43.69)	19.67 (± 46.47)
AM: Change at Week 8 (n=308,614,318,613)	7.42 (± 49.30)	25.70 (± 58.52)	12.22 (± 50.50)	23.18 (± 52.65)
AM: Change at Week 12 (n=305,608,314,608)	9.85 (± 50.40)	27.81 (± 65.30)	14.23 (± 56.18)	25.88 (± 57.09)
AM: Change at Week 24 (n=299,590,305,588)	5.55 (± 53.27)	28.71 (± 69.64)	15.43 (± 60.83)	23.74 (± 63.71)
AM: Change at Week 36 (n=289,576,297,564)	3.24 (± 61.68)	31.19 (± 71.59)	12.57 (± 61.88)	23.93 (± 65.04)
AM: Change at Week 52 (n=270,544,282,529)	2.85 (± 64.60)	29.86 (± 75.44)	10.99 (± 64.68)	26.67 (± 71.63)
PM: Change at Week 2 (n=313,617,319,629)	3.33 (± 36.81)	13.80 (± 40.59)	3.87 (± 33.98)	11.35 (± 36.10)
PM: Change at Week 4 (n=312,617,319,623)	5.01 (± 45.09)	17.94 (± 55.30)	2.73 (± 46.83)	14.90 (± 47.42)
PM: Change at Week 8 (n=308,613,315,610)	2.82 (± 50.10)	21.06 (± 61.80)	7.68 (± 56.73)	17.26 (± 53.37)

PM: Change at Week 12 (n=306,606,311,605)	3.24 (± 53.42)	19.75 (± 68.14)	8.52 (± 56.74)	18.70 (± 55.60)
PM: Change at Week 24 (n=299,583,300,585)	-4.89 (± 55.07)	19.95 (± 71.50)	7.56 (± 63.25)	15.82 (± 61.91)
PM: Change at Week 36 (n=286,570,291,557)	-6.75 (± 62.44)	21.79 (± 75.00)	2.64 (± 65.21)	14.35 (± 64.66)
PM: Change at Week 52 (n=269,526,268,523)	-6.43 (± 62.82)	18.77 (± 77.37)	2.83 (± 67.01)	15.58 (± 72.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Vital Capacity (FVC) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Forced Vital Capacity (FVC) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liter				
arithmetic mean (standard deviation)				
Change at Week 2 (n=315,610,313,625)	0.08 (± 0.42)	0.23 (± 0.44)	0.10 (± 0.37)	0.25 (± 0.46)
Change at Week 4 (n=307,613,311,614)	0.12 (± 0.39)	0.26 (± 0.45)	0.12 (± 0.38)	0.27 (± 0.47)
Change at Week 8 (n=305,604,311,609)	0.13 (± 0.41)	0.28 (± 0.45)	0.18 (± 0.42)	0.29 (± 0.50)
Change at Week 12 (n=307,611,313,610)	0.13 (± 0.41)	0.29 (± 0.49)	0.18 (± 0.44)	0.29 (± 0.51)
Change at Week 24 (n=300,599,296,596)	0.11 (± 0.45)	0.29 (± 0.48)	0.18 (± 0.46)	0.29 (± 0.51)
Change at Week 36 (n=289,590,301,584)	0.11 (± 0.45)	0.30 (± 0.52)	0.19 (± 0.47)	0.31 (± 0.52)
Change at Week 52 (n=240,477,250,488)	0.08 (± 0.45)	0.29 (± 0.53)	0.18 (± 0.45)	0.31 (± 0.50)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Flow (FEF) 25-75% at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Forced Expiratory Flow (FEF) 25-75% at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

FEF is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEF25-75% is defined as the mean forced expiratory flow between the 25% and 75% of the FVC. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liters/sec				
arithmetic mean (standard deviation)				
Change at Week 2 (n=315,610,313,625)	0.09 (± 0.40)	0.22 (± 0.47)	0.11 (± 0.44)	0.27 (± 0.48)
Change at Week 4 (n=307,613,311,614)	0.16 (± 0.45)	0.24 (± 0.48)	0.15 (± 0.44)	0.29 (± 0.48)
Change at Week 8 (n=305,604,311,609)	0.18 (± 0.45)	0.29 (± 0.52)	0.20 (± 0.49)	0.32 (± 0.51)
Change at Week 12 (n=307,611,313,610)	0.18 (± 0.46)	0.30 (± 0.53)	0.19 (± 0.50)	0.35 (± 0.53)
Change at Week 24 (n=300,599,296,596)	0.17 (± 0.47)	0.34 (± 0.57)	0.22 (± 0.56)	0.35 (± 0.54)
Change at Week 36 (n=289,590,301,584)	0.18 (± 0.49)	0.35 (± 0.59)	0.22 (± 0.49)	0.36 (± 0.56)
Change at Week 52 (n=240,477,250,488)	0.16 (± 0.50)	0.36 (± 0.63)	0.24 (± 0.55)	0.36 (± 0.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Post-Bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Analysis was performed ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: liter				
arithmetic mean (standard deviation)				
Change at Week 2 (n=310,609,311,617)	-0.07 (± 0.31)	0.10 (± 0.37)	-0.04 (± 0.33)	0.09 (± 0.34)
Change at Week 4 (n=308,614,311,615)	-0.02 (± 0.31)	0.10 (± 0.39)	-0.04 (± 0.36)	0.10 (± 0.36)
Change at Week 8 (n=305,607,305,604)	-0.02 (± 0.31)	0.12 (± 0.40)	0.03 (± 0.35)	0.11 (± 0.37)
Change at Week 12 (n=305,610,313,612)	-0.02 (± 0.33)	0.12 (± 0.40)	0.01 (± 0.35)	0.11 (± 0.38)
Change at Week 24 (n=302,599,302,601)	-0.05 (± 0.36)	0.13 (± 0.43)	-0.01 (± 0.40)	0.10 (± 0.39)
Change at Week 36 (n=290,586,302,589)	-0.03 (± 0.34)	0.12 (± 0.44)	0.01 (± 0.38)	0.11 (± 0.39)
Change at Week 52 (n=239,499,255,494)	-0.08 (± 0.38)	0.12 (± 0.44)	-0.02 (± 0.39)	0.11 (± 0.40)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Loss of Asthma Control (LOAC) Event During The 52-Week Treatment Period: ITT Population

End point title	Annualized Rate of Loss of Asthma Control (LOAC) Event During The 52-Week Treatment Period: ITT Population

End point description:

LOAC was defined as any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; increase in ICS >=4 times the dose at randomization; use of systemic corticosteroids for >=3 days; hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of LOAC that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: LOAC per subject-year				
number (confidence interval 95%)	2.972 (2.573 to 3.432)	1.853 (1.654 to 2.076)	2.965 (2.572 to 3.420)	1.740 (1.554 to 1.947)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population

End point title	Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population

End point description:

The time to first severe exacerbation was defined as follows: date of the first event - randomization date +1. For subjects who had no event on or before Visit 18 (Week 52) or last contact date, the time was censored at the date of Visit 18 or the last contact date, whichever was earlier. The median time to first severe exacerbation was not estimated; therefore, the probability of severe exacerbation at Weeks 12, 24, 36, and 52, are presented as the descriptive statistics. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: probability of severe exacerbation				
number (confidence interval 95%)				
Probability at Week 12	0.165 (0.127 to 0.209)	0.094 (0.073 to 0.119)	0.193 (0.152 to 0.238)	0.137 (0.112 to 0.166)
Probability at Week 24	0.275 (0.227 to 0.326)	0.177 (0.148 to 0.208)	0.297 (0.247 to 0.347)	0.211 (0.180 to 0.243)
Probability at Week 36	0.364 (0.311 to 0.418)	0.235 (0.203 to 0.270)	0.376 (0.322 to 0.428)	0.268 (0.234 to 0.303)
Probability at Week 52	0.434 (0.378 to 0.489)	0.295 (0.259 to 0.331)	0.437 (0.382 to 0.491)	0.325 (0.288 to 0.362)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First LOAC Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population

End point title	Time to First LOAC Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population

End point description:

The time to first LOAC event was defined as follows: date of the first event - first dose date +1. For subjects who had no event on or before last dose date + 14 days or last contact date, the time was censored at the last dose date + 14 days or the last contact date, whichever was earlier. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: days				
median (confidence interval 95%)	110.0 (84.00 to 144.00)	230.0 (187.00 to 276.00)	102.0 (74.00 to 130.00)	264.0 (207.00 to 319.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ACQ-5 Score at Weeks 2, 4, 8, 12, 36, and 52: ITT Population

End point title	Change From Baseline in ACQ-5 Score at Weeks 2, 4, 8, 12, 36, and 52: ITT Population

End point description:

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Subjects were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n=304,599,305,615)	-0.52 (± 0.85)	-0.88 (± 0.91)	-0.58 (± 0.97)	-0.89 (± 0.94)
Change at Week 4 (n=297,599,305,605)	-0.76 (± 0.90)	-1.07 (± 0.98)	-0.77 (± 1.01)	-1.06 (± 1.01)
Change at Week 8 (n=301,595,310,593)	-0.94 (± 0.96)	-1.26 (± 1.03)	-1.05 (± 1.04)	-1.24 (± 1.06)
Change at Week 12 (n=303,605,312,603)	-0.98 (± 1.00)	-1.33 (± 1.03)	-1.09 (± 1.09)	-1.35 (± 1.06)
Change at Week 36 (n=285,583,299,572)	-1.21 (± 1.01)	-1.50 (± 1.14)	-1.22 (± 1.09)	-1.52 (± 1.09)
Change at Week 52 (n=236,470,245,477)	-1.07 (± 1.08)	-1.50 (± 1.05)	-1.25 (± 1.05)	-1.50 (± 1.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire 7-item Version (ACQ-7) Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Asthma Control Questionnaire 7-item Version (ACQ-7) Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

The ACQ-7 has 7 questions, the first 5 questions assess the most common asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze plus short-acting bronchodilator use, and FEV1 (pre-bronchodilator % predicted). Subjects were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Clinic staff scored the FEV1% predicted on a 7-point scale. The questions were equally weighted and the ACQ-7 total score was mean of the scores of all 7 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n=304,599,305,615)	-0.46 (± 0.70)	-0.79 (± 0.77)	-0.50 (± 0.80)	-0.82 (± 0.81)

Change at Week 4 (n=297,599,305,605)	-0.65 (± 0.76)	-0.94 (± 0.85)	-0.65 (± 0.85)	-0.97 (± 0.87)
Change at Week 8 (n=301,595,310,593)	-0.81 (± 0.80)	-1.11 (± 0.90)	-0.90 (± 0.89)	-1.12 (± 0.92)
Change at Week 12 (n=303,605,312,603)	-0.85 (± 0.83)	-1.17 (± 0.90)	-0.92 (± 0.93)	-1.20 (± 0.92)
Change at Week 24 (n=296,590,297,585)	-0.89 (± 0.91)	-1.25 (± 0.92)	-1.01 (± 0.96)	-1.22 (± 0.96)
Change at Week 36 (n=285,583,299,572)	-1.04 (± 0.84)	-1.32 (± 1.01)	-1.05 (± 0.94)	-1.35 (± 0.95)
Change at Week 52 (n=236,470,245,477)	-0.91 (± 0.92)	-1.32 (± 0.91)	-1.07 (± 0.91)	-1.34 (± 0.93)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Morning Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

Morning asthma symptom score was determined using AM (ante meridiem) symptom scoring system which evaluated subject's overall asthma symptoms experienced during the night. It ranged from 0 to 4 as: 0 = No asthma symptoms, slept through the night, 1= Slept well, but some complaints in the morning, no night-time awakenings, 2= Woke up once because of asthma (including early awakening), 3= Woke up several times because of asthma (including early awakening), 4= Bad night, awake most of the night because of asthma. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n=314,624,321,631)	-0.07 (± 0.43)	-0.18 (± 0.49)	-0.09 (± 0.49)	-0.15 (± 0.50)
Change at Week 4 (n=313,623,319,627)	-0.16 (± 0.59)	-0.26 (± 0.59)	-0.16 (± 0.61)	-0.27 (± 0.64)
Change at Week 8 (n=308,620,318,615)	-0.26 (± 0.64)	-0.40 (± 0.68)	-0.25 (± 0.62)	-0.37 (± 0.70)
Change at Week 12 (n=306,614,315,609)	-0.30 (± 0.64)	-0.45 (± 0.71)	-0.30 (± 0.69)	-0.44 (± 0.72)
Change at Week 24 (n=302,602,306,592)	-0.35 (± 0.69)	-0.52 (± 0.76)	-0.36 (± 0.73)	-0.50 (± 0.73)
Change at Week 36 (n=292,583,299,572)	-0.38 (± 0.69)	-0.54 (± 0.81)	-0.38 (± 0.76)	-0.56 (± 0.77)

Change at Week 52 (n=275,553,286,540)	-0.41 (± 0.71)	-0.55 (± 0.84)	-0.41 (± 0.78)	-0.60 (± 0.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Evening Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

Evening asthma symptom score was determined using PM (post meridiem) symptom scoring system which evaluated subject's overall asthma symptoms experienced during the day. It ranged from 0 to 4 as: 0=very well, no asthma symptoms, 1=one episode of wheezing, cough, or breathlessness, 2=more than one episode of wheezing, cough, or breathlessness without interference of normal activities, 3=wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities, 4=asthma very bad, unable to carry out daily activities as usual. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n=313,624,320,631)	-0.05 (± 0.45)	-0.17 (± 0.48)	-0.06 (± 0.45)	-0.16 (± 0.52)
Change at Week 4 (n=313,623,319,628)	-0.11 (± 0.59)	-0.27 (± 0.61)	-0.14 (± 0.58)	-0.29 (± 0.64)
Change at Week 8 (n=308,619,318,612)	-0.24 (± 0.64)	-0.41 (± 0.70)	-0.22 (± 0.63)	-0.40 (± 0.70)
Change at Week 12 (n=307,612,314,606)	-0.26 (± 0.66)	-0.45 (± 0.72)	-0.30 (± 0.68)	-0.46 (± 0.73)
Change at Week 24 (n=301,596,301,590)	-0.33 (± 0.72)	-0.52 (± 0.78)	-0.36 (± 0.72)	-0.52 (± 0.73)
Change at Week 36 (n=289,576,292,566)	-0.39 (± 0.73)	-0.56 (± 0.81)	-0.39 (± 0.75)	-0.56 (± 0.80)
Change at Week 52 (n=274,536,270,535)	-0.41 (± 0.74)	-0.57 (± 0.84)	-0.42 (± 0.75)	-0.61 (± 0.78)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Number of Nocturnal Awakenings Per Night at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Number of Nocturnal Awakenings Per Night at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

Subjects recorded every morning on awakening the number of asthma-related nocturnal awakenings requiring use of rescue medication that occurred during the previous night. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: number of nocturnal awakenings/night				
arithmetic mean (standard deviation)				
Change at Week 2 (n=314,624,321,631)	-0.06 (± 0.49)	-0.15 (± 0.55)	-0.04 (± 0.62)	-0.11 (± 0.67)
Change at Week 4 (n=313,623,319,627)	-0.10 (± 0.61)	-0.19 (± 0.66)	-0.11 (± 0.70)	-0.20 (± 0.67)
Change at Week 8 (n=308,620,318,615)	-0.18 (± 0.65)	-0.29 (± 0.72)	-0.17 (± 0.62)	-0.24 (± 0.72)
Change at Week 12 (n=306,614,315,609)	-0.21 (± 0.66)	-0.33 (± 0.75)	-0.18 (± 0.67)	-0.28 (± 0.73)
Change at Week 24 (n=302,602,306,592)	-0.23 (± 0.78)	-0.36 (± 0.81)	-0.26 (± 0.65)	-0.30 (± 0.73)
Change at Week 36 (n=292,583,299,572)	-0.25 (± 0.74)	-0.34 (± 0.81)	-0.26 (± 0.71)	-0.36 (± 0.74)
Change at Week 52 (n=275,553,286,540)	-0.24 (± 0.69)	-0.35 (± 0.88)	-0.26 (± 0.74)	-0.41 (± 0.78)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Number of Puffs of Daily Reliever Medication Used Per 24 Hours at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Number of Puffs of Daily Reliever Medication Used Per 24 Hours at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population

End point description:

Subjects might administered salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed during the study. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations were recorded daily by the subjects in an electronic diary/peak expiratory flow (PEF) meter. In the case that Nebulizer solutions were used as an alternative delivery method, the nebulizer dose was converted to number of puffs as per following conversion factor: salbutamol/albuterol nebulizer solution

(2.5 mg) corresponds to 4 puffs. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: Number of puffs of reliever medication				
arithmetic mean (standard deviation)				
Change at Week 2 (n=313,623,318,630)	-0.21 (± 1.55)	-0.56 (± 1.96)	-0.10 (± 1.71)	-0.47 (± 1.91)
Change at Week 4 (n=312,622,319,626)	-0.26 (± 2.19)	-0.68 (± 2.61)	-0.34 (± 3.42)	-0.73 (± 2.42)
Change at Week 8 (n=308,617,314,607)	-0.50 (± 2.23)	-1.02 (± 2.86)	-0.65 (± 2.96)	-0.94 (± 2.86)
Change at Week 12 (n=306,610,310,603)	-0.52 (± 2.28)	-1.23 (± 3.03)	-0.89 (± 3.06)	-1.08 (± 2.72)
Change at Week 24 (n=294,588,300,582)	-0.77 (± 2.60)	-1.27 (± 3.05)	-0.99 (± 3.21)	-1.15 (± 2.83)
Change at Week 36 (n=285,564,287,558)	-0.99 (± 2.49)	-1.30 (± 2.99)	-1.06 (± 3.57)	-1.23 (± 3.01)
Change at Week 52 (n=270,522,265,521)	-0.90 (± 2.58)	-1.45 (± 3.33)	-1.12 (± 3.64)	-1.39 (± 2.97)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in AQLQ (S) Self-Administered Global Score at Weeks 12, 36, and 52: ITT Population

End point title	Change From Baseline in AQLQ (S) Self-Administered Global Score at Weeks 12, 36, and 52: ITT Population

End point description:

The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to subjects with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=286,573,308,586)	0.90 (± 0.97)	1.09 (± 1.03)	0.94 (± 1.01)	1.09 (± 1.09)
Change at Week 36 (n=271,554,295, 548)	1.05 (± 1.08)	1.26 (± 1.17)	1.08 (± 1.16)	1.33 (± 1.15)
Change at Week 52 (n=224,465,243,459)	1.00 (± 1.12)	1.28 (± 1.16)	1.02 (± 1.10)	1.34 (± 1.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Weeks 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Weeks 12, 24, 36, and 52: ITT Population

End point description:

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L-VAS records subject's self-rated health on a vertical VAS that allows them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable). Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	317	631	321	633
Units: scores on a scale				
arithmetic mean (standard deviation)				
Single Index: Change at Week 12(n=280,567,301,576)	0.07 (± 0.17)	0.09 (± 0.18)	0.08 (± 0.18)	0.09 (± 0.18)

Single Index: Change at Week 24(n=275,552,292,559)	0.07 (± 0.17)	0.09 (± 0.17)	0.08 (± 0.18)	0.08 (± 0.20)
Single Index: Change at Week 36(n=264,548,290,537)	0.08 (± 0.19)	0.09 (± 0.20)	0.10 (± 0.18)	0.09 (± 0.20)
Single Index: Change at Week 52(n=220,457,238,448)	0.07 (± 0.20)	0.10 (± 0.19)	0.08 (± 0.19)	0.10 (± 0.20)
VAS Score: Change at Week 12 (n=280,567,301,576)	7.69 (± 17.43)	11.10 (± 18.90)	6.39 (± 20.42)	9.80 (± 19.56)
VAS Score: Change at Week 24 (n=275,552,292,559)	8.33 (± 17.58)	11.44 (± 18.48)	8.59 (± 20.37)	9.21 (± 19.61)
VAS Score: Change at Week 36 (n=264,548,290,537)	9.70 (± 18.24)	11.61 (± 19.09)	9.31 (± 20.09)	11.41 (± 19.40)
VAS Score: Change at Week 52 (n=220,457,238,448)	8.35 (± 18.51)	12.98 (± 18.71)	9.52 (± 20.81)	11.90 (± 19.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Weeks 12, 24, 36, and 52: ITT Population

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Weeks 12, 24, 36, and 52: ITT Population

End point description:

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales. The instrument is comprised of 14 items: 7 related to anxiety (HADS-A) and 7 to depression (HADS-D). Each item on the questionnaire is scored from 0-3. The anxiety/depression score is the sum of the scores of the 7 related items; one can score between 0 and 21 for either anxiety or depression. And the total score is the sum of the scores of the 14 items ranging from 0 (no symptoms) to 42 (severe symptoms), with higher scores indicating higher anxiety/depression complains. Analysis was performed on ITT population; 29 participants in Japan who received an incorrectly translated HADS questionnaire were excluded. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	311	621	317	624
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=274,551,297,569)	-2.11 (± 5.29)	-1.91 (± 5.65)	-1.55 (± 6.11)	-1.98 (± 5.89)
Change at Week 24 (n=270,537,286,552)	-2.17 (± 5.71)	-1.93 (± 5.97)	-1.73 (± 6.36)	-1.88 (± 6.39)
Change at Week 36 (n=260,535,286,532)	-2.52 (± 5.89)	-2.02 (± 6.34)	-2.67 (± 6.80)	-2.13 (± 6.67)
Change at Week 52 (n=213,443,234,438)	-2.00 (± 6.29)	-2.36 (± 6.28)	-1.86 (± 6.79)	-2.17 (± 7.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 22-Item Sino Nasal Outcome Test (SNOT-22) Score at Weeks 12, 24, 36, and 52: ITT Population With Bilateral Nasal Polyposis/Chronic Rhinosinusitis

End point title	Change From Baseline in 22-Item Sino Nasal Outcome Test (SNOT-22) Score at Weeks 12, 24, 36, and 52: ITT Population With Bilateral Nasal Polyposis/Chronic Rhinosinusitis

End point description:

The SNOT-22 is a validated measure of health related quality of life in sinonasal disease. It is a 22 item questionnaire with each item assigned a score ranging from 0-5. The total score may range from 0 (no disease) -110 (worst disease), lower scores represent better health related quality of life. Analysis was performed on ITT population with bilateral nasal polyposis/chronic rhinosinusitis. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	126	70	123
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=51,113,61,102)	-6.82 (± 17.19)	-13.55 (± 16.85)	-11.30 (± 16.11)	-16.07 (± 20.54)
Change at Week 24 (n=52,111,58,102)	-7.21 (± 17.10)	-14.68 (± 18.77)	-9.55 (± 16.04)	-17.41 (± 20.81)
Change at Week 36 (n=49,111,57,100)	-6.10 (± 19.03)	-15.23 (± 18.20)	-8.51 (± 20.36)	-18.86 (± 21.34)
Change at Week 52 (n=42,89,49,85)	-6.95 (± 17.10)	-15.78 (± 17.72)	-9.98 (± 18.01)	-19.81 (± 22.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, Ages 12+ (RQLQ[S]+12) Score at Weeks 12, 24, 36, and 52: ITT Population With Comorbid Allergic Rhinitis

End point title	Change From Baseline in Standardized Rhinoconjunctivitis

	Quality Of Life Questionnaire, Ages 12+ (RQLQ[S]+12) Score at Weeks 12, 24, 36, and 52: ITT Population With Comorbid Allergic Rhinitis

End point description:

RQLQ(S)+12 is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on RQLQ(S) in 7 domains: activities (3 items), sleep (3 items), non-nose/eye symptoms (7 items), practical problems (3 items), nasal symptoms (4 items), eye symptoms (4 items) and emotional (4 items). RQLQ(S)+12 responses are based on 7-point likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within RQLQ(S)+12 are equally weighted. The overall score is calculated as the mean score of all items. Higher scores indicated more health-related quality of life impairment (lower scores better). Analysis was performed on ITT population with comorbid allergic rhinitis. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 52

End point values	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w	Dupilumab 300 mg q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	194	390	214	409
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=167,332,192,348)	-0.50 (± 0.98)	-0.70 (± 0.99)	-0.44 (± 1.05)	-0.64 (± 1.06)
Change at Week 24 (n=164,322,182,342)	-0.50 (± 0.92)	-0.73 (± 1.09)	-0.54 (± 1.10)	-0.60 (± 1.10)
Change at Week 36 (n=158,323,184,332)	-0.56 (± 0.96)	-0.78 (± 1.15)	-0.58 (± 1.20)	-0.75 (± 1.12)
Change at Week 52 (n=129,263,149,274)	-0.41 (± 0.97)	-0.90 (± 1.17)	-0.47 (± 1.33)	-0.76 (± 1.13)

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 64) or entry in the LTS12551 open-label extension study regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment emergent AEs that developed/worsened during 'treatment-emergent period' (from first dose of IMP until 98 days after last dose of IMP or entry in the LTS12551 study). Safety population: all subjects who received at least 1 dose or part of a dose of IMP, analyzed according to treatment that subjects actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo (for Dupilumab 200 mg) q2w

Reporting group description:

2 subcutaneous injections of matched Placebo (for Dupilumab 200 mg) as a loading dose on Day 1 (Week 0), followed by a single injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. 2 subjects were excluded, who were randomized to this arm but received single injection of Dupilumab 200 mg q2w and 300 mg q2w, respectively.

Reporting group title	Dupilumab 200 mg q2w

Reporting group description:

2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 (Week 0), followed by a single 200 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. 2 subject were included, who were randomized to Placebo (for Dupilumab 200 mg) arm and Dupilumab 300 mg arm, respectively but both received Dupilumab 200 mg.

Reporting group title	Placebo (for Dupilumab 300 mg) q2w

Reporting group description:

2 subcutaneous injections of matched Placebo (for Dupilumab 300 mg) as a loading dose on Day 1 (Week 0), followed by a single injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 (Week 0), followed by a single 300 mg injection q2w from Week 2 to Week 50 in combination with stable ICS and up to 2 other controller medicines (second or third controller therapy). Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. 1 subject was excluded, who was randomized to this arm but received single injection of Dupilumab 200 mg q2w. 1 subject was included, who was randomized to Placebo (for Dupilumab 200 mg) arm but received Dupilumab 300 mg.

Serious adverse events	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 313 (8.31%)	51 / 631 (8.08%)	28 / 321 (8.72%)

number of deaths (all causes) number of deaths resulting from adverse events	3	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic Thyroid Cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	0 / 313 (0.00%)	2 / 631 (0.32%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear Cell Renal Cell Carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysplastic Naevus			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioblastoma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary Thyroid Cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestine Carcinoma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Threatened			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic Pregnancy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired Healing			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection Site Erythema			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection Site Inflammation			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injection Site Oedema			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Shock			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Pregnancy Of Partner			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Victim Of Sexual Abuse			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Cyst			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			

subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	10 / 313 (3.19%)	11 / 631 (1.74%)	5 / 321 (1.56%)
occurrences causally related to treatment / all	0 / 12	0 / 14	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic Pneumonia Chronic			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Oedema			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal Polyps			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Noninfective Bronchitis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	1 / 313 (0.32%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory Depression			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment Disorder With Depressed Mood			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 313 (0.00%)	2 / 631 (0.32%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial Bones Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibula Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Rupture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Injuries			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Traumatic			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-Traumatic Pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Thoracic Procedure Complication			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural Pneumothorax			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	2 / 321 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Injury			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Sickle Cell Anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Cardiomyopathy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal Detachment			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Tear			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal Hernia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular Perforation			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum Intestinal			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Volvulus			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus Hernia			

subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired Gastric Emptying			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Motility Disorder			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Ulcer			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Strangulated Umbilical Hernia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Chronic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal Vein Thrombosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Infarct			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Incontinence			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Primary Hyperaldosteronism			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	2 / 321 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological Fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polychondritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Abscess			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical Pneumonia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Capnocytophaga Infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Sinusitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis A			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical Device Site Infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	2 / 321 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Cellulitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Chronic			
subjects affected / exposed	1 / 313 (0.32%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tick-Borne Viral Encephalitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 631 (0.00%)	1 / 321 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 313 (0.00%)	1 / 631 (0.16%)	0 / 321 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 300 mg q2w		
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 632 (8.86%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaplastic Thyroid Cancer			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Basal Cell Carcinoma				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast Cancer				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clear Cell Renal Cell Carcinoma				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysplastic Naevus				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemangioblastoma				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant Melanoma				
subjects affected / exposed	2 / 632 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Papillary Thyroid Cancer				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal Adenocarcinoma				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small Intestine Carcinoma				

subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis Superficial			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Threatened			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ectopic Pregnancy			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pregnancy				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest Pain				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired Healing				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injection Site Erythema				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injection Site Inflammation				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injection Site Oedema				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac Chest Pain				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic Reaction				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Anaphylactic Shock			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Pregnancy Of Partner			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Victim Of Sexual Abuse			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical Cyst			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian Cyst			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 632 (1.11%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eosinophilic Pneumonia Chronic			

subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial Lung Disease				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal Oedema				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal Polyps				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Noninfective Bronchitis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax Spontaneous				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				

subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Depression				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Adjustment Disorder With Depressed Mood				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Completed Suicide				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Major Depression				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine Aminotransferase Increased				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial Bones Fracture			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	2 / 632 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula Fracture			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot Fracture			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament Rupture			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lower Limb Fracture			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Injuries			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax Traumatic			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post-Traumatic Pain			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative Thoracic Procedure Complication			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural Pneumothorax			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius Fracture			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib Fracture			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road Traffic Accident			

subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Compression Fracture				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Injury				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna Fracture				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper Limb Fracture				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist Fracture				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Sickle Cell Anaemia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Coronary Syndrome				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Acute Myocardial Infarction			
subjects affected / exposed	2 / 632 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Angina Pectoris			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular Block Second Degree			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Congestive			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardio-Respiratory Arrest			
subjects affected / exposed	2 / 632 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Coronary Artery Disease			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial Ischaemia			

subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachyarrhythmia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss Of Consciousness				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal Detachment			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal Tear			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticular Perforation			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diverticulum				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum Intestinal				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric Volvulus				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus Hernia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired Gastric Emptying				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large Intestine Polyp				

subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal Motility Disorder				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal Ulcer				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Strangulated Umbilical Hernia				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical Hernia				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis Acute				
subjects affected / exposed	2 / 632 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis Chronic				

subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Portal Vein Thrombosis			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Infarct			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Incontinence			
subjects affected / exposed	1 / 632 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Primary Hyperaldosteronism			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal Chest Pain				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	2 / 632 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pathological Fracture				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polychondritis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical Pneumonia				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	2 / 632 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Capnocytophaga Infection				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic Sinusitis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis A				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis C				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				

subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Medical Device Site Infection				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis Media				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 632 (0.63%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Post Procedural Cellulitis				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Chronic				
subjects affected / exposed	0 / 632 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tick-Borne Viral Encephalitis				
subjects affected / exposed	1 / 632 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				

subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	0 / 632 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo (for Dupilumab 200 mg) q2w	Dupilumab 200 mg q2w	Placebo (for Dupilumab 300 mg) q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 313 (59.11%)	363 / 631 (57.53%)	197 / 321 (61.37%)
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	16 / 313 (5.11%)	31 / 631 (4.91%)	16 / 321 (4.98%)
occurrences (all)	17	34	16
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 313 (8.31%)	47 / 631 (7.45%)	25 / 321 (7.79%)
occurrences (all)	34	71	37
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	13 / 313 (4.15%)	76 / 631 (12.04%)	22 / 321 (6.85%)
occurrences (all)	30	329	96
Injection Site Oedema			
subjects affected / exposed	2 / 313 (0.64%)	23 / 631 (3.65%)	5 / 321 (1.56%)
occurrences (all)	3	65	9
Respiratory, thoracic and mediastinal disorders			
Rhinitis Allergic			
subjects affected / exposed	16 / 313 (5.11%)	21 / 631 (3.33%)	15 / 321 (4.67%)
occurrences (all)	22	22	16
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	16 / 313 (5.11%)	30 / 631 (4.75%)	7 / 321 (2.18%)
occurrences (all)	16	35	8
Infections and infestations			
Bronchitis			
subjects affected / exposed	47 / 313 (15.02%)	73 / 631 (11.57%)	43 / 321 (13.40%)
occurrences (all)	72	98	70
Influenza			
subjects affected / exposed	29 / 313 (9.27%)	36 / 631 (5.71%)	22 / 321 (6.85%)
occurrences (all)	35	41	28
Sinusitis			
subjects affected / exposed	27 / 313 (8.63%)	36 / 631 (5.71%)	29 / 321 (9.03%)
occurrences (all)	40	43	35
Upper Respiratory Tract Infection			
subjects affected / exposed	37 / 313 (11.82%)	70 / 631 (11.09%)	48 / 321 (14.95%)
occurrences (all)	57	111	77
Urinary Tract Infection			
subjects affected / exposed	17 / 313 (5.43%)	17 / 631 (2.69%)	12 / 321 (3.74%)
occurrences (all)	25	20	12
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	60 / 313 (19.17%)	121 / 631 (19.18%)	64 / 321 (19.94%)
occurrences (all)	76	166	104

Non-serious adverse events	Dupilumab 300 mg q2w		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	378 / 632 (59.81%)		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	34 / 632 (5.38%)		
occurrences (all)	42		
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 632 (6.33%)		
occurrences (all)	83		
General disorders and administration site conditions			

Injection Site Erythema subjects affected / exposed occurrences (all) Injection Site Oedema subjects affected / exposed occurrences (all)	 98 / 632 (15.51%) 353 40 / 632 (6.33%) 119		
Respiratory, thoracic and mediastinal disorders Rhinitis Allergic subjects affected / exposed occurrences (all)	 18 / 632 (2.85%) 18		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	 25 / 632 (3.96%) 28		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all) Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	 70 / 632 (11.08%) 104 38 / 632 (6.01%) 44 26 / 632 (4.11%) 34 77 / 632 (12.18%) 110 20 / 632 (3.16%) 22 112 / 632 (17.72%) 154		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2015	It included following changes: - Stratification on ICS dose (medium/high) was added; - Number of randomization strata for age, eosinophil count was reduced.
21 September 2015	It included following changes: - The biomarkers were splitted into 3 subgroups; - The vaccine category considered for evaluation were limited; - Clinical handling of subjects with missed dose(s) of investigational medicinal product (IMP) was clarified; - Hepatitis/human immunodeficiency virus (HIV)/anti-nuclear antibody (ANA) test at Visit 17 was added for subjects who plan to participate in the open label extension (OLE) study; - hepatitis B virus (HBV) deoxyribonucleic acid (DNA) test was added for subjects believed to be false positive for (hepatitis C virus) HBc antibody (Ab) or if the HBV serological status was unclear and HCV ribonucleic acid (RNA) was added for subjects believed to be false positive for HCV Ab at Visits 1 & 17; - The eligibility criteria regarding IMP compliance was deleted for OLE study; - Exclusion criteria regarding hepatitis and tuberculosis was modified; - Exclusion criteria regarding washout period of live attenuated vaccinations was modified; - Exclusion criteria on birth control for male subjects with a female partner of childbearing potential was modified; - Lactate dehydrogenase & differentiation in conjugated and non-conjugated bilirubin was added in case of total bilirubin above normal into serum chemistry panel; - Post-bronchodilator FEV1 at Visit 2 was added; - Spirometry operation requirement was clarified; - Table of handling procedures for dupilumab and anti-drug antibody (ADA) was removed; - Difference between withdrawal from IMP and withdrawal from the study and how this should be documented was clarified; - Local amendments 1 and 3 were incorporated into global protocol; - Lower limit of pre-bronchodilator FEV1 was removed in inclusion criteria for all subjects and the upper limit of pre-bronchodilator FEV1 was revised in inclusion criteria for adolescents to decrease screening failure rate and to adapt the criterion to adolescent values of pre-bronchodilator FEV1.
09 August 2016	It included following changes: Criteria for adverse event of special interest (AESI) was changed; - Study procedures were simplified for subjects who permanently discontinued the study; - Sampling times of ADA was changed, ADA response definitions were added; - Sample size and planned database lock date was modified; - Loading dose analysis was added; - The recognized controller classes were clarified; - Temporary and permanent treatment discontinuation criteria were clarified; - Hepatitis serology testing and interpretation of the results in context of eligibility criteria were clarified - Chest X-Ray or MRI (MRI for Germany only) at Visit 17 was introduced for subjects who plan to participate in the OLE study and if available chest imaging was over 12 months from entry into the open label extension study; - Height measurement was added for adolescents at each site visit for accurate calculation of spirometry parameters when doing spirometry; - Local amendments 5 and 6 were incorporated into global protocol.
26 May 2017	It included following changes: - Wording referring to the sample size was modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported