Clinical trial results:
A Randomized, Double Blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Persistent Asthma

Summary

EudraCT number	2022-002375-11
Trial protocol	Outside EU/EEA
Global end of trial date	21 May 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	EFC13995

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03782532
WHO universal trial number (UTN)	U1111-1175-0772

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab in subjects with persistent asthma.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adult and adolescent subjects. The parent(s) or guardian(s) 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. Adult subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 412
Country: Number of subjects enrolled	India: 74
Worldwide total number of subjects	486
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	419
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 65 active sites in China and India. A total of 1022 subjects were screened from 25 Jan 2019 to 10 August 2021, out of which 536 were screen failure. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

Randomised subjects to dupilumab or placebo arm by interactive voice/web response system (1:1 ratio). Stratified by age (less than [<]18 years, greater than or equal to [>=]18 years), eosinophil count (<150 cells per microlitre[mcL], 150-299 cells/mcL & >=300 cells/mcL), Baseline oral corticosteroid maintenance (yes/no) & region (China & non-China)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab

Arm description:

Subjects without oral corticosteroids (OCS) maintenance therapy received dupilumab 400 milligrams (mg) loading dose (2 doses of 200 mg) subcutaneous (SC) injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection every 2 weeks (q2w) for 24 weeks. Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks.

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

Dosage and administration details:

Dupilumab 200 mg (175 mg per millilitres [mg/mL] in 1.14 mL) or Dupilumab 300 mg (150 mg/mL in 2 mL) SC injection q2w for 24 weeks. Loading dose (400 mg or 600 mg) SC injection on Day 1 of Week 0.

Arm title	Placebo

Arm description:

Subjects without OCS maintenance therapy received placebo loading dose (matching dupilumab 400 mg) SC on Day 1 (Week 0) followed by placebo (matching dupilumab 200 mg) SC injection q2w for 24 weeks. Subjects on OCS maintenance therapy received placebo loading dose (matching dupilumab 600 mg) SC injection on Day 1 (Week 0) followed by placebo (matching dupilumab 300 mg) SC injection q2w for 24 weeks.

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, 1.14 mL (matching dupilumab 200 mg) and 2 mL (matching dupilumab 300 mg), SC injection q2w for 24 weeks with a loading dose (matching dupilumab 400 mg or 600 mg) SC injection on Day 1 of Week 0.

Number of subjects in period 1	Dupilumab	Placebo
Started	242	244
Safety population	241	243
Received 200 mg dose/1.14 mL	224 [1]	225
Received 300 mg dose/2 mL	17 [2]	18 [3]
Type-2 non-OCS population	205 [4]	209 [5]
Completed	225	222
Not completed	17	22
Other-unspecified	7	6
Randomised and not exposed	1	1
Adverse event	4	2
Poor compliance to protocol	3	-
Withdrawal by subject	2	12
Lack of efficacy	-	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: Subjects without OCS maintenance therapy that received dupilumab 200 mg.

[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: Subjects on OCS maintenance therapy that received dupilumab 300 mg.

[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: Subjects on OCS maintenance therapy that received placebo 2 mL (matching dupilumab 300 mg).

[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: Type 2 inflammatory asthma phenotype without OCS maintenance population (Type-2 non-OCS population): all randomised subjects with type 2 inflammatory asthma phenotype (screening blood eosinophils count >=150 cells/mcL or screening fractional exhaled nitric oxide (FeNO) level >=25 parts per billion [ppb]) that received dupilumab 200 mg and were not on OCS maintenance therapy.

[5] - 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: All randomised subjects with type 2 inflammatory asthma phenotype (screening blood

eosinophils count >=150 cells/mcL or screening FeNO level >=25 ppb) that received placebo (matching dupilumab 200 mg) and were not on OCS maintenance therapy.

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab

Reporting group description:

Subjects without oral corticosteroids (OCS) maintenance therapy received dupilumab 400 milligrams (mg) loading dose (2 doses of 200 mg) subcutaneous (SC) injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection every 2 weeks (q2w) for 24 weeks. Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects without OCS maintenance therapy received placebo loading dose (matching dupilumab 400 mg) SC on Day 1 (Week 0) followed by placebo (matching dupilumab 200 mg) SC injection q2w for 24 weeks. Subjects on OCS maintenance therapy received placebo loading dose (matching dupilumab 600 mg) SC injection on Day 1 (Week 0) followed by placebo (matching dupilumab 300 mg) SC injection q2w for 24 weeks.

Reporting group values	Dupilumab	Placebo	Total
Number of subjects	242	244	486
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 50.4 ± 11.4	 51.5 ± 12.2	 -
Gender categorical Units: Subjects			
Female	135	142	277
Male	107	102	209

End points

End points reporting groups

Reporting group title	Dupilumab

Reporting group description:

Subjects without oral corticosteroids (OCS) maintenance therapy received dupilumab 400 milligrams (mg) loading dose (2 doses of 200 mg) subcutaneous (SC) injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection every 2 weeks (q2w) for 24 weeks. Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects without OCS maintenance therapy received placebo loading dose (matching dupilumab 400 mg) SC on Day 1 (Week 0) followed by placebo (matching dupilumab 200 mg) SC injection q2w for 24 weeks. Subjects on OCS maintenance therapy received placebo loading dose (matching dupilumab 600 mg) SC injection on Day 1 (Week 0) followed by placebo (matching dupilumab 300 mg) SC injection q2w for 24 weeks.

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

Subject analysis set description:

Subjects without OCS maintenance therapy received dupilumab 400 mg loading dose (2 doses of 200 mg) SC injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection q2w for 24 weeks.

Subject analysis set title	Dupilumab 300 mg q2w
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks.

Subject analysis set title	Placebo 1.14 mL q2w
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects without OCS maintenance therapy received placebo 1.14 mL (i.e., matching to dupilumab 200 mg) SC injection q2w for 24 weeks.

Subject analysis set title	Placebo 2 mL q2w
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects on OCS maintenance therapy received placebo 2 mL (i.e., matching to dupilumab 300 mg) SC injection q2w for 24 weeks.

Primary: Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in one Second (FEV1) at Week 12

End point title	Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in one Second (FEV1) at Week 12

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. Least square (LS) mean and standard error (SE) was obtained from mixed-effect model with repeated measures (MMRM) analysis which included subjects who had Baseline, at least one post-baseline value up to Week 12 and no missing covariates. Analysis was performed on type 2 inflammatory asthma phenotype without OCS maintenance population (Type 2 non-OCS) population which included all randomised subjects with type 2 inflammatory asthma phenotype (screening blood eosinophils count >=150 cells/mcL or screening FeNO level >=25 ppb) who were allocated in dupilumab 200 mg q2w/matching placebo groups and were not on OCS maintenance. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	204		
Units: litre				
least squares mean (standard error)	0.37 (± 0.04)	0.06 (± 0.04)		

Statistical analyses

Statistical analysis title	Dupilumab 200 mg versus Placebo

Statistical analysis description:

MMRM model with change from Baseline in pre-bronchodilator FEV1 values up to Week 12 as the response variable, and intervention, age, sex, height, region, screening blood eosinophil level, screening FeNO level, visit, intervention-by-visit interaction, Baseline pre-bronchodilator FEV1 value and Baseline value-by-visit interaction as covariates.

Comparison groups	Dupilumab 200 mg q2w v Placebo 1.14 mL q2w
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.39

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when primary endpoint was statistically significant at two-sided 0.05 level.
[2] - Threshold of significance at 0.05.

Secondary: Change From Baseline in Asthma Control Questionnaire 5 Question Version (ACQ-5) Mean Score at Week 24

End point title	Change From Baseline in Asthma Control Questionnaire 5 Question Version (ACQ-5) Mean Score at Week 24

End point description:

ACQ-5 had 5 questions, assessed 5 symptoms: frequency in past week awoken by asthma during night, severity of asthma symptoms in morning, limitation of daily activities due to asthma, shortness of breath due to asthma and wheeze. Subjects recalled how their asthma had been during previous week and responded to each of 5 symptom questions on 7-point scale, ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total mean score: mean of scores of all 5 questions, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score = lower asthma control. LS Mean SE from MMRM model. Analysis was performed on Type 2 non-OCS population. Here, "number of subjects analysed" = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	205		
Units: score on a scale				
least squares mean (standard error)	-1.29 (± 0.07)	-1.09 (± 0.06)		

Statistical analyses

Statistical analysis title	Dupilumab 200 mg versus Placebo

Statistical analysis description:

MMRM model with change from Baseline in ACQ-5 score values up to Week 24 as response variable and intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline ACQ-5 score value and Baseline value-by-visit interaction as covariates.

Comparison groups	Dupilumab 200 mg q2w v Placebo 1.14 mL q2w
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0097 [4]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.05

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints were reported and continued when previous endpoints was statistically significant at two-sided 0.05 level.
[4] - Threshold of significance at 0.05.

Secondary: Annualised Rate of Severe Exacerbation Events During the 24-week Placebo-controlled Treatment Period

End point title	Annualised Rate of Severe Exacerbation Events During the 24-week Placebo-controlled Treatment Period

End point description:

A severe asthma exacerbation event was defined as a deterioration of asthma during the 24-week placebo-controlled treatment period requiring: use of systemic corticosteroids for >= 3 days; use of systemic corticosteroids at least double the current dose and at least 5 milligrams per day (mg/day) prednisone dose increase or equivalent 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 with onset period from randomisation up to the Week 24 visit or last contact date (whichever came earlier) per subject-year. Analysis was performed on Type 2 non-OCS population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	209		
Units: exacerbations per subject-years				
number (confidence interval 95%)	0.177 (0.088 to 0.357)	0.466 (0.256 to 0.849)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pre-bronchodilator FEV1 at Week 12

End point title	Percent Change From Baseline in Pre-bronchodilator FEV1 at Week 12

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 mean and SE was derived from MMRM model with percent change from Baseline in pre-bronchodilator FEV1 values up to Week 12 as the response variable, and intervention, age, sex, height, region, screening blood eosinophil level, screening FeNO level, visit, intervention-by-visit interaction, Baseline pre-bronchodilator FEV1 value and Baseline value-by-visit interaction as covariates. Analysis was performed on Type 2 non-OCS population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	204		
Units: percent change				
least squares mean (standard error)	28.09 (± 3.25)	4.48 (± 3.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Rate of Loss of Asthma Control (LOAC) Event During the 24-week Placebo-controlled Treatment Period

End point title	Annualised Rate of Loss of Asthma Control (LOAC) Event

	During the 24-week Placebo-controlled Treatment Period

End point description:

LOAC event: any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in 24-hour period (compared with Baseline) on 2 consecutive days, >=20% decrease in pre-bronchodilator FEV1 compared with Baseline, increase in inhaled corticosteroid (ICS) dose >=4 times than dose at randomisation, decrease in morning/evening peak expiratory flow (PEF) of 30%/more on 2 consecutive days of treatment, based on stability limit (mean morning/evening PEF obtained over last 7 days prior to Day 1) and severe exacerbation event (systemic corticosteroids [SC] use >=3 days; SC use at least double current dose and at least 5 mg/day prednisone dose increase/equivalent and/or hospitalisation/emergency visit requiring SC treatment). Annualised rate of LOAC event during 24-week treatment period: number of LOAC events with onset period from randomisation up to Week 24 visit or last contact date (whichever came earlier) per subject-year. Type 2 non-OCS population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	209		
Units: LOAC per subject-year				
number (confidence interval 95%)	0.674 (0.465 to 0.977)	2.214 (1.649 to 2.973)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Rate of Severe Exacerbation Events Resulting in Hospitalisation or Emergency Room Visit During the 24-week Placebo-controlled Treatment Period

End point title	Annualised Rate of Severe Exacerbation Events Resulting in Hospitalisation or Emergency Room Visit During the 24-week Placebo-controlled Treatment Period

End point description:

A severe asthma exacerbation event was defined as a deterioration of asthma during the 24-week placebo-controlled treatment period requiring: use of systemic corticosteroids for >=3 days; use of systemic corticosteroids at least double the current dose and at least 5 mg/day prednisone dose increase or equivalent 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 with onset period from randomisation up to the Week 24 visit or last contact date (whichever came earlier) per subject-year. Annualised rate of severe exacerbation events resulting in hospitalisation or emergency room visit during the 24-week placebo-controlled treatment period was reported in this endpoint. Analysis was performed on Type 2 non-OCS population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	209		
Units: exacerbations per subject-years				
number (confidence interval 95%)	0.048 (0.015 to 0.160)	0.114 (0.042 to 0.311)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Exacerbation Event During the 24-week Placebo-controlled Treatment Period

End point title	Time to First Severe Exacerbation Event During the 24-week Placebo-controlled Treatment Period

End point description:

The time (in days) to first severe exacerbation was defined as onset date of the first severe exacerbation event minus randomisation date +1. A severe asthma exacerbation event was defined as a deterioration of asthma during the 24-week treatment period requiring either use of systemic corticosteroids >=3 days for subjects; use of systemic corticosteroids at least double the current dose and at least 5 mg/day prednisone dose increase or equivalent or hospitalisation or emergency room visit because of asthma, requiring systemic corticosteroids treatment. Kaplan-Meier method was used for analysis. Analysis was performed on Type 2 non-OCS population.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	209		
Units: days				
number (confidence interval 95%)				
12 Weeks	0.049 (0.025 to 0.085)	0.154 (0.109 to 0.206)		
24 Weeks	0.079 (0.047 to 0.121)	0.189 (0.139 to 0.245)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First LOAC During the 24-week Placebo Controlled Treatment Period

End point title	Time to First LOAC During the 24-week Placebo Controlled Treatment Period

End point description:

Time (in days) to first LOAC event was date of first LOAC event minus first dose date +1. LOAC event was defined as deterioration of asthma during 24-week treatment period that resulted in any of the following: 1) >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with Baseline) on 2 consecutive days, 2) >=20% decrease in pre-bronchodilator FEV1 compared with Baseline, 3) increase in ICS dose >=4 times than the dose at randomisation, 4) a decrease in morning or evening PEF of 30% or more on 2 consecutive days of treatment, based on defined stability limit (mean morning/evening PEF obtained over last 7 days prior to Day 1), 5) severe exacerbation event (SC use >=3 days; SC use at least double current dose and at least 5 mg/day prednisone dose increase/equivalent and/or hospitalisation/emergency visit requiring SC treatment). Kaplan-Meier method was used for analysis. Type 2 non-OCS population.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	209		
Units: days				
number (confidence interval 95%)				
12 Weeks	0.152 (0.107 to 0.205)	0.432 (0.364 to 0.498)		
24 Weeks	0.212 (0.158 to 0.270)	0.550 (0.479 to 0.614)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire 7 Question Version (ACQ-7) Score at Week 24

End point title	Change From Baseline in Asthma Control Questionnaire 7 Question Version (ACQ-7) Score at Week 24

End point description:

ACQ-7 had 7 questions: frequency in past week awoken by asthma during night, severity of asthma symptoms in morning, limitation of daily activities due to asthma, shortness of breath due to asthma, wheeze, short-acting bronchodilator use & FEV1 (pre-bronchodilator & % predicted). Subjects recalled how their asthma was during previous week & responded to symptom questions on 7-point scale (0=no impairment, 6=maximum impairment). Total score: mean of scores of all 7 questions; ranged from 0 (totally controlled) to 6 (severely uncontrolled), higher score=lower asthma control. LS means SE: MMRM model with change from Baseline in ACQ-7 score values up to Week 24 as response variable, & intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline ACQ-7 score value & Baseline value-by-visit interaction as covariates. Type 2 non-OCS population. "Number of subjects analysed"=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	205		
Units: score on a scale				
least squares mean (standard error)	-1.17 (± 0.06)	-0.87 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning and Evening Asthma Symptom Score at Week 24

End point title	Change From Baseline in Morning and Evening Asthma Symptom Score at Week 24

End point description:

Morning asthma symptom score (ASS) evaluated subject's overall asthma symptoms experienced during previous night. Score ranged from 0 (no asthma symptoms, slept through night) to 4 (bad night, awake most of night because of asthma). Evening ASS evaluated subject's overall asthma symptoms experienced during day since morning. Score ranged from 0 (very well, no asthma symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual). For morning and evening ASS, lower scores=more mild symptoms. LS Mean and SE:MMRM model with change from Baseline in morning/evening symptom score values up to Week 24 as the response variable, and intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline morning/evening symptom score value and Baseline value-by-visit interaction as covariates. Type 2 non-OCS population. 'Number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198	206		
Units: score on a scale				
least squares mean (standard error)				
Morning Symptom Score	-0.54 (± 0.05)	-0.35 (± 0.05)		
Evening Symptom Score	-0.47 (± 0.05)	-0.30 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Nocturnal Awakenings per Night at Week 24

End point title	Change From Baseline in Nocturnal Awakenings per Night at Week 24

End point description:

Subjects recorded every morning the number of asthma-related nocturnal awakenings that occurred during the previous night. LS Mean and SE derived from MMRM model with change from Baseline in number of nocturnal awakenings/night up to Week 24 as the response variable, and intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline number of nocturnal awakenings/night and Baseline value-by-visit interaction as covariates. Analysis was performed on Type 2 non-OCS population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198	206		
Units: nocturnal awakenings per night				
least squares mean (standard error)	-0.34 (± 0.03)	-0.24 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Number of Puffs of Daily Reliever Medication Used Per 24 Hours at Week 24

End point title	Change From Baseline in Number of Puffs of Daily Reliever Medication Used Per 24 Hours at Week 24

End point description:

Subjects might be administered salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed. Number of reliever medication inhalations were recorded daily in electronic diary. When nebuliser solutions were used as alternative delivery method, nebuliser dose was 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. LS Mean and SE: MMRM model with change from Baseline in numbers of puffs of reliever medication/24 hours values up to Week 24 as the response variable, and intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline number of puffs of reliever medication/24 hours and Baseline value-by-visit interaction as covariates. Analysis was performed on Type 2 non-OCS population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198	206		
Units: puffs of reliever medication per 24 hour				
least squares mean (standard error)	-0.64 (± 0.11)	-0.32 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Quality Of Life Questionnaire With Standardised Activities (>=12 years) (AQLQ) at Week 24

End point title	Change From Baseline in Asthma Quality Of Life Questionnaire With Standardised Activities (>=12 years) (AQLQ) at Week 24

End point description:

AQLQ was designed to measure functional impairments that were most troublesome to subjects as a result of their asthma. The AQLQ comprised of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item was scored on 7-point likert scale (1=severely impaired to 7=not impaired). 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired). Higher scores indicated better quality of life. LS Mean SE derived from MMRM model with change from Baseline in AQLQ score values up to Week 24 as the response variable, and intervention, age, region, screening blood eosinophil level, screening FeNO level, visit, intervention by-visit interaction, Baseline AQLQ score value and Baseline value-by-visit interaction as covariates. Type 2 non-OCS population. 'Number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	203		
Units: score on a scale				
least squares mean (standard error)	1.09 (± 0.08)	0.76 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) at Week 24

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) at Week 24

End point description:

EQ-5D-5L: standardised subject-rated questionnaire to assess health related quality of life (HRQOL), included 2 components: EQ-5D descriptive system and EQ Visual Analog Scale (VAS). EQ-5D descriptive system comprised 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. Each dimension had 5-levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Response options were measured with 5-point Likert scale. The 5D-5L

systems were converted into a single index utility score between 0 to 1. Higher score=better health state. EQ-5D-5L VAS rated subject's current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). LS Mean SE from MMRM model. Analysis was performed on Type 2 non-OCS population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Dupilumab 200 mg q2w	Placebo 1.14 mL q2w		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	203		
Units: score on a scale				
least squares mean (standard error)				
Single Index Score	0.11 (± 0.01)	0.07 (± 0.01)		
VAS	7.47 (± 1.26)	3.88 (± 1.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAE) and Adverse Events of Special Interest (AESI)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAE) and Adverse Events of Special Interest (AESI)

End point description:

AE: any untoward medical occurrence in subjects who received investigational medicinal product (IMP) & not necessarily have causal relationship with treatment. TEAEs: AEs developed/worsened in grade/become serious during TEAE period (from 1st IMP dose up to 98 days after last IMP dose).SAE: any untoward medical occurrence at any dose resulted in death, was life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was congenital anomaly/birth defect or was medically important event. AESI:AE(serious/non-serious) of scientific & medical concern specific to Sponsor's product/program, for which ongoing monitoring & immediate notification by Investigator to Sponsor required. Safety population: all randomised subjects who had taken at least 1 dose of IMP, regardless of amount of treatment administered. Safety data collection & analysis: planned separately per doses for dupilumab &

End point type	Secondary

End point timeframe:

From first dose of IMP administration up to last dose of IMP administration + 98 days (i.e., Up to Week 36)

End point values	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Placebo 1.14 mL q2w	Placebo 2 mL q2w
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	224	17	225	18
Units: subjects				
number (not applicable)				
TEAEs	187	16	177	13
TESAEs	21	0	21	2
AESIs	9	1	8	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of IMP up to 98 days after last dose of IMP (maximum duration: up to Week 36)

Adverse event reporting additional description:

Reported AEs were TEAEs that developed or worsened or became serious during the TEAE period (defined as the time from the first dose of the IMP up to 98 days after last dose of the IMP). Analysed on safety population. Safety data was planned to be collected and reported separately for each dose of dupilumab and each volume of placebo administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo 1.14 mL q2w

Reporting group description:

Subjects without OCS maintenance therapy received placebo 1.14 mL (i.e., matching to dupilumab 200 mg) SC injection q2w for 24 weeks.

Reporting group title	Dupilumab 200 mg q2w

Reporting group description:

Subjects without OCS maintenance therapy received dupilumab 400 mg loading dose (2 doses of 200 mg) SC injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection q2w for 24 weeks.

Reporting group title	Placebo 2 mL q2w

Reporting group description:

Subjects without OCS maintenance therapy received placebo 2 mL (i.e., matching to dupilumab 300 mg) SC injection q2w for 24 weeks.

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks.

Serious adverse events	Placebo 1.14 mL q2w	Dupilumab 200 mg q2w	Placebo 2 mL q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 225 (9.33%)	21 / 224 (9.38%)	2 / 18 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	9 / 225 (4.00%)	7 / 224 (3.13%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 13	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Cavitation			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal Cord Polyp			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic Attack			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	2 / 225 (0.89%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cor Pulmonale Chronic			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain Stem Infarction			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Chalazion			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Functional Gastrointestinal Disorder			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Polyps			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			

subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 225 (0.44%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Osteoarthritis			

subjects affected / exposed	0 / 225 (0.00%)	2 / 224 (0.89%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bartholin's Abscess			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 Pneumonia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 225 (0.89%)	1 / 224 (0.45%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 300 mg q2w		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Cavitation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vocal Cord Polyp			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic Attack			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius Fracture			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cor Pulmonale Chronic			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary Artery Disease			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain Stem Infarction			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Functional Gastrointestinal Disorder			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric Polyps			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large Intestine Polyp			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small Intestinal Obstruction			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			

subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoporosis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Osteoarthritis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bartholin's Abscess				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Covid-19 Pneumonia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo 1.14 mL q2w	Dupilumab 200 mg q2w	Placebo 2 mL q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 225 (56.89%)	146 / 224 (65.18%)	13 / 18 (72.22%)
General disorders and administration site conditions			
Face Oedema			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injection Site Erythema			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injection Site Pain			
subjects affected / exposed	0 / 225 (0.00%)	3 / 224 (1.34%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Injection Site Reaction			
subjects affected / exposed	3 / 225 (1.33%)	10 / 224 (4.46%)	0 / 18 (0.00%)
occurrences (all)	4	27	0
Injection Site Swelling			
subjects affected / exposed	1 / 225 (0.44%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pyrexia			

subjects affected / exposed	10 / 225 (4.44%)	7 / 224 (3.13%)	0 / 18 (0.00%)
occurrences (all)	11	8	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	14 / 225 (6.22%)	13 / 224 (5.80%)	3 / 18 (16.67%)
occurrences (all)	17	17	3
Haemoptysis			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	5 / 225 (2.22%)	4 / 224 (1.79%)	1 / 18 (5.56%)
occurrences (all)	5	4	2
Productive Cough			
subjects affected / exposed	2 / 225 (0.89%)	4 / 224 (1.79%)	1 / 18 (5.56%)
occurrences (all)	2	4	1
Rhinitis Allergic			
subjects affected / exposed	8 / 225 (3.56%)	7 / 224 (3.13%)	1 / 18 (5.56%)
occurrences (all)	13	7	1
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	8 / 225 (3.56%)	18 / 224 (8.04%)	0 / 18 (0.00%)
occurrences (all)	9	22	0
Blood Glucose Increased			
subjects affected / exposed	3 / 225 (1.33%)	9 / 224 (4.02%)	2 / 18 (11.11%)
occurrences (all)	3	11	2
Eosinophil Count Increased			
subjects affected / exposed	3 / 225 (1.33%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Protein Urine Present			

subjects affected / exposed	4 / 225 (1.78%)	5 / 224 (2.23%)	1 / 18 (5.56%)
occurrences (all)	4	5	1
Qrs Axis Abnormal			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Skin Laceration			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 225 (1.78%)	5 / 224 (2.23%)	0 / 18 (0.00%)
occurrences (all)	4	5	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 225 (0.00%)	5 / 224 (2.23%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Leukocytosis			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 225 (0.44%)	2 / 224 (0.89%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Abdominal Pain			
subjects affected / exposed	2 / 225 (0.89%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Abdominal Pain Upper			

subjects affected / exposed	1 / 225 (0.44%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Chronic Gastritis			
subjects affected / exposed	2 / 225 (0.89%)	1 / 224 (0.45%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Gingival Pain			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 225 (0.44%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	4 / 225 (1.78%)	5 / 224 (2.23%)	1 / 18 (5.56%)
occurrences (all)	4	5	2
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	2 / 225 (0.89%)	7 / 224 (3.13%)	1 / 18 (5.56%)
occurrences (all)	4	7	1
Dermatitis Atopic			
subjects affected / exposed	2 / 225 (0.89%)	2 / 224 (0.89%)	1 / 18 (5.56%)
occurrences (all)	2	2	1
Skin Irritation			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal Cyst			
subjects affected / exposed	1 / 225 (0.44%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 225 (1.78%)	11 / 224 (4.91%)	0 / 18 (0.00%)
occurrences (all)	5	11	0
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 225 (0.89%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	2	1	0

Osteoarthritis			
subjects affected / exposed	1 / 225 (0.44%)	3 / 224 (1.34%)	1 / 18 (5.56%)
occurrences (all)	1	3	1
Pain In Extremity			
subjects affected / exposed	2 / 225 (0.89%)	4 / 224 (1.79%)	0 / 18 (0.00%)
occurrences (all)	2	4	0
Tenosynovitis			
subjects affected / exposed	0 / 225 (0.00%)	2 / 224 (0.89%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Infections and infestations			
Bacterial Infection			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Bronchitis			
subjects affected / exposed	10 / 225 (4.44%)	10 / 224 (4.46%)	1 / 18 (5.56%)
occurrences (all)	14	15	1
Conjunctivitis			
subjects affected / exposed	4 / 225 (1.78%)	6 / 224 (2.68%)	0 / 18 (0.00%)
occurrences (all)	4	6	0
Gastroenteritis			
subjects affected / exposed	7 / 225 (3.11%)	9 / 224 (4.02%)	0 / 18 (0.00%)
occurrences (all)	7	10	0
Influenza			
subjects affected / exposed	0 / 225 (0.00%)	3 / 224 (1.34%)	1 / 18 (5.56%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	13 / 225 (5.78%)	14 / 224 (6.25%)	0 / 18 (0.00%)
occurrences (all)	17	22	0
Respiratory Tract Infection			
subjects affected / exposed	7 / 225 (3.11%)	6 / 224 (2.68%)	0 / 18 (0.00%)
occurrences (all)	9	9	0
Tonsillitis			
subjects affected / exposed	2 / 225 (0.89%)	1 / 224 (0.45%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Upper Respiratory Tract Infection			

subjects affected / exposed	58 / 225 (25.78%)	54 / 224 (24.11%)	4 / 18 (22.22%)
occurrences (all)	85	87	4
Urinary Tract Infection			
subjects affected / exposed	7 / 225 (3.11%)	6 / 224 (2.68%)	0 / 18 (0.00%)
occurrences (all)	7	6	0
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	5 / 225 (2.22%)	7 / 224 (3.13%)	0 / 18 (0.00%)
occurrences (all)	8	8	0
Hypokalaemia			
subjects affected / exposed	5 / 225 (2.22%)	4 / 224 (1.79%)	1 / 18 (5.56%)
occurrences (all)	8	4	1
Metabolic Disorder			
subjects affected / exposed	0 / 225 (0.00%)	0 / 224 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Dupilumab 300 mg q2w		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)		
General disorders and administration site conditions			
Face Oedema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injection Site Erythema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Injection Site Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injection Site Reaction			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Injection Site Swelling			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	5		
Haemoptysis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oropharyngeal Pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Productive Cough			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Rhinitis Allergic			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Blood Glucose Increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eosinophil Count Increased			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Protein Urine Present			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Qrs Axis Abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Skin Laceration			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Leukocytosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Abdominal Pain			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Abdominal Pain Upper subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Chronic Gastritis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Gingival Pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hepatobiliary disorders Hepatic Function Abnormal subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3		
Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Dermatitis Atopic subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Skin Irritation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Renal and urinary disorders Renal Cyst subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		

Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pain In Extremity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Tenosynovitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bacterial Infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory Tract Infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tonsillitis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	11		
Urinary Tract Infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Metabolic Disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2018	Following changes were done: Changed the dose regimen from 4 arms to 2 arms, specified the dose regimens and added the rationale for dose selection. Optimised study procedures. Removed data monitoring committee. Optimised inclusion and exclusion criteria. Allowed OCS dependent subjects to be enrolled in the study. Optimised IMP and non-investigational medicinal product (NIMP) management. Prohibited traditional Chinese medicine or other herbal medications during study. Updated information related to cytochrome P450 substrates. Re-organised endpoints based on new product data and selected doses. Updated AESI list and safety instruction. Changed statistical considerations based on new product data and the changes on the study design.
25 November 2019	Following changes were done: Modified primary population to 'persistent asthma subjects with type 2 inflammation'. Rationale and definition were added to reflect revised primary population (persistent asthma subjects with type 2 inflammation). Added inclusion criteria "For subjects not requiring maintenance OCS, screening blood eosinophil count >=150 cells/mcL or FENO >=25 ppb; for subjects requiring maintenance OCS, there was no minimum requirement for blood eosinophil count and FENO level". Updated exclusion criteria to make it more precise. Subjects with history of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients, should be excluded from study. When failure of a subject to meet inclusion criteria was caused by incidental transitory conditions (e.g. subjects did not fill in ACQ correctly), subject was be allowed to be re-screened. Removed description of population 'subjects with 200 mg q2w regimen' in primary, secondary and other endpoints. Removed key secondary endpoint 'absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in overall population'. Added 'spirometry would be performed centrally, and all recordings would be centrally read by independent experts'. Modified ACQ-7 as 'Subject should complete first 6 items of ACQ-7 before spirometry test'. Changed 'Nitrate' to 'Nitrite'. Removed example for method of test and name of company. Added measurement for blood eosinophil count and FENO as 'Entry criteria at Visit 1 include blood eosinophil count >=150 cells/mcL or FENO >=25ppb for non-OCS maintenance subjects'. Modified as 'anaphylactic reactions or systemic allergic reactions that were related to IMP and required treatment'. Sample size was recalculated based on observed effect size from QUEST study in revised primary analysis population of subjects with type 2 inflammation. Analysis and definition of ADA modified. Updated general guidance for follow up laboratory abnormalities. Added two appendices.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported