Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Children 6 to <12 Years of Age with Uncontrolled Persistent Asthma

Summary

EudraCT number	2016-001607-23
Trial protocol	HU LT PL ES Outside EU/EEA IT RO
Global end of trial date	26 August 2020

Results information

Result version number	v1 (current)
This version publication date	13 March 2021
First version publication date	13 March 2021

Trial information

Trial identification

Sponsor protocol code	EFC14153

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02948959
WHO universal trial number (UTN)	U1111-1179-4851

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	23 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab in children 6 to less than (<) 12 years of age with uncontrolled persistent asthma.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients. 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 minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy:

Stable-dose background therapy of medium dose inhaled corticosteroid (ICS) with a second controller medication (i.e., long-acting β2 agonist [LABA], long acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA] or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication, for at least 3 months with a stable dose greater than or equal to (>=) 1 month prior to screening Visit 1. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Evidence for comparator: -

Actual start date of recruitment	21 April 2017
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: 57
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Chile: 37
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Mexico: 61
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Ukraine: 52
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Hungary: 28

Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Lithuania: 18
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	408
EEA total number of subjects	78

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)	408
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 90 active centres in 17 countries. A total of 631 subjects were screened between 21 April 2017 and 22 July 2019, of which 408 subjects were enrolled and randomised to receive dupilumab or placebo. A total of 223 subjects failed screening mainly due to failure to meet inclusion criteria.

Pre-assignment

Screening details:

Randomisation: stratified by ICS dose level (medium and high), blood eosinophils count (< 0.3 Giga cells/litre [L] and greater than or equal to [>=] 0.3 Giga cells/L), and region (Latin America, Eastern Europe and Western countries). Assignment by Interactive Voice/Web Response System (2:1 ratio) to receive dupilumab/placebo.

Period 1

Period 1 title	52 Weeks Treatment 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

Arm description:

Placebo (for Dupilumab), subcutaneous (SC) injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/ levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

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

Dosage and administration details:

Placebo (for Dupilumab), SC injection q2w for 52 weeks.

Arm title	Dupilumab

Arm description:

Dupilumab 200 milligrams (mg) (in 1.14 mL for >30 kilograms [kg] bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

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

Dosage and administration details:

Dupilumab 200 mg (in 1.14 mL for >30 kg BW) or 100 mg (in 0.67 mL for <= 30 kg BW), SC injection

q2w for 52 weeks.

Number of subjects in period 1	Placebo	Dupilumab
Started	135	273
Treated	135	270
Safety Population	134	271
Type 2 Inflammatory Asthma Phenotype	114 [1]	236 [2]
Baseline Eosinophils Count >=0.3 Giga/L	84 [3]	175 [4]
Completed	130	248
Not completed	5	25
Randomised and not treated	-	3
Consent withdrawn by subject	2	2
Subject used protocol prohibited vaccine	1	6
Randomised by error	-	5
Adverse Event	2	5
Change of residence location	-	1
Poor compliance to protocol	-	2
Non-compliant to study treatment	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Randomised subjects with baseline blood eosinophils >=0.15 G iga/L or baseline fractional exhaled nitric oxide (FeNO) >=20 parts per billion (ppb).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Randomised subjects with baseline blood eosinophils >=0.15 G iga/L or baseline FeNO >=20 ppb.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Randomised subjects with baseline blood eosinophil count >=0 .3 Giga/L.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Randomised subjects with baseline blood eosinophil count >=0 .3 Giga/L.

Period 2

Period 2 title	12 Weeks Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo (for Dupilumab), subcutaneous (SC) injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/ levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

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

Dosage and administration details:

Placebo (for Dupilumab), SC injection q2w for 52 weeks.

Arm title	Dupilumab

Arm description:

Dupilumab 200 milligrams (mg) (in 1.14 mL for >30 kilograms [kg] bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), SC injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

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

Dosage and administration details:

Dupilumab 200 mg (in 1.14 mL for >30 kg BW) or 100 mg (in 0.67 mL for <= 30 kg BW), SC injection q2w for 52 weeks.

Number of subjects in period 2[5]	Placebo	Dupilumab
Started	9	31
Completed	4	19
Not completed	5	12
Consent withdrawn by subject	3	3
Study site closure	1	-
Randomised by error	-	3

Adverse Event	-	2
Change of residence location	-	2
Poor compliance to protocol	1	2

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only subjects who completed treatment, did not continue to 1-year long-term open-label extension study (LTS14424; 2017-003317-25) entered Period 2 (12-week posttreatment follow-up period).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (for Dupilumab), subcutaneous (SC) injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/ levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).	
Reporting group title	Dupilumab
Reporting group description:	
Dupilumab 200 milligrams (mg) (in 1.14 mL for >30 kilograms [kg] bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).	

Reporting group values	Placebo	Dupilumab	Total
Number of subjects	135	273	408
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8.9	8.9	
standard deviation	± 1.6	± 1.7	-
Gender categorical Units: Subjects			
Female	48	98	146
Male	87	175	262
Race Units: Subjects			
Caucasian/White	118	242	360
Black/of African descent	9	11	20
Asian/Oriental	0	2	2
American Indian or Alaska Native	0	1	1
Other	8	17	25

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo (for Dupilumab), subcutaneous (SC) injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/ levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Reporting group title	Dupilumab

Reporting group description:

Dupilumab 200 milligrams (mg) (in 1.14 mL for >30 kilograms [kg] bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Reporting group title	Placebo

Reporting group description:

Placebo (for Dupilumab), subcutaneous (SC) injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/ levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Reporting group title	Dupilumab

Reporting group description:

Dupilumab 200 milligrams (mg) (in 1.14 mL for >30 kilograms [kg] bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), SC injection every 2 weeks (q2w) for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Subject analysis set title	Dupilumab 100 mg q2w
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Dupilumab 100 mg (in 0.67 mL for <=30 kg BW), SC injection q2w for 52 weeks in combination with stable dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/
salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Subject analysis set title	Dupilumab 200 mg q2w
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Dupilumab 200 mg (in 1.14 mL for >30 kg BW), SC injection q2w for 52 weeks in combination with stable dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Primary: Annualised Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point title	Annualised Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point description:

A severe asthma exacerbation event was defined as a deterioration of asthma during the 52-week treatment period requiring: use of systemic corticosteroids for >=3 days; and/or hospitalisation or emergency room visit because of asthma requiring systemic corticosteroid treatment. Annualised event rate was defined as the total number of severe exacerbation events that occurred during the 52-week

treatment period divided by the total number of subject-years followed in the 52-week treatment period. Analysis was performed on type 2 inflammatory asthma phenotype population which included the randomised subjects with baseline blood eosinophil count >=150 cells per microlitre or baseline FeNO >=20 ppb.

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	236		
Units: exacerbations per subject-years				
number (confidence interval 95%)	0.748 (0.542 to 1.034)	0.305 (0.223 to 0.416)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

Risk ratio and p-value was derived using negative binomial model with total number of events onset from randomisation up to Week 52 visit or last contact date (whichever comes earlier) as response variable, with treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to study as covariates and log-transformed standardised observation duration as an offset variable.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Negative binomial model
Parameter estimate	Risk ratio (RR)
Point estimate	0.407
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.274
upper limit	0.605

Notes:

[1] - To control the type-I error rate for the analysis of outcome measure, a hierarchical testing procedure was applied at a 2-sided 5% significant level. Testing was then performed sequentially in the order endpoints were reported. Hierarchical testing sequence continued only if the previous endpoint was statistically significant. Risk ratio, also called relative risk compares the risk (rate) of an event among one group with the risk (rate) among another group.

[2] - Threshold for statistical significance at 5% significant level.

Primary: Annualised Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Annualised Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

A severe asthma exacerbation event was defined as a deterioration of asthma during the 52-week treatment period requiring: use of systemic corticosteroids for >=3 days; and/or hospitalisation or emergency room visit because of asthma requiring systemic corticosteroid treatment. Annualised event rate was defined as the total number of severe exacerbation events that occurred during the 52-week treatment period divided by the total number of subject-years followed in the 52-week treatment period. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population which included the randomised subjects with baseline blood eosinophil count >=300 cells per microlitre.

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	175		
Units: exacerbations per subject-years				
number (confidence interval 95%)	0.665 (0.467 to 0.949)	0.235 (0.160 to 0.345)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

Risk ratio and p-value was derived using negative binomial model with total number of events onset from randomisation up to Week 52 visit or last contact date (whichever comes earlier) as response variable, with treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to study as covariates and log-transformed standardised observation duration as an offset variable.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Negative binomial model
Parameter estimate	Risk ratio (RR)
Point estimate	0.353
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.222
upper limit	0.562

Notes:

[3] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant). Risk ratio, also called relative risk compares the risk (rate) of an event among one group with the risk (rate) among another group.
[4] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Pre-bronchodilator Percent (%) Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 12: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Pre-bronchodilator Percent (%) Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 12: Type 2 Inflammatory Asthma Phenotype Population

End point description:

FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Least square (LS) means and standard error (SE) were derived from mixed-effect model with repeated measures (MMRM) model with change from baseline in pre-bronchodilator % predicted FEV1 value up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here,'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: percent predicted FEV1				
least squares mean (standard error)	5.32 (± 1.36)	10.53 (± 1.01)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 value up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0009 [6]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	5.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.14
upper limit	8.27

Notes:

[5] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[6] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Pre-bronchodilator Percent Predicted Forced

Expiratory Volume in 1 Second at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 value up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here,'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: percent predicted FEV1				
least squares mean (standard error)	4.83 (± 1.54)	10.15 (± 1.12)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 value up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0036 [8]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	5.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.76
upper limit	8.88

Notes:

[7] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[8] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version (ACQ-7-IA) at Week 24: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version (ACQ-7-IA) at Week 24: Type 2 Inflammatory Asthma Phenotype Population

End point description:

ACQ-7-IA: 7 questions, which assessed: frequency of nocturnal awakenings, severity of asthma symptoms in mornings, limitation of daily activities, shortness of breath due to asthma and wheeze, reliever medication use, and FEV1 (% predicted). Subjects recalled their previous week asthma and answered 5 symptom questions on 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Total score: mean of scores of all 7 questions; ranging from 0 (totally controlled) to 6 (severely uncontrolled), higher score indicated lower asthma control. LS means and SE were derived from MMRM model with change from baseline in ACQ-7-IA values up to Week 52 as response variable, and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-7-IA value and baseline-by-visit interaction as covariates. Analysed on type 2 inflammatory asthma phenotype population. 'Number of subjects=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	227		
Units: scores on a scale				
least squares mean (standard error)	-0.99 (± 0.07)	-1.32 (± 0.05)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in ACQ-7-IA up to Week 52 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0001 [10]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.16

Notes:

[9] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[10] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version at Week 24: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version at Week 24: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

ACQ-7-IA: 7 questions, assessed frequency of nocturnal awakenings, severity of asthma symptoms in mornings, limitation of daily activities, shortness of breath due to asthma and wheeze, reliever medication use and FEV1 (% predicted). Subjects recalled previous week asthma and answered 5 symptom questions on 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Total score: mean of scores of all 7 questions; ranging from 0 (totally controlled) to 6 (severely uncontrolled), higher score indicated lower asthma control. LS means and SE: derived from MMRM model with change from baseline in ACQ-7-IA values up to Week 52 as response variable, and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-7-IA value and baseline-by-visit interaction as covariates. Analysed on baseline blood eosinophils >=300 cells per microlitre population. 'Number of subjects=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	166		
Units: scores on a scale				
least squares mean (standard error)	-0.88 (± 0.09)	-1.34 (± 0.06)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in ACQ-7-IA up to Week 52 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.26

Notes:

[11] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[12] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Type 2 Inflammatory Asthma Phenotype Population

End point description:

FeNO is a surrogate marker for airway inflammation. FeNO was analysed using a NIOX instrument or similar analyser using a flow rate of 50 mL/second, and reported in ppb. LS means and SE were derived from MMRM model with change from baseline in FeNO up to Week 12 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline ICS level, visit, treatment by-visit interaction, baseline FeNO value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	226		
Units: parts per billion				
least squares mean (standard error)	-1.13 (± 1.43)	-18.97 (± 1.04)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in FeNO up to Week 12 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FeNO value and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	-17.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.05
upper limit	-14.63

Notes:

[13] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[14] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

FeNO is a surrogate marker for airway inflammation. FeNO was analysed using a NIOX instrument or similar analyser using a flow rate of 50 mL/second, and reported in ppb. LS means and SE were derived from MMRM model with change from baseline in FeNO up to Week 12 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline ICS level, visit, treatment by-visit interaction, baseline FeNO value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	165		
Units: parts per billion				
least squares mean (standard error)	-0.81 (± 1.69)	-21.40 (± 1.21)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

P-value and LS mean difference were derived from MMRM model with change from baseline in FeNO up to Week 12 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FeNO value and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Mixed-effect model with repeated measure
Parameter estimate	LS mean difference
Point estimate	-20.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.6
upper limit	-16.59

Notes:

[15] - Testing was performed according to the hierarchical testing procedure (continued only if the previous endpoint was statistically significant).
[16] - Threshold for statistical significance at 5% significant level.

Secondary: Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: percent predicted FEV1				
least squares mean (standard error)				
Change at Week 2	4.84 (± 1.29)	8.11 (± 0.95)		
Change at Week 4	3.55 (± 1.30)	9.97 (± 0.97)		
Change at Week 8	4.27 (± 1.29)	10.27 (± 0.96)		
Change at Week 24	4.27 (± 1.40)	10.92 (± 1.04)		
Change at Week 36	6.63 (± 1.49)	11.46 (± 1.10)		
Change at Week 52	4.36 (± 1.50)	12.15 (± 1.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre

	Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: percent predicted of FEV1				
least squares mean (standard error)				
Change at Week 2	3.94 (± 1.51)	7.49 (± 1.08)		
Change at Week 4	2.19 (± 1.53)	9.09 (± 1.12)		
Change at Week 8	2.48 (± 1.42)	9.75 (± 1.04)		
Change at Week 24	3.45 (± 1.63)	11.10 (± 1.19)		
Change at Week 36	6.87 (± 1.81)	11.47 (± 1.31)		
Change at Week 52	4.08 (± 1.80)	12.43 (± 1.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During 52-week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point title	Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During 52-week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point description:

The time to first severe exacerbation was defined as date of the first severe exacerbation event - randomisation date +1. A severe asthma exacerbation event was defined as a deterioration of asthma during the 52-week treatment period requiring: use of systemic corticosteroids for >=3 days; and/or hospitalisation related to asthma symptoms or emergency room visit because of asthma requiring systemic corticosteroid treatment. Kaplan-Meier method was used for analysis. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, '99999' has been used as space filler which indicates that median, upper and lower limit 95% confidence interval (CI) was not estimable due to less than 50% of subjects with events.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	236		
Units: days				
median (confidence interval 95%)	99999 (366.0 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During 52-week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During 52-week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

The time to first severe exacerbation was defined as date of the first severe exacerbation event - randomisation date +1. A severe asthma exacerbation event was defined as a deterioration of asthma during the 52-week treatment period requiring: use of systemic corticosteroids for >=3 days; and/or hospitalisation related to asthma symptoms or emergency room visit because of asthma requiring systemic corticosteroid treatment. Kaplan-Meier method was used for analysis. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, '99999' has been used as space filler which indicates that median, upper and lower limit 95% CI was not estimable due to very low number of subjects with events.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	175		
Units: days				
median (confidence interval 95%)	366.0 (265.00 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Loss of Asthma Control (LOAC) Event: Kaplan-Meier Estimates During 52-week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point title	Time to First Loss of Asthma Control (LOAC) Event: Kaplan-Meier Estimates During 52-week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population

End point description:

Time to first LOAC event was date of first LOAC event - first dose date +1. A LOAC event was defined as deterioration of asthma during 52-week treatment period that resulted in any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in 24-hour period (compared to baseline) on 2 consecutive days; increase in ICS dose >=4 times than dose at Visit 2 (Week 0); a decrease in ante meridiem (AM)/post meridiem (PM) peak flow of 30% or more on 2 consecutive days of treatment, based on defined stability limit (defined as respective mean AM/PM peak expiratory flow obtained over last 7 days prior to randomisation (Day 1); severe exacerbation event. Kaplan- Meier method was used for analysis. Analysis was performed on type 2 inflammatory asthma phenotype population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	236		
Units: days				
median (confidence interval 95%)	63.5 (42.00 to 84.00)	140.0 (103.00 to 217.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Loss of Asthma Control Event: Kaplan-Meier Estimates During 52-week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Time to First Loss of Asthma Control Event: Kaplan-Meier Estimates During 52-week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

Time to first LOAC event was date of first LOAC event - first dose date +1. A LOAC event was defined as deterioration of asthma during 52-week treatment period that resulted in any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in 24-hour period (compared to baseline) on 2 consecutive days; increase in ICS dose >=4 times than dose at Visit 2 (Week 0); a decrease in AM/PM peak flow of 30% or more on 2 consecutive days of treatment, based on defined stability limit (defined as respective mean AM/PM peak expiratory flow obtained over last 7 days prior to randomisation (Day 1); severe exacerbation event. Kaplan-Meier method was used for analysis. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	175		
Units: days				
median (confidence interval 95%)	47.5 (38.00 to 84.00)	135.0 (82.00 to 219.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator FEV1 values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-bronchodilator FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.08 (± 0.03)	0.14 (± 0.02)		
Change at Week 4	0.06 (± 0.03)	0.18 (± 0.02)		
Change at Week 8	0.09 (± 0.03)	0.21 (± 0.02)		
Change at Week 12	0.12 (± 0.03)	0.22 (± 0.02)		
Change at Week 24	0.14 (± 0.03)	0.27 (± 0.02)		
Change at Week 36	0.23 (± 0.03)	0.33 (± 0.02)		
Change at Week 52	0.24 (± 0.03)	0.41 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator FEV1 values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-bronchodilator FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.07 (± 0.03)	0.13 (± 0.02)		
Change at Week 4	0.04 (± 0.03)	0.17 (± 0.02)		
Change at Week 8	0.06 (± 0.03)	0.20 (± 0.02)		
Change at Week 12	0.12 (± 0.03)	0.22 (± 0.02)		
Change at Week 24	0.13 (± 0.03)	0.28 (± 0.03)		
Change at Week 36	0.24 (± 0.04)	0.33 (± 0.03)		
Change at Week 52	0.25 (± 0.04)	0.42 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Percent Change From Baseline in Pre-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: percent change				
least squares mean (standard error)				
Change at Week 2	8.07 (± 2.00)	13.38 (± 1.47)		
Change at Week 4	6.73 (± 2.10)	16.01 (± 1.55)		
Change at Week 8	7.68 (± 1.87)	16.33 (± 1.41)		
Change at Week 12	8.87 (± 2.10)	16.94 (± 1.56)		
Change at Week 24	7.66 (± 2.12)	17.61 (± 1.57)		
Change at Week 36	10.88 (± 2.85)	19.19 (± 2.06)		
Change at Week 52	7.92 (± 2.81)	20.06 (± 2.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Percent Change From Baseline in Pre-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

FEV1 was the volume of air (in litres) exhaled from the lungs in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in pre-bronchodilator % predicted FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: percent change				
least squares mean (standard error)				
Change at Week 2	7.55 (± 2.41)	12.76 (± 1.73)		
Change at Week 4	5.81 (± 2.57)	15.20 (± 1.87)		
Change at Week 8	6.09 (± 2.10)	16.01 (± 1.56)		
Change at Week 12	9.56 (± 2.45)	17.14 (± 1.79)		
Change at Week 24	7.44 (± 2.54)	18.09 (± 1.85)		
Change at Week 36	12.15 (± 3.67)	19.65 (± 2.61)		
Change at Week 52	8.50 (± 3.58)	20.97 (± 2.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning (AM) Peak Expiratory Flow (PEF) at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Morning (AM) Peak Expiratory Flow (PEF) at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype 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 AM PEF was performed in morning prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication. Baseline AM PEF was the mean AM measurement recorded for the 7 days prior to the first dose of investigational product. LS means and SE were derived from MMRM model with change from baseline in AM PEF (litres/minute) values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline AM PEF (litres/minute) value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: litres/minute				
least squares mean (standard error)				
Change at Week 2	5.57 (± 2.66)	6.50 (± 2.00)		
Change at Week 4	7.10 (± 3.31)	12.81 (± 2.43)		
Change at Week 8	7.37 (± 3.56)	18.05 (± 2.59)		
Change at Week 12	5.37 (± 3.93)	19.38 (± 2.85)		
Change at Week 24	8.76 (± 4.53)	23.32 (± 3.25)		
Change at Week 36	17.70 (± 4.99)	26.77 (± 3.56)		

Change at Week 52	19.88 (± 5.16)	31.45 (± 3.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening (PM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Evening (PM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype 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 PM PEF was performed in evening prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication. Baseline PM PEF was the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. LS means and SE were derived from MMRM model with change from baseline in PM PEF (litres/minute) values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PM PEF (litres/minute) value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: litres/minute				
least squares mean (standard error)				
Change at Week 2	7.62 (± 2.94)	10.60 (± 2.20)		
Change at Week 4	6.92 (± 3.42)	15.23 (± 2.52)		
Change at Week 8	5.52 (± 3.60)	20.17 (± 2.64)		
Change at Week 12	1.71 (± 3.92)	19.68 (± 2.85)		
Change at Week 24	3.78 (± 4.61)	22.75 (± 3.32)		
Change at Week 36	12.55 (± 5.06)	24.69 (± 3.62)		
Change at Week 52	16.46 (± 5.20)	28.20 (± 3.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning (AM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre

Population

End point title	Change From Baseline in Morning (AM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre 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 AM PEF was performed in morning prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication. Baseline AM PEF was the mean AM measurement recorded for the 7 days prior to the first dose of investigational product. LS means and SE were derived from MMRM model with change from baseline in AM and PM PEF (litres/minute) values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline AM PEF (litres/minute) value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: litres/minute				
least squares mean (standard error)				
Change at Week 2	5.85 (± 2.97)	7.94 (± 2.21)		
Change at Week 4	5.62 (± 3.80)	11.75 (± 2.76)		
Change at Week 8	5.54 (± 4.09)	17.32 (± 2.96)		
Change at Week 12	4.77 (± 4.65)	19.25 (± 3.34)		
Change at Week 24	4.78 (± 5.05)	23.62 (± 3.61)		
Change at Week 36	14.80 (± 5.77)	26.78 (± 4.08)		
Change at Week 52	19.75 (± 6.33)	32.80 (± 4.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening (PM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Evening (PM) Peak Expiratory Flow at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre 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 PM PEF was performed in evening prior to taking any salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication. Baseline PM PEF was the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. LS means and SE were derived from MMRM model with change from baseline in PM PEF (litres/minute) values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PM PEF (litres/minute) value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects

evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: litres/minute				
least squares mean (standard error)				
Change at Week 2	5.64 (± 3.42)	10.02 (± 2.53)		
Change at Week 4	4.36 (± 3.96)	13.09 (± 2.89)		
Change at Week 8	0.92 (± 4.05)	17.51 (± 2.96)		
Change at Week 12	-1.37 (± 4.57)	17.73 (± 3.30)		
Change at Week 24	-1.37 (± 5.21)	20.30 (± 3.74)		
Change at Week 36	7.52 (± 6.01)	23.23 (± 4.26)		
Change at Week 52	14.67 (± 6.39)	26.60 (± 4.54)		

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, 52: Type 2 Inflammatory Asthma Phenotype Population

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

End point description:

FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air (in litres) that can be forcibly blown out after full inspiration in the upright position, measured in litres. LS means and SE were derived from MMRM model with change from baseline in FVC values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FVC value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.07 (± 0.02)	0.07 (± 0.02)		
Change at Week 4	0.07 (± 0.03)	0.11 (± 0.02)		
Change at Week 8	0.10 (± 0.02)	0.13 (± 0.02)		
Change at Week 12	0.12 (± 0.03)	0.14 (± 0.02)		
Change at Week 24	0.16 (± 0.03)	0.20 (± 0.02)		
Change at Week 36	0.22 (± 0.03)	0.28 (± 0.02)		
Change at Week 52	0.27 (± 0.03)	0.37 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Vital Capacity at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Forced Vital Capacity at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air (in litres) that can be forcibly blown out after full inspiration in the upright position, measured in liters. LS means and SE were derived from MMRM model with change from baseline in FVC values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FVC value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.07 (± 0.03)	0.06 (± 0.02)		
Change at Week 4	0.08 (± 0.03)	0.09 (± 0.02)		
Change at Week 8	0.09 (± 0.03)	0.13 (± 0.02)		
Change at Week 12	0.13 (± 0.03)	0.14 (± 0.02)		
Change at Week 24	0.17 (± 0.03)	0.22 (± 0.03)		
Change at Week 36	0.24 (± 0.04)	0.28 (± 0.03)		
Change at Week 52	0.29 (± 0.04)	0.38 (± 0.03)		

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, 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Forced Expiratory Flow (FEF) 25-75% at Weeks 2, 4, 8, 12, 24, 36, 52: Type 2 Inflammatory Asthma Phenotype 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. FEF 25-75% was defined as the mean FEF between 25% and 75% of the FVC, where FVC was defined as the volume of air that can be forcibly blown out after full inspiration in the upright position. LS means and SE were derived from MMRM model with change from baseline in FEF25-75% values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEF 25-75% value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	229		
Units: litres/second				
least squares mean (standard error)				
Change at Week 2	0.11 (± 0.05)	0.28 (± 0.04)		
Change at Week 4	0.07 (± 0.05)	0.34 (± 0.04)		
Change at Week 8	0.10 (± 0.05)	0.39 (± 0.04)		
Change at Week 12	0.14 (± 0.05)	0.41 (± 0.04)		
Change at Week 24	0.16 (± 0.05)	0.44 (± 0.04)		
Change at Week 36	0.29 (± 0.05)	0.49 (± 0.04)		
Change at Week 52	0.29 (± 0.06)	0.60 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Flow 25-75% at Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Forced Expiratory Flow 25-75% at

	Weeks 2, 4, 8, 12, 24, 36, 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre 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. FEF 25-75% was defined as the mean FEF between 25% and 75% of the FVC, where FVC was defined as the volume of air that can be forcibly blown out after full inspiration in the upright position. LS means and SE were derived from MMRM model with change from baseline in FEF25-75% values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEF 25-75% value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	168		
Units: litres/second				
least squares mean (standard error)				
Change at Week 2	0.07 (± 0.05)	0.29 (± 0.04)		
Change at Week 4	0.00 (± 0.05)	0.33 (± 0.04)		
Change at Week 8	0.02 (± 0.06)	0.40 (± 0.04)		
Change at Week 12	0.10 (± 0.05)	0.42 (± 0.04)		
Change at Week 24	0.12 (± 0.06)	0.47 (± 0.04)		
Change at Week 36	0.27 (± 0.06)	0.51 (± 0.05)		
Change at Week 52	0.26 (± 0.07)	0.65 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Post-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

Subjects were assessed for post-bronchodilator FEV1 30 minutes after bronchodilator administration (200 to 400 mg [2 to 4 puffs] of albuterol/salbutamol or 45 to 90 micrograms [2 to 4 puffs] of levalbuterol/levosalbutamol). FEV1 was the volume of air (in litres) exhaled in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in post-bronchodilator FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline post-bronchodilator FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	230		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.61 (± 1.26)	1.51 (± 0.92)		
Change at Week 4	-0.02 (± 1.15)	2.42 (± 0.86)		
Change at Week 8	-0.79 (± 1.21)	2.85 (± 0.90)		
Change at Week 12	-0.32 (± 1.23)	2.48 (± 0.91)		
Change at Week 24	-0.50 (± 1.31)	2.60 (± 0.96)		
Change at Week 36	0.55 (± 1.46)	3.15 (± 1.07)		
Change at Week 52	-0.75 (± 1.48)	3.62 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Post-Bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

Subjects were assessed for post-bronchodilator FEV1 30 minutes after bronchodilator administration (200 to 400 mg [2 to 4 puffs] of albuterol/salbutamol or 45 to 90 micrograms [2 to 4 puffs] of levalbuterol/levosalbutamol). FEV1 was the volume of air (in litres) exhaled in the first second of a forced expiration as measured by spirometer. LS means and SE were derived from MMRM model with change from baseline in post-bronchodilator FEV1 values up to Week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline post-bronchodilator FEV1 value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre opulation. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	169		
Units: litres				
least squares mean (standard error)				
Change at Week 2	0.10 (± 1.49)	0.52 (± 1.07)		
Change at Week 4	-0.29 (± 1.35)	1.44 (± 1.00)		
Change at Week 8	-2.05 (± 1.31)	1.81 (± 0.98)		
Change at Week 12	-0.61 (± 1.44)	2.28 (± 1.04)		
Change at Week 24	-0.80 (± 1.54)	2.25 (± 1.12)		
Change at Week 36	0.72 (± 1.80)	2.87 (± 1.31)		
Change at Week 52	-0.52 (± 1.79)	3.13 (± 1.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning (AM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Morning (AM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

The morning asthma symptom score: evaluated subject’s overall asthma symptoms experienced during the previous night. It ranged from 0 (no asthma symptoms, slept through night) to 4 (bad night, awake most of night due to asthma), where lower scores indicate more mild symptoms and higher scores indicate more severe symptoms. LS means and SE were derived from MMRM model with change from baseline in AM asthma symptom score values up to Week 52 as response variable and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline AM asthma symptom score value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.22 (± 0.04)	-0.18 (± 0.03)		
Change at Week 4	-0.29 (± 0.05)	-0.34 (± 0.04)		
Change at Week 8	-0.37 (± 0.05)	-0.39 (± 0.04)		
Change at Week 12	-0.34 (± 0.05)	-0.48 (± 0.04)		
Change at Week 24	-0.46 (± 0.05)	-0.56 (± 0.04)		
Change at Week 36	-0.48 (± 0.05)	-0.56 (± 0.04)		
Change at Week 52	-0.50 (± 0.05)	-0.61 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening (PM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Evening (PM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

The evening asthma symptom score evaluated subject's overall asthma symptom experienced during the day; ranged from 0 (very well, no asthma symptom) to 4(asthma very bad, unable to carry out daily activities as usual), where lower score indicate mild symptoms and higher scores indicate more severe symptoms. LS means and SE were derived from MMRM model with change from baseline in PM asthma symptom score values up to Week 52 as response variable and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PM asthma symptom score value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma population. 'Number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.17 (± 0.05)	-0.13 (± 0.03)		
Change at Week 4	-0.25 (± 0.05)	-0.29 (± 0.04)		
Change at Week 8	-0.33 (± 0.06)	-0.40 (± 0.04)		
Change at Week 12	-0.30 (± 0.06)	-0.45 (± 0.04)		
Change at Week 24	-0.44 (± 0.06)	-0.53 (± 0.04)		
Change at Week 36	-0.47 (± 0.06)	-0.55 (± 0.04)		
Change at Week 52	-0.50 (± 0.06)	-0.59 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning (AM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per

Microlitre Population

End point title	Change From Baseline in Morning (AM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

The morning asthma symptom score: evaluated subject's overall asthma symptoms experienced during the previous night. It ranged from 0 (no asthma symptoms, slept through night) to 4 (bad night, awake most of night due to asthma), where lower scores indicate more mild symptoms and higher scores indicate more severe symptoms. LS means and SE were derived from MMRM model with change from baseline in AM asthma symptom score values up to Week 52 as response variable and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline AM asthma symptom score value and baseline-by-visit interaction as covariates.Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.24 (± 0.05)	-0.20 (± 0.04)		
Change at Week 4	-0.32 (± 0.06)	-0.34 (± 0.04)		
Change at Week 8	-0.38 (± 0.06)	-0.40 (± 0.05)		
Change at Week 12	-0.33 (± 0.06)	-0.48 (± 0.04)		
Change at Week 24	-0.45 (± 0.06)	-0.55 (± 0.04)		
Change at Week 36	-0.46 (± 0.06)	-0.56 (± 0.04)		
Change at Week 52	-0.50 (± 0.06)	-0.62 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Evening (PM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Evening (PM) Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

The evening asthma symptom score evaluated subject's overall asthma symptom experienced during the day; ranged from 0 (very well, no asthma symptom) to 4(asthma very bad, unable to carry out daily activities as usual), where lower score indicate mild symptoms and higher scores indicate more severe symptoms. LS means and SE were derived from MMRM model with change from baseline in PM asthma symptom score values up to Week 52 as response variable and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PM AS score value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells/microlitre population. 'Number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.18 (± 0.05)	-0.15 (± 0.04)		
Change at Week 4	-0.27 (± 0.06)	-0.29 (± 0.04)		
Change at Week 8	-0.30 (± 0.06)	-0.41 (± 0.05)		
Change at Week 12	-0.29 (± 0.07)	-0.48 (± 0.05)		
Change at Week 24	-0.42 (± 0.06)	-0.53 (± 0.05)		
Change at Week 36	-0.43 (± 0.06)	-0.56 (± 0.05)		
Change at Week 52	-0.51 (± 0.06)	-0.60 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 5-question Version (ACQ-5-IA) at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 5-question Version (ACQ-5-IA) at Weeks 2, 4, 8, 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

ACQ-5-IA has 5 questions, reflecting top-scoring 5 asthma symptoms (AS):frequency of nocturnal awakenings, severity of AS in mornings, limitation of daily activities, shortness of breath and wheeze. Subjects recalled their asthma during the previous week; responded to each of 5 symptom questions on 7-point scale ranging from 0 (no impairment) to 6 (maximum impairment). ACQ-5-IA total score: mean of scores of all 5 questions; ranged from 0 (totally controlled) to 6 (severely uncontrolled), higher scores indicated lower asthma control. LS means and SE were derived from MMRM model with change from baseline in ACQ-5-IA values up to Week 52 as response variable and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-5-IA value and baseline-by-visit interaction as covariates. Analysed on type 2 inflammatory asthma phenotype population. Here, 'Number of subjects analysed=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	227		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.72 (± 0.09)	-0.77 (± 0.06)		
Change at Week 4	-0.86 (± 0.08)	-1.09 (± 0.06)		
Change at Week 8	-1.04 (± 0.09)	-1.24 (± 0.07)		
Change at Week 12	-1.04 (± 0.08)	-1.35 (± 0.06)		
Change at Week 24	-1.18 (± 0.08)	-1.46 (± 0.06)		
Change at Week 36	-1.25 (± 0.08)	-1.57 (± 0.06)		
Change at Week 52	-1.30 (± 0.07)	-1.70 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 5-question Version at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 5-question Version at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

ACQ-5-IA: 5 questions, reflecting top-scoring 5 AS: frequency of nocturnal awakenings, severity of AS in mornings, limitation of daily activities, shortness of breath and wheeze. Subjects recalled asthma during the previous week; responded to each of 5 symptom questions on 7-point scale ranging from 0 (no impairment) to 6 (maximum impairment). ACQ-5-IA total score: mean of scores of all 5 questions; ranged from 0 (totally controlled) to 6 (severely uncontrolled), higher scores indicated lower asthma control. LS means and SE were derived from MMRM model with change from baseline in ACQ-5-IA values up to Week 52 as response variable and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-5-IA value and baseline-by-visit interaction as covariates. Analysed on baseline blood eosinophils >=300 cells per microlitre population.. Here, 'Number of subjects evaluable=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	166		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.63 (± 0.11)	-0.76 (± 0.08)		
Change at Week 4	-0.75 (± 0.10)	-1.10 (± 0.07)		
Change at Week 8	-0.98 (± 0.10)	-1.27 (± 0.07)		
Change at Week 12	-1.00 (± 0.10)	-1.37 (± 0.07)		
Change at Week 24	-1.06 (± 0.09)	-1.48 (± 0.07)		

Change at Week 36	-1.17 (± 0.09)	-1.59 (± 0.07)		
Change at Week 52	-1.25 (± 0.08)	-1.71 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version at Weeks 2, 4, 8, 12, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version at Weeks 2, 4, 8, 12, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

ACQ-7-IA had 7 questions, assessed: frequency of nocturnal awakenings, severity of asthma symptoms in mornings, limitation of daily activities, shortness of breath due to asthma and wheeze, reliever medication use, and FEV1 (% predicted). Subjects recalled their previous week asthma and answered 5 symptom questions on 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Total score: mean of scores of all 7 questions; ranging from 0 (totally controlled) to 6 (severely uncontrolled), higher score indicated lower asthma control. LS means and SE were derived from MMRM model with change from baseline in ACQ-7-IA values up to Week 52 as response variable, and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-7-IA value and baseline-by-visit interaction as covariates. Analysed on type 2 inflammatory asthma phenotype population. 'Number of subjects=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	227		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.60 (± 0.08)	-0.72 (± 0.06)		
Change at Week 4	-0.74 (± 0.07)	-1.03 (± 0.05)		
Change at Week 8	-0.91 (± 0.08)	-1.14 (± 0.06)		
Change at Week 12	-0.89 (± 0.07)	-1.23 (± 0.05)		
Change at Week 36	-1.09 (± 0.07)	-1.41 (± 0.05)		
Change at Week 52	-1.09 (± 0.06)	-1.53 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire-Interviewer

Administered, 7-question Version (ACQ-7-IA) at Weeks 2, 4, 8, 12, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version (ACQ-7-IA) at Weeks 2, 4, 8, 12, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

ACQ-7-IA:7 questions, assessed frequency of nocturnal awakenings, severity of asthma symptoms in mornings, limitation of daily activities, shortness of breath due to asthma and wheeze, reliever medication use, and FEV1 (% predicted). Subjects recalled previous week asthma and answered 5 symptom questions on 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Total score:mean of scores of all 7 questions; ranging from 0 (totally controlled) to 6 (severely uncontrolled), higher score indicated lower asthma control. LS means and SE were derived from MMRM model with change from baseline in ACQ-7-IA values up to Week 52 as response variable, and treatment, age, baseline: weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, ACQ-7-IA value and baseline-by-visit interaction as covariates. Analysed on baseline blood eosinophils >=300 cells per microlitre population. 'Number of subjects=subjects evaluable for this endpoint

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	166		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 2	-0.50 (± 0.09)	-0.70 (± 0.07)		
Change at Week 4	-0.64 (± 0.09)	-1.02 (± 0.06)		
Change at Week 8	-0.83 (± 0.09)	-1.16 (± 0.06)		
Change at Week 12	-0.85 (± 0.09)	-1.24 (± 0.06)		
Change at Week 36	-1.01 (± 0.08)	-1.43 (± 0.06)		
Change at Week 52	-1.04 (± 0.08)	-1.54 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Subjects might had salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication. Number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations recorded daily. In case nebuliser solution used as an alternative delivery method, nebuliser dose converted to number of puffs as per conversion factor: salbutamol/albuterol nebuliser solution (2.5 mg) and levosalbutamol/levalbuterol (1.25 mg) corresponds to 4 puffs. Change From Baseline in number of puffs of reliever medication used per 24 hours at specified weeks was reported in this endpoint. LS means, SE derived from MMRM. Analysis was performed on Type 2 Inflammatory Asthma Phenotype Population. Here, 'number of

subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: puffs of reliever medication per 24 hour				
least squares mean (standard error)				
Change at Week 2	-0.78 (± 0.17)	-0.65 (± 0.12)		
Change at Week 4	-0.99 (± 0.17)	-1.02 (± 0.13)		
Change at Week 8	-1.24 (± 0.17)	-1.28 (± 0.13)		
Change at Week 12	-0.93 (± 0.18)	-1.41 (± 0.13)		
Change at Week 24	-1.43 (± 0.17)	-1.61 (± 0.13)		
Change at Week 36	-1.37 (± 0.17)	-1.60 (± 0.13)		
Change at Week 52	-1.59 (± 0.16)	-1.72 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Number of Puffs of Reliever Medication Used Per 24 Hours at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Number of Puffs of Reliever Medication Used Per 24 Hours at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

Subjects might had salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication. Number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations recorded daily. In case nebuliser solution used as an alternative delivery method, nebuliser dose converted to number of puffs as per conversion factor: salbutamol/albuterol nebuliser solution (2.5 mg) and levosalbutamol/levalbuterol (1.25 mg) corresponds to 4 puffs. Change From Baseline in number of puffs of reliever medication used per 24 hours at specified weeks was reported in this endpoint. LS means, SE derived from MMRM. Analysis was performed on baseline blood eosinophils >=300 cells per microliter population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: puffs of reliever medication per 24 hour				
least squares mean (standard error)				
Change at Week 2	-0.75 (± 0.19)	-0.67 (± 0.14)		
Change at Week 4	-1.02 (± 0.20)	-1.01 (± 0.15)		
Change at Week 8	-1.15 (± 0.20)	-1.29 (± 0.14)		
Change at Week 12	-1.02 (± 0.20)	-1.39 (± 0.14)		
Change at Week 24	-1.25 (± 0.20)	-1.53 (± 0.15)		
Change at Week 36	-1.20 (± 0.21)	-1.49 (± 0.15)		
Change at Week 52	-1.45 (± 0.19)	-1.58 (± 0.14)		

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: Type 2 Inflammatory Asthma Phenotype Population

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

End point description:

Subjects recorded every morning the number of asthma-related nocturnal awakenings requiring use of rescue medication that occurred during the previous night. Change from baseline in number of nocturnal awakenings per night at specified weeks was reported. LS means and SE were derived from MMRM model with change from baseline in number of nocturnal awakenings values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline number of nocturnal awakenings value and baseline-by-visit interaction as covariates. Analysis was performed on type 2 inflammatory asthma phenotype population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	228		
Units: nocturnal awakenings per night				
least squares mean (standard error)				
Change at Week 2	-0.13 (± 0.03)	-0.13 (± 0.02)		
Change at Week 4	-0.16 (± 0.03)	-0.21 (± 0.03)		
Change at Week 8	-0.21 (± 0.04)	-0.21 (± 0.03)		
Change at Week 12	-0.17 (± 0.04)	-0.26 (± 0.03)		
Change at Week 24	-0.23 (± 0.03)	-0.29 (± 0.02)		
Change at Week 36	-0.25 (± 0.03)	-0.29 (± 0.02)		

Change at Week 52	-0.26 (± 0.03)	-0.32 (± 0.02)		

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: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Number of Nocturnal Awakenings Per Night at Weeks 2, 4, 8, 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

Subjects recorded every morning the number of asthma-related nocturnal awakenings requiring use of rescue medication that occurred during the previous night. Change from baseline in number of nocturnal awakenings per night at specified weeks was reported. LS means and SE were derived from MMRM model with change from baseline in number of nocturnal awakenings values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline number of nocturnal awakenings value and baseline-by-visit interaction as covariates. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	167		
Units: nocturnal awakenings per night				
least squares mean (standard error)				
Change at Week 2	-0.15 (± 0.03)	-0.12 (± 0.02)		
Change at Week 4	-0.19 (± 0.04)	-0.21 (± 0.03)		
Change at Week 8	-0.22 (± 0.05)	-0.20 (± 0.04)		
Change at Week 12	-0.16 (± 0.04)	-0.25 (± 0.03)		
Change at Week 24	-0.21 (± 0.04)	-0.28 (± 0.03)		
Change at Week 36	-0.25 (± 0.04)	-0.27 (± 0.03)		
Change at Week 52	-0.26 (± 0.03)	-0.32 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Paediatric Asthma Quality of Life (QoL) Questionnaire With Standardised Activities-Interviewer Administered (PAQLQ[S]

IA) Scores at Weeks 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point title	Change From Baseline in Paediatric Asthma Quality of Life (QoL) Questionnaire With Standardised Activities-Interviewer Administered (PAQLQ[S] IA) Scores at Weeks 12, 24, 36, and 52: Type 2 Inflammatory Asthma Phenotype Population

End point description:

PAQLQ(S)-IA is a disease-specific, interviewer-administered QoL questionnaire, measured functional impairments in children >=7 years with asthma. PAQLQ(S)-IA comprises of 23 items (I) in 3 domains: symptoms (10 I), activity limitation (5 I) and emotional function (8 I). Each item was scored on 7-point likert scale (1=maximal impairment to 7=no impairment). 23 items were averaged to give 1 overall QoL score ranged 1 (severely impaired) to 7 (not impaired at all), higher scores indicated better quality of life. LS means and SE were derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as response variable and treatment, age, baseline - weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score value and baseline-by-visit interaction as covariates. Type 2 inflammatory asthma phenotype population. 'Number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	201		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 12	0.97 (± 0.09)	1.08 (± 0.07)		
Change at Week 24	1.11 (± 0.09)	1.30 (± 0.07)		
Change at Week 36	1.15 (± 0.09)	1.48 (± 0.07)		
Change at Week 52	1.19 (± 0.08)	1.53 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Paediatric Asthma Quality of Life Questionnaire With Standardised Activities-Interviewer Administered Scores at Weeks 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Change From Baseline in Paediatric Asthma Quality of Life Questionnaire With Standardised Activities-Interviewer Administered Scores at Weeks 12, 24, 36, and 52: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

PAQLQ(S)-IA: disease-specific, interviewer-administered QoL questionnaire, measured functional impairments in children >=7 years with asthma. It comprises of 23 items (I) in 3 domains: symptoms (10 I), activity limitation (5 I) and emotional function (8 I). Each item was scored on 7-point likert scale (1=maximal impairment to 7=no impairment). 23 items were averaged to 1 overall QoL score ranged 1 (severely impaired) to 7 (not impaired at all), higher scores indicated better quality of life. LS means and SE were derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as response variable and treatment, age, baseline - weight group, region, eosinophil level, FeNO level, ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score value and baseline-by-visit interaction as covariates. baseline blood eosinophils >=300 cells per microlitre population. 'Number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	149		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 12	0.90 (± 0.10)	1.11 (± 0.08)		
Change at Week 24	1.06 (± 0.10)	1.36 (± 0.08)		
Change at Week 36	1.07 (± 0.10)	1.51 (± 0.08)		
Change at Week 52	1.23 (± 0.09)	1.56 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilisation (HCRU): Number of School and Work Days Missed Due to LOAC: Type 2 Inflammatory Asthma Phenotype Population

End point title	Healthcare Resource Utilisation (HCRU): Number of School and Work Days Missed Due to LOAC: Type 2 Inflammatory Asthma Phenotype Population

End point description:

The number of days missed from school by the subject and the number of days missed from work by the caregiver of subject due to a LOAC were collected in the electronic-case report form (eCRF). Cumulative number of missed days (school days and work days) up to week 52 were computed and summarised using mean and standard deviation (SD). Analysis was performed on type 2 inflammatory asthma phenotype population. For the caregiver data, population assessed was children subject only and the work days missed by their caregiver were counted.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	236		
Units: days				
arithmetic mean (standard deviation)				
Number of missed school days	2.1 (± 4.2)	1.0 (± 2.3)		
Number of missed work days	0.7 (± 1.9)	0.2 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilisation: Number of School and Work Days Missed Due to LOAC: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Healthcare Resource Utilisation: Number of School and Work Days Missed Due to LOAC: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

The number of days missed from school by the subject and the number of days missed from work by the caregiver of subject due to a LOAC were collected in the eCRF. Cumulative number of missed days (school days and work days) up to week 52 were computed and summarised using mean and SD. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population. For the caregiver data, population assessed was children subject only and the work days missed by their caregiver were counted.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	175		
Units: days				
arithmetic mean (standard deviation)				
Number of missed school days	2.0 (± 3.5)	0.9 (± 2.0)		
Number of missed work days	0.6 (± 1.8)	0.2 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilisation: Percentage of Subjects Who Had Missed Greater Than or Equal to 5 School/Work Days Due to LOAC: Type 2 Inflammatory Asthma Phenotype Population

End point title	Healthcare Resource Utilisation: Percentage of Subjects Who Had Missed Greater Than or Equal to 5 School/Work Days Due to LOAC: Type 2 Inflammatory Asthma Phenotype Population

End point description:

The number of days missed from school for the subject and the missed number of days from work for the caregiver due to a LOAC were collected in the eCRF. The percentage of subjects who had at least 5 days (school days and work days) missed due to LOAC over the study period was reported. Analysis was performed on type 2 inflammatory asthma phenotype population.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	236		
Units: percentage of subjects				
number (not applicable)				
Percentage of subjects >=5 school days	17.6	9.8		
Percentage of subjects >=5 work days	7	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilisation: Percentage of Subjects Who Had Missed Greater Than or Equal to 5 School/Work Days Due to LOAC: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point title	Healthcare Resource Utilisation: Percentage of Subjects Who Had Missed Greater Than or Equal to 5 School/Work Days Due to LOAC: Baseline Blood Eosinophils >=300 Cells Per Microlitre Population

End point description:

The number of days missed from school for the subject and the missed number of days from work for the caregiver due to a LOAC were collected in the eCRF. The percentage of subjects who had at least 5 days (school days and work days) missed due to LOAC over the study period was reported. Analysis was performed on baseline blood eosinophils >=300 cells per microlitre population.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	175		
Units: percentage of subjects				
number (not applicable)				
Percentage of subjects >=5 school days	17.9	8.6		
Percentage of subjects >=5 work days	6	0.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With any Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With any Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and did not necessary have to had a causal relationship with treatment. TEAEs were defined as AEs that developed or worsened in grade or became serious during TEAE period which was defined as the period from the time of first dose of study drug to the end of post-treatment period. An SAE was any untoward medical occurrence that at any dose resulted in:death; or life-threatening experience; or required inpatient hospitalisation or prolongation of existing hospitalisation; or resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect or a medically important event. TEAEs included both SAEs and non-SAEs. Analysis was performed on safety population which included all subjects who actually received at least 1 dose or part of a dose of IMP and were analysed according to the actual treatment received.

End point type	Secondary

End point timeframe:

From Baseline up to Week 64

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: subjects				
Any TEAE	107	225		
TESAE	6	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Assessment: Functional Dupilumab Concentration in Serum

End point title	Pharmacokinetics (PK) Assessment: Functional Dupilumab Concentration in Serum

End point description:

Data for this outcome measure was planned to be collected and analysed separately for dupilumab 100 mg and 200 mg dose and not planned to be collected and analysed for placebo arm. Analysis was performed on the PK population which consisted of all subjects who actually received at least 1 dose or part of a dose of the IMP, analysed according to the treatment actually received with at least one non-missing result for functional dupilumab concentration in serum. Here, 'number analysed'=number of subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6, 12, 24, 52, 64

End point values	Dupilumab 100 mg q2w	Dupilumab 200 mg q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	179		
Units: nanograms per millilitre				
geometric mean (geometric coefficient of variation)				
Baseline (n = 90, 178)	0.00 (± 948.683)	0.00 (± 0.000)		
Week 6 (n = 87, 172)	28566.81 (± 47.114)	50269.81 (± 46.667)		
Week 12 (n = 90, 174)	37741.97 (± 46.516)	63476.17 (± 44.444)		
Week 24 (n = 90, 173)	42283.09 (± 47.910)	49525.35 (± 52.806)		
Week 52 (n = 86, 171)	41467.97 (± 49.368)	45295.35 (± 56.990)		
Week 64 (n = 4, 15)	39.00 (± 0.000)	39.00 (± 0.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response

End point title	Percentage of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response[17]

End point description:

ADA response was categorised as: treatment emergent and treatment boosted response. 1) Treatment emergent was defined as an ADA positive response in assay post first dose, when baseline results were negative or missing. 2) Treatment boosted was defined as: an ADA positive response in assay post first dose that was greater-than or equal to 4-fold over baseline titer levels, when baseline results were positive. The criteria for positive was defined as "30 to >10,000", where low titer (< 1,000); moderate (1,000 <= titer <=10,000) and high titer (>10,000). Analysis was performed on ADA population which consisted of all subjects who actually received at least 1 dose or part of a dose of the IMP, analysed according to treatment actually received and had at least one non-missing ADA result (either ADA negative or ADA positive) in the ADA assay after first dose of IMP. Data for this outcome measure was planned to be collected and analysed separately for dupilumab 100 mg and 200 mg dose.

End point type	Secondary

End point timeframe:

From Baseline up to Week 64

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be collected and analysed separately for dupilumab 100 mg and 200 mg dose and not planned to be collected and analysed for overall dupilumab arm.

End point values	Placebo	Dupilumab 100 mg q2w	Dupilumab 200 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	91	178	
Units: percentage of subjects				
number (not applicable)				
Treatment-emergent ADA	3.0	4.4	7.3	

Treatment-boosted ADA	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion

End point title	Percentage of Subjects With Seroconversion

End point description:

Seroconversion was defined as a post-vaccination titer >=40 (1/dilution) for those with a pre-vaccination titer <10 (1/dilution), or a >=4-fold increase in post-vaccination titer for those with a pre-vaccination titer >=10 (1/dilution). Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 52

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of subjects				
number (not applicable)	62.5	79.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to end of post-treatment period (i.e., up to Week 64) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported AEs were treatment emergent AEs that developed/worsened in grade or became serious during 'TEAE period' (from the time of first dose of study drug to the end of post-treatment period [i.e., up to Week 64]). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Dupilumab

Reporting group description:

Dupilumab 200 mg (in 1.14 mL for >30 kg BW) or 100 mg (in 0.67 mL for <=30 kg BW), SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Reporting group title	Placebo

Reporting group description:

Placebo (for Dupilumab), SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication. Subjects were followed up for 12 weeks after last dose (i.e. up to Week 64).

Serious adverse events	Dupilumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 271 (4.80%)	6 / 134 (4.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hand Fracture			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	2 / 271 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune Thrombocytopenia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy To Chemicals			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic Reaction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Hypersensitivity			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Milk Allergy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Vision Blurred			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 271 (1.48%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (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 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Viral Infection			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis Viral			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 271 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	Dupilumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	161 / 271 (59.41%)	89 / 134 (66.42%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 271 (6.64%)	10 / 134 (7.46%)	
occurrences (all)	29	17	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	15 / 271 (5.54%)	1 / 134 (0.75%)	
occurrences (all)	15	1	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	35 / 271 (12.92%)	13 / 134 (9.70%)	
occurrences (all)	153	93	
Injection Site Oedema			
subjects affected / exposed	28 / 271 (10.33%)	7 / 134 (5.22%)	
occurrences (all)	72	15	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	15 / 271 (5.54%)	9 / 134 (6.72%)	
occurrences (all)	17	10	
Rhinitis Allergic			
subjects affected / exposed	16 / 271 (5.90%)	16 / 134 (11.94%)	
occurrences (all)	27	19	
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 271 (6.27%)	14 / 134 (10.45%)	
occurrences (all)	21	22	
Influenza			
subjects affected / exposed	20 / 271 (7.38%)	12 / 134 (8.96%)	
occurrences (all)	22	17	
Nasopharyngitis			
subjects affected / exposed	50 / 271 (18.45%)	29 / 134 (21.64%)	
occurrences (all)	76	45	
Pharyngitis			
subjects affected / exposed	23 / 271 (8.49%)	14 / 134 (10.45%)	
occurrences (all)	27	19	
Sinusitis			
subjects affected / exposed	9 / 271 (3.32%)	7 / 134 (5.22%)	
occurrences (all)	11	10	
Upper Respiratory Tract Infection			
subjects affected / exposed	35 / 271 (12.92%)	18 / 134 (13.43%)	
occurrences (all)	59	30	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	33 / 271 (12.18%)	13 / 134 (9.70%)	
occurrences (all)	41	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2017	• FeNO results were not blinded to Investigators or site personnel. • Exclusion criterion - to clearly define the interval between live (attenuated) vaccines administration and IMP administration and be consistent with other dupilumab trials. • To correct the description of PAQLQ domains and PAQLQ(S)-IA periodicity. • To correct the values for medium and high dose of beclometasone dipropionate (chlorofluorocarbon and hydrofluoroalkane) and budesonide (dry powder inhaler). • Clarification of PEF meter. • To add IMP compliance check. • To clarify that a separate informed assent form had to be obtained from female subjects who started menstruating • Clarification of subject monitoring. • Clarification of PK sample blood volume for paediatric study. • Clarification of vaccination response. • To remove suicidal behavior from the list of AEs of special interests.
18 June 2018	• To increase the sample size due to an update on the assumptions based on the concluded Phase 3 dupilumab clinical trial in adult and adolescent subjects with asthma. • Clarification of an inclusion criterion: reversibility attempts definition during the screening period. • To include new countries/sites in the trial. • Change in schedule of collection of blood samples: change of last possible date for post vaccination sample collection from Week 48 to Week 50. • Clarification that potent dermatological topical corticosteroids were prohibited concomitant medications. • Removal of using prior assessments for re-screening. • To include reliever medication baseline definition. • Change of safety monitoring parameter: to adjust the neutrophil count defining neutropenia (<1000/cubic millimetre) in the study population age group (paediatric trial).
18 October 2019	• To change the study primary efficacy analysis population from an overall uncontrolled persistent asthma population to the population with evidence of either asthma with baseline eosinophil count >=0.3 Giga/L or, more broadly, asthma with the type 2 inflammatory asthma phenotype. • To change the sample size. • To specify the different hierarchy orders used for the United States (US) and US reference countries and European Union (EU) countries and EU reference countries. • Removal of the limit in enrolling subjects according to background therapy with medium dose ICS or blood eosinophil count level. • To describe the planned database lock. • To classify FeNO as a secondary endpoint instead of an exploratory endpoint. • To describe the fasting status. • To allow for home dosing start after Visit 9. • To clarify that ACQ-5 data collected on Visit 2 can be used for inclusion criterion. • To clarify how ACQ-7 value was calculated for statistical analysis. • To clarify deoxyribonucleic acid sample collection timeline. • To remove a sentence on the possible hurdle to public health value of the study in case of study withdrawal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported