Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate Dupilumab in Patients with Moderate to Severe Uncontrolled Asthma

Summary

EudraCT number	2013-000856-16
Trial protocol	IT ES PL
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	20 April 2016

Trial information

Trial identification

Sponsor protocol code	DRI12544

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01854047
WHO universal trial number (UTN)	U1111-1138-3962

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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of different doses and regimens of Dupilumab in subjects with moderate-to-severe, uncontrolled asthma.

Protection of trial 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. 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:

Inhaled corticosteroid (ICS)/long-acting beta-2 agonist (LABA) therapy, stable moderate- or high-dose for at least 1 month prior to screening and continued throughout the study.

Evidence for comparator: -	
Actual start date of recruitment	10 June 2013
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	Poland: 30
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Argentina: 64
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Chile: 68
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Mexico: 25
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Turkey: 41
Country: Number of subjects enrolled	Ukraine: 62

Country: Number of subjects enrolled	United States: 193
Worldwide total number of subjects	776
EEA total number of subjects	112

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	702
From 65 to 84 years	73
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 174 centers in 15 countries. A total of 1532 subjects were screened between June 2013 and June 2014, of which, 776 subjects were randomized and 769 were treated. 756 subjects were screen failure mainly due to exclusion criteria met and inclusion criteria not met.

Pre-assignment

Screening details:

Randomization was stratified according to blood eosinophils count [high eosinophils(HEos)≥0.3 G/L; eosinophils 0.2 to 0.299 G/L; eosinophils<0.2 G/L] and country. Assignment to arms was done centrally using Interactive Voice/Web Response System in 1:1:1:1:1 ratio for Placebo and Dupilumab [300 mg q2w; 200 mg q2w; 300 mg q4w and 200 mg q4w].

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 q2w

Arm description:

2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection every 2 weeks (q2w) from Week 2 to Week 22 in combination with stable ICS/LABA therapy.

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

Dosage and administration details:

Subcutaneous injection (2 ml) in the abdomen or upper thigh.

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, followed by a single 300 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.

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 ml) in the abdomen or upper thigh.

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, followed by a single 200 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.

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/2 ml) in the abdomen or upper thigh.

Arm title	Dupilumab 300 mg q4w

Arm description:

2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 300 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.

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 ml) in the abdomen or upper thigh.

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

Dosage and administration details:

Subcutaneous injection (2 ml) in the abdomen or upper thigh.

Arm title	Dupilumab 200 mg q4w

Arm description:

2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 200 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.

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/ 2 ml) in the abdomen or upper thigh.

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

Dosage and administration details:

Subcutaneous injection (2 ml) in the abdomen or upper thigh.

Number of subjects in period 1	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Started	158	157	150
Treated	158	156	148
Completed 12-week study treatment	153	149	141
Completed	146	149	137
Not completed	12	8	13
Adverse Event	5	4	6
Randomized but not treated	-	1	2
Other than specified	3	3	3
Poor compliance to protocol	3	-	2
Lack of efficacy	1	-	-

Number of subjects in period 1	Dupilumab 300 mg q4w	Dupilumab 200 mg q4w
Started	157	154
Treated	157	150
Completed 12-week study treatment	146	143
Completed	142	135
Not completed	15	19
Adverse Event	10	7
Randomized but not treated	-	4
Other than specified	5	8
Poor compliance to protocol	-	-
Lack of efficacy	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo q2w
Reporting group description:	
2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection every 2 weeks (q2w) from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
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, followed by a single 300 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
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, followed by a single 200 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
Reporting group title	Dupilumab 300 mg q4w
Reporting group description:	
2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 300 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
Reporting group title	Dupilumab 200 mg q4w
Reporting group description:	
2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 200 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	

Reporting group values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Number of subjects	158	157	150
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49	47.5	51
standard deviation	± 12.7	± 12.4	± 13.4
Gender categorical Units: Subjects			
Female	104	103	96
Male	54	54	54
Number of Subjects with Blood Eosinphil Count Units: Subjects			
<0.3 Giga/L	90	93	85
≥ 0.3 Giga/L	68	64	65

Reporting group values	Dupilumab 300 mg q4w	Dupilumab 200 mg q4w	Total
Number of subjects	157	154	776

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	47.9	47.9	
standard deviation	± 13.1	± 13.1	-
Gender categorical Units: Subjects			
Female	100	87	490
Male	57	67	286
Number of Subjects with Blood Eosinphil Count Units: Subjects			
<0.3 Giga/L	91	92	451
≥ 0.3 Giga/L	66	62	325

End points

End points reporting groups

Reporting group title	Placebo q2w
Reporting group description:	
2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1 followed by a single injection every 2 weeks (q2w) from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
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, followed by a single 300 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
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, followed by a single 200 mg injection q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
Reporting group title	Dupilumab 300 mg q4w
Reporting group description:	
2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 300 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	
Reporting group title	Dupilumab 200 mg q4w
Reporting group description:	
2 subcutaneous injections of Dupilumab 200 mg (for a total of 400 mg) as a loading dose on Day 1 followed by a Placebo alternating with single 200 mg injection of Dupilumab q2w from Week 2 to Week 22 in combination with stable ICS/LABA therapy.	

Primary: Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Week 12 - Intent-to-Treat (ITT) Population

End point title	Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Week 12 - Intent-to-Treat (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 that included all randomized population analyzed according to the treatment group allocated by randomization, regardless of whether the treatment was actually received. Number of subjects analyzed = subjects of ITT population. Here 'n' signifies number of subjects with available data for specified category.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	157	150	157
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=158,157,150,157,154)	1.82 (± 0.55)	1.85 (± 0.53)	1.79 (± 0.52)	1.86 (± 0.57)

Week 12 (n=129,146,136,134,134)	2.01 (± 0.69)	2.12 (± 0.59)	2.12 (± 0.68)	2.14 (± 0.69)
Change from baseline (n=129,146,136,134,134)	0.13 (± 0.37)	0.26 (± 0.39)	0.32 (± 0.38)	0.24 (± 0.4)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=158,157,150,157,154)	1.88 (± 0.54)			
Week 12 (n=129,146,136,134,134)	2.07 (± 0.63)			
Change from baseline (n=129,146,136,134,134)	0.2 (± 0.41)			

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo q2w

Statistical analysis description:

Analysis was performed using mixed-effect model with repeated measures (MMRM) model including available FEV1 data from baseline to Week 12 and treatment group as a factor. A step-down procedure was used to strongly control the overall type I error rate for testing multiple doses against placebo. The hierarchy was 300 mg q2w, 200 mg q2w, 300 mg q4w and 200 mg q4w.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [1]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.25

Notes:

[1] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 200 mg q2w vs Placebo q2w
Comparison groups	Dupilumab 200 mg q2w v Placebo q2w
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.28

Notes:

[2] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 300 mg q4w vs Placebo q2w
Comparison groups	Dupilumab 300 mg q4w v Placebo q2w
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.21

Notes:

[3] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 200 mg q4w vs Placebo q2w
Comparison groups	Dupilumab 200 mg q4w v Placebo q2w
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0304 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Notes:

[4] - Threshold for significance at 0.05.

Primary: Change From Baseline in FEV1 at Week 12 - ITT Population with Elevated Baseline Blood Eosinophils (HEos-ITT Population)

End point title	Change From Baseline in FEV1 at Week 12 - ITT Population with Elevated Baseline Blood Eosinophils (HEos-ITT Population)

End point description:

Analysis was performed on HEos ITT population defined as the ITT population with baseline blood eosinophils ≥0.3 G/L. Number of subjects analyzed = subjects of HEos-ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	64	65	66
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=68,64,65,66,62)	1.86 (± 0.68)	1.77 (± 0.5)	1.8 (± 0.52)	1.87 (± 0.6)
Week 12 (n=58,59,57,55,53)	2.13 (± 0.78)	2.12 (± 0.54)	2.26 (± 0.68)	2.26 (± 0.7)
Change from baseline (n=58,59,57,55,53)	0.18 (± 0.38)	0.36 (± 0.46)	0.45 (± 0.4)	0.35 (± 0.43)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=68,64,65,66,62)	1.8 (± 0.49)			
Week 12 (n=58,59,57,55,53)	2.09 (± 0.54)			
Change from baseline (n=58,59,57,55,53)	0.26 (± 0.47)			

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs Placebo q2w

Statistical analysis description:

Analysis was performed using MMRM model including available FEV1 data from baseline to Week 12 and treatment group as a factor. A step-down procedure was used to strongly control the overall type I error rate for testing multiple doses against placebo. The hierarchy was 300 mg q2w, 200 mg q2w, 300 mg q4w, and 200 mg q4w.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.36

Notes:

[5] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 200 mg q2w vs Placebo q2w
Comparison groups	Dupilumab 200 mg q2w v Placebo q2w
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.4

Notes:

[6] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 300 mg q4w vs Placebo q2w
Comparison groups	Dupilumab 300 mg q4w v Placebo q2w
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0212 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.32

Notes:

[7] - Threshold for significance at 0.05.

Statistical analysis title	Dupilumab 200 mg q4w vs Placebo q2w
Comparison groups	Dupilumab 200 mg q4w v Placebo q2w

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2774 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.23

Notes:

[8] - Threshold for significance at 0.05.

Secondary: Relative Change From Baseline in FEV1 at Week 12

End point title	Relative Change From Baseline in FEV1 at Week 12

End point description:

Analysis was performed on ITT population and HEos-ITT population. Number of subjects analyzed=subjects of ITT population. Here "n" signifies number of subjects with available data at Week 12 for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	157	150	157
Units: Percent change				
arithmetic mean (standard deviation)				
ITT Population (n=129,146,136,134,134)	7.04 (± 19.26)	16.64 (± 27.78)	19.15 (± 23.53)	13.55 (± 23.01)
HEos ITT Population (n=58,59,57,55,53)	10.07 (± 19.65)	25.29 (± 36.15)	27.42 (± 25.68)	20.68 (± 24.86)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Percent change				
arithmetic mean (standard deviation)				
ITT Population (n=129,146,136,134,134)	13.04 (± 24.21)			
HEos ITT Population (n=58,59,57,55,53)	18.07 (± 29.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Event Rate of Loss of Asthma Control (LOAC) During The Treatment Period

End point title	Annualized Event Rate of Loss of Asthma Control (LOAC) During The Treatment Period

End point description:

LOAC was defined as any of 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 inhaled corticosteroid ≥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 and HEos-ITT population. Number of subjects analyzed=subjects of the ITT population who were treated. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	156	148	157
Units: LOAC per subject-year				
number (confidence interval 95%)				
ITT Population (n=158,156,148,157,150)	1.107 (0.801 to 1.53)	0.326 (0.206 to 0.515)	0.347 (0.217 to 0.555)	0.73 (0.508 to 1.048)
HEos ITT Population (n=68,64,64,66,59)	1.312 (0.804 to 2.142)	0.322 (0.153 to 0.677)	0.446 (0.231 to 0.864)	0.788 (0.458 to 1.355)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: LOAC per subject-year				
number (confidence interval 95%)				
ITT Population (n=158,156,148,157,150)	0.563 (0.378 to 0.839)			
HEos ITT Population (n=68,64,64,66,59)	0.424 (0.212 to 0.851)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First LOAC Event During the Treatment Period: Kaplan-Meier Estimates at Week 12 and Week 24

End point title	Time to First LOAC Event During the Treatment Period: Kaplan-Meier Estimates at Week 12 and Week 24

End point description:

The time-to-event variable was defined as the time from the date of first dose to the date of the first LOAC event. For subjects who had no LOAC event on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. The probability of LOAC at Week 12 and Week 24 was provided. Analysis was performed on ITT population and HEos-ITT population. Number of subjects analyzed=subjects of the ITT population who were treated. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	156	148	157
Units: Probability of LOAC				
number (confidence interval 95%)				
ITT Population at Week 12(n=158,156,148,157,150)	0.258 (0.192 to 0.329)	0.112 (0.068 to 0.168)	0.09 (0.051 to 0.144)	0.145 (0.095 to 0.206)
ITT Population at Week 24(n=158,156,148,157,150)	0.338 (0.265 to 0.413)	0.146 (0.095 to 0.207)	0.112 (0.067 to 0.169)	0.242 (0.177 to 0.314)
HEos ITT Population at Week 12 (n=68,64,64,66,59)	0.3 (0.195 to 0.411)	0.115 (0.05 to 0.208)	0.113 (0.05 to 0.206)	0.126 (0.059 to 0.22)
HEos ITT Population at Week 24 (n=68,64,64,66,59)	0.392 (0.275 to 0.507)	0.166 (0.085 to 0.269)	0.113 (0.05 to 0.206)	0.207 (0.117 to 0.314)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: Probability of LOAC				
number (confidence interval 95%)				
ITT Population at Week 12(n=158,156,148,157,150)	0.096 (0.055 to 0.15)			
ITT Population at Week 24(n=158,156,148,157,150)	0.209 (0.147 to 0.279)			

HEos ITT Population at Week 12 (n=68,64,64,66,59)	0.052 (0.014 to 0.13)			
HEos ITT Population at Week 24 (n=68,64,64,66,59)	0.162 (0.079 to 0.269)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Event Rate of Severe Exacerbation During The Treatment Period

End point title	Annualized Event Rate of Severe Exacerbation During The Treatment Period

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 and HEos-ITT population. Number of subjects analyzed=subjects of the ITT population who were treated. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	156	148	157
Units: Exacerbation per subject-year				
number (confidence interval 95%)				
ITT Population (n=158,156,148,157,150)	0.897 (0.619 to 1.3)	0.265 (0.157 to 0.445)	0.269 (0.157 to 0.461)	0.599 (0.396 to 0.907)
HEos ITT Population (n=68,64,64,66,59)	1.044 (0.572 to 1.904)	0.201 (0.078 to 0.517)	0.3 (0.133 to 0.678)	0.678 (0.356 to 1.29)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: Exacerbation per subject-year				
number (confidence interval 95%)				
ITT Population (n=158,156,148,157,150)	0.415 (0.26 to 0.664)			
HEos ITT Population (n=68,64,64,66,59)	0.358 (0.158 to 0.809)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Exacerbation Event During the Treatment Period: Kaplan-Meier Estimates at Week 12 and 24

End point title	Time to First Severe Exacerbation Event During the Treatment Period: Kaplan-Meier Estimates at Week 12 and 24

End point description:

The time-to-event variable was defined as the time from the date of first dose to the date of the first severe exacerbation event. For subjects who had no severe exacerbation event on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. Analysis was performed on ITT population and HEos-ITT population. Number of subjects analyzed=subjects of the ITT population who were treated. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	156	148	157
Units: Probability of Severe Exacerbation				
number (confidence interval 95%)				
ITT Population at Week 12 (n=158,156,148,157,150)	0.207 (0.147 to 0.274)	0.092 (0.053 to 0.145)	0.07 (0.036 to 0.119)	0.112 (0.068 to 0.168)
ITT Population at Week 24 (n=158,156,148,157,150)	0.266 (0.199 to 0.338)	0.112 (0.068 to 0.169)	0.091 (0.051 to 0.145)	0.195 (0.136 to 0.262)
HEos ITT Population at Week 12 (n=68,64,64,66,59)	0.21 (0.122 to 0.314)	0.082 (0.03 to 0.167)	0.082 (0.03 to 0.167)	0.094 (0.038 to 0.181)
HEos ITT Population at Week 24 (n=68,64,64,66,59)	0.287 (0.184 to 0.398)	0.116 (0.051 to 0.21)	0.082 (0.03 to 0.167)	0.175 (0.093 to 0.278)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: Probability of Severe Exacerbation				
number (confidence interval 95%)				
ITT Population at Week 12 (n=158,156,148,157,150)	0.075 (0.04 to 0.125)			
ITT Population at Week 24 (n=158,156,148,157,150)	0.16 (0.106 to 0.225)			

HEos ITT Population at Week 12 (n=68,64,64,66,59)	0.052 (0.014 to 0.13)			
HEos ITT Population at Week 24 (n=68,64,64,66,59)	0.125 (0.055 to 0.226)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning Asthma Symptom Score at Week 12

End point title	Change From Baseline in Morning Asthma Symptom Score at Week 12

End point description:

AM (ante meridiem) symptom scoring system rates were subject's overall asthma symptoms experienced during the night. It ranges from 0 to 4 as: 0 = No asthma symptoms, slept through the night, 1= Slept well, but some complaints in the morning. No nighttime 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 and HEos-ITT population. Number of subjects analyzed = subjects of ITT population. Here 'n' signifies number of subjects with available data at Week 12 for specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	157	150	157
Units: Scores on a scale				
arithmetic mean (standard deviation)				
ITT Population (n=143,148,138,148,140)	-0.23 (± 0.7)	-0.43 (± 0.7)	-0.46 (± 0.75)	-0.52 (± 0.65)
HEos ITT Population (n=62,59,58,61,56)	-0.29 (± 0.7)	-0.66 (± 0.67)	-0.55 (± 0.75)	-0.57 (± 0.63)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
ITT Population (n=143,148,138,148,140)	-0.54 (± 0.64)			
HEos ITT Population (n=62,59,58,61,56)	-0.57 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening Asthma Symptom Score at Week 12

End point title	Change From Baseline in Evening Asthma Symptom Score at Week 12

End point description:

PM (post meridiem) symptom scoring system rates were subject's overall asthma symptoms experienced during the day. It ranges 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 and HEos ITT population. Number of subjects analyzed = subjects of ITT population. Here 'n' signifies number of subjects with available data at Week 12 for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	157	150	157
Units: Scores on a scale				
arithmetic mean (standard deviation)				
ITT Population (n=143,148,136,148,140)	-0.27 (± 0.76)	-0.52 (± 0.79)	-0.52 (± 0.8)	-0.59 (± 0.79)
HEos ITT Population (n=62,59,58,61,56)	-0.35 (± 0.71)	-0.84 (± 0.87)	-0.62 (± 0.7)	-0.73 (± 0.77)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
ITT Population (n=143,148,136,148,140)	-0.54 (± 0.71)			
HEos ITT Population (n=62,59,58,61,56)	-0.69 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change From Baseline in FEV1 at Week 12 - ITT Population With Baseline Blood Eosinophil <0.3 Giga/L

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

End point description:

Analysis was performed on ITT population with baseline blood eosinophil count <0.3 Giga/L. Number of subjects analyzed = subjects of ITT population with baseline blood eosinophil count <0.3 Giga/L. Here 'n' signifies number of subjects with available data for specified category.

End point type	Post-hoc

End point timeframe:

Baseline to Week 12

End point values	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w	Dupilumab 300 mg q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	93	85	91
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=90,93,85,91,92)	1.79 (± 0.42)	1.9 (± 0.55)	1.79 (± 0.53)	1.85 (± 0.56)
Week 12 (n=71,87,79,79,81)	1.92 (± 0.61)	2.12 (± 0.63)	2.02 (± 0.67)	2.05 (± 0.68)
Change from Baseline (n=71,87,79,79,81)	0.09 (± 0.36)	0.19 (± 0.31)	0.23 (± 0.33)	0.16 (± 0.36)

End point values	Dupilumab 200 mg q4w			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: Liter				
arithmetic mean (standard deviation)				
Baseline (n=90,93,85,91,92)	1.94 (± 0.56)			
Week 12 (n=71,87,79,79,81)	2.06 (± 0.68)			
Change from Baseline (n=71,87,79,79,81)	0.17 (± 0.36)			

Statistical analyses

No statistical analyses for this end point

Adverse events

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 40) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths were treatment emergent AEs developed/worsened & deaths occurred during 'treatment-emergent period'(from first dose of study drug injection up to end of 16-week post-treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo q2w

Reporting group description:

Subjects exposed to Placebo (for Dupilumab) in combination with stable ICS/LABA therapy (mean exposure of 23 weeks).

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

Subjects exposed to Dupilumab 300 mg q2w in combination with stable ICS/LABA therapy (mean exposure of 23 weeks).

Reporting group title	Dupilumab 200 mg q2w

Reporting group description:

Subjects exposed to Dupilumab 200 mg q2w in combination with stable ICS/LABA therapy (mean exposure of 23 weeks).

Reporting group title	Dupilumab 300 mg q4w

Reporting group description:

Subjects exposed to Dupilumab 300 mg alternating with placebo q2w in combination with stable ICS/LABA therapy (mean exposure of 23 weeks).

Reporting group title	Dupilumab 200 mg q4w

Reporting group description:

Subjects exposed to Dupilumab 200 mg alternating with placebo q2w in combination with stable ICS/LABA therapy (mean exposure of 23 weeks).

Serious adverse events	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 158 (5.70%)	13 / 156 (8.33%)	10 / 148 (6.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm Of Thyroid Gland			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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

Bowen's Disease			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Breast Cancer Metastatic			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Colon Cancer			
subjects affected / exposed	1 / 158 (0.63%)	0 / 156 (0.00%)	0 / 148 (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
Hypergammaglobulinaemia Benign Monoclonal			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Metastatic Gastric Cancer			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	1 / 148 (0.68%)
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, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	2 / 148 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			

subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Drug Hypersensitivity			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Reproductive system and breast disorders			
Uterine Prolapse			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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	4 / 158 (2.53%)	1 / 156 (0.64%)	5 / 148 (3.38%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising Pneumonia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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			
Suicide Attempt			

subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Injury, poisoning and procedural complications			
Bone Fissure			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Comminuted Fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 156 (0.00%)	0 / 148 (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
Joint Dislocation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Procedural Intestinal Perforation			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Procedural Pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft Tissue Injury			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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 disorders			
Atrioventricular Block Complete			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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 Acute			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Cor Pulmonale Acute			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			

subjects affected / exposed	1 / 158 (0.63%)	0 / 156 (0.00%)	0 / 148 (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
Subileus			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Hepatitis Cholestatic			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Eczema			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 158 (0.63%)	1 / 156 (0.64%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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

Epiglottitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	0 / 148 (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
Gastroenteritis			
subjects affected / exposed	0 / 158 (0.00%)	2 / 156 (1.28%)	0 / 148 (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
Herpes Zoster			
subjects affected / exposed	1 / 158 (0.63%)	0 / 156 (0.00%)	0 / 148 (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
Pneumonia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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 Bacterial			
subjects affected / exposed	0 / 158 (0.00%)	1 / 156 (0.64%)	0 / 148 (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
Sinusitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 156 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 300 mg q4w	Dupilumab 200 mg q4w	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 157 (10.19%)	6 / 150 (4.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm Of Thyroid Gland			
subjects affected / exposed	0 / 157 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's Disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer Metastatic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon Cancer			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypergammaglobulinaemia Benign Monoclonal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Gastric Cancer			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			

subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Hypersensitivity			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Prolapse			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 157 (1.27%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising Pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			

subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Bone Fissure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted Fracture			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 157 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Intestinal Perforation			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Soft Tissue Injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Limb Fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular Block Complete			
subjects affected / exposed	0 / 157 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cor Pulmonale Acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis Cholestatic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 157 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo q2w	Dupilumab 300 mg q2w	Dupilumab 200 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 158 (55.70%)	95 / 156 (60.90%)	81 / 148 (54.73%)
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 158 (12.66%)	17 / 156 (10.90%)	17 / 148 (11.49%)
occurrences (all)	26	21	28
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	12 / 158 (7.59%)	34 / 156 (21.79%)	21 / 148 (14.19%)
occurrences (all)	15	130	81
Injection Site Oedema			
subjects affected / exposed	1 / 158 (0.63%)	8 / 156 (5.13%)	4 / 148 (2.70%)
occurrences (all)	2	16	15
Injection Site Pain			
subjects affected / exposed	7 / 158 (4.43%)	14 / 156 (8.97%)	7 / 148 (4.73%)
occurrences (all)	18	28	16
Injection Site Pruritus			
subjects affected / exposed	5 / 158 (3.16%)	12 / 156 (7.69%)	10 / 148 (6.76%)
occurrences (all)	7	40	25
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 158 (3.16%)	11 / 156 (7.05%)	4 / 148 (2.70%)
occurrences (all)	7	12	4
Oropharyngeal Pain			
subjects affected / exposed	3 / 158 (1.90%)	6 / 156 (3.85%)	1 / 148 (0.68%)
occurrences (all)	3	6	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 158 (5.70%)	3 / 156 (1.92%)	3 / 148 (2.03%)
occurrences (all)	9	3	3
Back Pain			

subjects affected / exposed	6 / 158 (3.80%)	12 / 156 (7.69%)	8 / 148 (5.41%)
occurrences (all)	6	12	8
Infections and infestations			
Bronchitis			
subjects affected / exposed	16 / 158 (10.13%)	19 / 156 (12.18%)	11 / 148 (7.43%)
occurrences (all)	19	21	14
Influenza			
subjects affected / exposed	5 / 158 (3.16%)	9 / 156 (5.77%)	6 / 148 (4.05%)
occurrences (all)	5	9	6
Nasopharyngitis			
subjects affected / exposed	15 / 158 (9.49%)	16 / 156 (10.26%)	15 / 148 (10.14%)
occurrences (all)	18	23	18
Pharyngitis			
subjects affected / exposed	8 / 158 (5.06%)	5 / 156 (3.21%)	3 / 148 (2.03%)
occurrences (all)	9	5	7
Sinusitis			
subjects affected / exposed	11 / 158 (6.96%)	6 / 156 (3.85%)	5 / 148 (3.38%)
occurrences (all)	14	7	7
Upper Respiratory Tract Infection			
subjects affected / exposed	28 / 158 (17.72%)	20 / 156 (12.82%)	22 / 148 (14.86%)
occurrences (all)	39	29	35

Non-serious adverse events	Dupilumab 300 mg q4w	Dupilumab 200 mg q4w	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 157 (61.15%)	74 / 150 (49.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 157 (12.10%)	9 / 150 (6.00%)	
occurrences (all)	32	14	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	12 / 157 (7.64%)	13 / 150 (8.67%)	
occurrences (all)	25	34	
Injection Site Oedema			
subjects affected / exposed	0 / 157 (0.00%)	2 / 150 (1.33%)	
occurrences (all)	0	3	

Injection Site Pain			
subjects affected / exposed	6 / 157 (3.82%)	5 / 150 (3.33%)	
occurrences (all)	13	8	
Injection Site Pruritus			
subjects affected / exposed	0 / 157 (0.00%)	3 / 150 (2.00%)	
occurrences (all)	0	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 157 (4.46%)	3 / 150 (2.00%)	
occurrences (all)	7	3	
Oropharyngeal Pain			
subjects affected / exposed	9 / 157 (5.73%)	3 / 150 (2.00%)	
occurrences (all)	9	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 157 (4.46%)	7 / 150 (4.67%)	
occurrences (all)	7	7	
Back Pain			
subjects affected / exposed	4 / 157 (2.55%)	7 / 150 (4.67%)	
occurrences (all)	5	8	
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 157 (7.01%)	10 / 150 (6.67%)	
occurrences (all)	14	13	
Influenza			
subjects affected / exposed	13 / 157 (8.28%)	10 / 150 (6.67%)	
occurrences (all)	14	12	
Nasopharyngitis			
subjects affected / exposed	19 / 157 (12.10%)	9 / 150 (6.00%)	
occurrences (all)	24	15	
Pharyngitis			
subjects affected / exposed	7 / 157 (4.46%)	3 / 150 (2.00%)	
occurrences (all)	8	4	
Sinusitis			
subjects affected / exposed	13 / 157 (8.28%)	12 / 150 (8.00%)	
occurrences (all)	14	14	

Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	19 / 157 (12.10%) 26	22 / 150 (14.67%) 33	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2013	Following changes were made: Increase in the total expected number of subjects from 600 to 750 subjects to have 300 subjects with HEos due to lower rate for HEos subjects than expected; reliever medication collection data was changed to specify the criterion for qualifying an asthma exacerbation event based on nebulizer use using the nebulizer-to-puff conversion factor for application to LOAC definition; permitted concomitant medications were changed to provide more information on the potential effect of dupilumab on cytochrome P450 (CYP450) and a list of CYP450 substrates with narrow therapeutic window and dose adjustment following the initiation and stopping of dupilumab; exclusion criteria was changed to minimize the impact on the primary endpoint, additional exclusion criteria were implemented for oral corticosteroids and methylxanthines prior to the screening period: pregnancy and breast-feeding were also added; dosing schedule was changed to provide additional instructions on the invetigational medicinal product (IMP) administration related to administration of loading dose and q2w injections; prohibited concomitant medication was changed to correct information for lipoxygenase inhibitor examples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported