Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel-group, 52-week pivotal study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation

Summary

EudraCT number	2018-001953-28
Trial protocol	DE SE DK FI CZ HU PL SK BG IT RO
Global end of trial date	02 May 2023

Results information

Result version number	v1 (current)
This version publication date	27 April 2024
First version publication date	27 April 2024

Trial information

Trial identification

Sponsor protocol code	EFC15804

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03930732
WHO universal trial number (UTN)	U1111-1211-8804

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab 300 milligrams (mg) administered every 2 weeks (q2w) in participants with acute moderate or severe chronic obstructive pulmonary disease (COPD) as measured by annualized rate of acute moderate or severe COPD exacerbation (AECOPD).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of 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 trail, 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	15 April 2019
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: 76
Country: Number of subjects enrolled	Bulgaria: 49
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Chile: 99
Country: Number of subjects enrolled	China: 107
Country: Number of subjects enrolled	Czechia: 31
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 5
Country: Number of subjects enrolled	Mexico: 50
Country: Number of subjects enrolled	Poland: 37

Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Slovakia: 23
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	United States: 104
Worldwide total number of subjects	939
EEA total number of subjects	306

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	393
From 65 to 84 years	546
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 275 centers in 24 countries. A total of 2599 participants were screened from 09 May 2019 to 12 Jan 2022, of which 1660 were screen failures due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 939 participants were randomized in a 1:1 ratio to receive either dupilumab 300 mg q2w or matching placebo for 52 weeks.

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, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to dupilumab 300 mg as subcutaneous (SC) injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, end of treatment [EOT] visit occurred 2 weeks after last administration of treatment i.e., at Week 52).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered in identically matched glass pre-filled syringe to deliver 2 milliliter (mL) which matched dupilumab 300 mg q2w up to 52 weeks. SC injection sites alternated between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during consecutive visits.

Arm title	Dupilumab 300 mg q2w

Arm description:

Participants received dupilumab 300 mg administered as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52).

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	SAR231893/REGN668, Dupixent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dupilumab was administered for SC administration and supplied as 150 mg/mL solution in 2.25 mL prefilled glass syringes to deliver 300 mg in 2.0 mL q2w up to 52 weeks. SC injection sites alternated between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during consecutive visits.

Number of subjects in period 1	Placebo	Dupilumab 300 mg q2w
Started	471	468
Completed	434	440
Not completed	37	28
Consent withdrawn by subject	23	11
Other, not related to Coronavirus Disease-2019	5	8
Adverse event, non-fatal	9	7
Poor compliance to protocol	-	1
Other, related to Coronavirus Disease-2019	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab 300 mg as subcutaneous (SC) injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, end of treatment [EOT] visit occurred 2 weeks after last administration of treatment i.e., at Week 52).	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Participants received dupilumab 300 mg administered as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52).	

Reporting group values	Placebo	Dupilumab 300 mg q2w	Total
Number of subjects	471	468	939
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.2	65.0	
standard deviation	± 8.1	± 8.0	-
Gender categorical Units: Subjects			
Female	149	170	319
Male	322	298	620
Race Units: Subjects			
American Indian or Alaska Native	4	3	7
Asian	67	67	134
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	3	5
White	397	393	790
More than one race	0	2	2
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab 300 mg as subcutaneous (SC) injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, end of treatment [EOT] visit occurred 2 weeks after last administration of treatment i.e., at Week 52).	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Participants received dupilumab 300 mg administered as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52).	
Subject analysis set title	Dupilumab 300 mg q2w-Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received dupilumab 300 mg administered as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52). One participant was exposed to different treatment other than planned (was randomized to placebo arm but received dupilumab on Day 40). The actual arm was considered as dupilumab 300 mg q2w. In safety analyses, the actual arms are used.	

Primary: Annualized Rate of Moderate or Severe COPD Exacerbations Over the 52-Week Treatment Period

End point title	Annualized Rate of Moderate or Severe COPD Exacerbations Over the 52-Week Treatment Period
End point description:	
Moderate exacerbations were recorded by the Investigator and defined as AECOPD that required either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations were also recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they were separated by at least 14 days. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated. Events were adjudicated by independent third party. The intent-to-treat (ITT) population consisted of the randomized population analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to Week 52	

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	468		
Units: exacerbation per participant-year				
number (confidence interval 95%)	1.01 (0.931 to 1.301)	0.776 (0.645 to 0.934)		

Statistical analyses

Statistical analysis title	Annualized rate-COPD exacerbations over 52 weeks

Statistical analysis description:

Derived using negative binomial model with the total number of the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), inhaled corticosteroid (ICS) dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	939
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0005
Method	Negative binomial model
Parameter estimate	Risk difference (RD)
Point estimate	-0.324
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.508
upper limit	-0.14

Notes:

[1] - A hierarchical testing procedure was used to control type I error and handle primary and a few secondary endpoint analyses at a 2-sided significance level of 0.049. Testing was then performed sequentially in the order the endpoints are reported (till OM 9). The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.049 level. Parameter estimate derived using delta method.

Secondary: Change From Baseline in Pre-Bronchodilator (BD) Forced Expiratory Volume in one Second (FEV1) at Week 12

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

End point description:

The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed after a wash out period of bronchodilators according to their action duration. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 12

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	466		
Units: liters				
least squares mean (standard error)	0.077 (± 0.018)	0.160 (± 0.018)		

Statistical analyses

Statistical analysis title	Change from Baseline in Pre-BD FEV1 at Week 12

Statistical analysis description:

Derived from mixed-effect model with repeated measures (MMRM) model with the change from baseline in pre-BD FEV1 up to Week 12 as response variables, and treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-BD FEV1, and FEV1 baseline-by-visit interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	MMRM model
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.125

Notes:

[2] - Threshold for significance at 0.049 level.

Secondary: Change From Baseline in Pre-BD FEV1 at Week 52

End point title	Change From Baseline in Pre-BD FEV1 at Week 52

End point description:

The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed after a wash out period of bronchodilators according to their action duration. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	466		
Units: liters				
least squares mean (standard error)	0.070 (± 0.019)	0.153 (± 0.019)		

Statistical analyses

Statistical analysis title	Change from Baseline in Pre-BD FEV1 at Week 52

Statistical analysis description:

Derived from MMRM model with the change from baseline in pre-BD FEV1 up to Week 52 as response variables, and treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at

screening, visit, treatment-by-visit interaction, baseline pre-BD FEV1, and FEV1 baseline-by-visit interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [3]
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.128

Notes:

[3] - Threshold for significance at 0.049 level.

Secondary: Change From Baseline in Pre-BD FEV1 at Week 12 in Subgroup of Participants With Baseline Fractional Exhaled Nitric Oxide (FeNO) >=20 Parts per Billion (Ppb)

End point title	Change From Baseline in Pre-BD FEV1 at Week 12 in Subgroup of Participants With Baseline Fractional Exhaled Nitric Oxide (FeNO) >=20 Parts per Billion (Ppb)

End point description:

FeNO is a demonstrated biomarker of type 2 airway inflammation in respiratory diseases. FeNO was analyzed using a NIOX instrument or similar analyzer using a flow rate of 50 milliliter per second (mL/s) and reported in ppb. This assessment was conducted prior to spirometry and following a fast of at least 1 hour. The subgroup of participants with baseline FeNO >=20 ppb within the ITT population were included. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 12

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	193		
Units: liters				
least squares mean (standard error)	0.108 (± 0.035)	0.232 (± 0.034)		

Statistical analyses

Statistical analysis title	Change from baseline-subgroup FeNO>=20 ppb:Week 12

Statistical analysis description:

Derived from MMRM model with the change from baseline in pre-BD FEV1 up to Week 12 as response variables, and treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-BD FEV1, and FEV1 baseline-by-visit

interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [4]
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.203

Notes:

[4] - Threshold for significance at 0.049 level.

Secondary: Change From Baseline in Pre-BD FEV1 at Week 52 in Subgroup of Participants With Baseline FeNO >=20 Ppb

End point title	Change From Baseline in Pre-BD FEV1 at Week 52 in Subgroup of Participants With Baseline FeNO >=20 Ppb

End point description:

FeNO is a demonstrated biomarker of type 2 airway inflammation in respiratory diseases. FeNO was analyzed using a NIOX instrument or similar analyzer using a flow rate of 50 mL/s and reported in ppb. This assessment was conducted prior to spirometry and following a fast of at least 1 hour. The subgroup of participants with baseline FeNO >=20 ppb within the ITT population were included. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	193		
Units: liters				
least squares mean (standard error)	0.120 (± 0.037)	0.247 (± 0.036)		

Statistical analyses

Statistical analysis title	Change from baseline-subgroup FeNO>=20 ppb:Week 52

Statistical analysis description:

Derived from MMRM model with the change from baseline in pre-BD FEV1 up to Week 52 as response variables, and treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-BD FEV1, and FEV1 baseline-by-visit interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034 [5]
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.212

Notes:

[5] - Threshold for significance at 0.049 level.

Secondary: Change From Baseline in Saint (St.) George's Respiratory Questionnaire (SGRQ) Total Score at Week 52

End point title	Change From Baseline in Saint (St.) George's Respiratory Questionnaire (SGRQ) Total Score at Week 52

End point description:

The SGRQ was a 50-item self-administered questionnaire designed to measure and quantify health status in adult participants with chronic airflow limitation and rated on electronic diary. Scores by dimension were calculated for 3 domains: symptoms, activity and impacts (psycho-social) as well as a total score. Global and domain scores range from 0 to 100, with 100 representing the worst possible health status and 0 indicating the best possible health status. Higher score indicates worse health status/heath related quality of life. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	456	456		
Units: score on a scale				
least squares mean (standard error)	-6.369 (± 0.816)	-9.732 (± 0.810)		

Statistical analyses

Statistical analysis title	Change from baseline in SGRQ total score: Week 52

Statistical analysis description:

Derived from MMRM model with the change from baseline in SGRQ total score up to Week 52 as response variables, and treatment group, region (pooled country), ICS dose, smoking status at screening, treatment-by-visit interaction, baseline SGRQ total score, and SGRQ baseline-by-visit interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [6]
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	-3.363
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.459
upper limit	-1.266

Notes:

[6] - Threshold for significance at 0.049 level.

Secondary: Percentage of Participants With SGRQ Improvement >=4 Points at Week 52

End point title	Percentage of Participants With SGRQ Improvement >=4 Points at Week 52

End point description:

A responder was defined as a participant with improvement from baseline in SGRQ total score at Week 52 by >=4 points. Participants with improvement <4 points or with missing values were considered as non-responders. The percentage (%) of participants (pts) who achieved a clinically meaningful response in SGRQ total score (reduction [improvement] by >=4 points)/responders are reported. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	468		
Units: percentage of participants				
number (not applicable)	43.1	51.5		

Statistical analyses

Statistical analysis title	% of pts-SGRQ Improvement >=4 points: Week 52

Statistical analysis description:

Derived from logistic regression model which includes treatment group, region (pooled country), ICS dose, smoking status at screening, and baseline SGRQ total score as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	939
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.439
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.096
upper limit	1.89

Notes:

[7] - Threshold for significance at 0.049 level.

Secondary: Change From Baseline in Evaluating Respiratory Symptoms (E-RS) in COPD (E-RS: COPD) RS-Total Score at Week 52

End point title	Change From Baseline in Evaluating Respiratory Symptoms (E-RS) in COPD (E-RS: COPD) RS-Total Score at Week 52

End point description:

The E-RS in COPD scale was a part of the exacerbations of chronic pulmonary disease tool (EXACT). It was a derivative instrument used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD. E-RS: COPD RS-Total Score was derived based on weekly averages of daily assessed 11 respiratory symptom items contained in the 14-item EXACT questionnaire. The RS-Total Score represented overall respiratory symptom severity, ranged from 0 to 40. Summation procedure was used to derive the three daily domain scores: 1). RS-Breathlessness (range 0–17), 2) RS-Cough and Sputum (score range 0–11), 3) RS-Chest Symptoms (score range 0–12). The higher the score, more severe were the symptoms. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	461		
Units: score on a scale				
least squares mean (standard error)	-1.558 (± 0.256)	-2.694 (± 0.257)		

Statistical analyses

Statistical analysis title	Change from Baseline: E-RS: COPD RS Total Score

Statistical analysis description:

Derived from MMRM model with the change from baseline in E-RS: COPD RS-Total Score to Week 52 as response variables, and treatment group, region (pooled country), ICS dose, smoking status at screening, visit, treatment-by-visit interaction, baseline E-RS: COPD RS-Total Score, and baseline E-RS: COPD RS-Total Score-by-visit interaction as covariates. Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	928
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [8]
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	-1.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.823
upper limit	-0.45

Notes:

[8] - Threshold for significance at 0.049 level.

Secondary: Annualized Rate of Moderate or Severe COPD Exacerbation Over the 52-Week Treatment Period in Subgroup of Participants With Baseline FeNO >=20 Ppb

End point title	Annualized Rate of Moderate or Severe COPD Exacerbation Over the 52-Week Treatment Period in Subgroup of Participants With Baseline FeNO >=20 Ppb

End point description:

Moderate exacerbations were recorded by the Investigator and defined as AECOPD that required either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations were also recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they were separated by at least 14 days. Annualized event rate among participants with baseline FeNO >=20 ppb was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated. Events were adjudicated by independent third party. The subgroup of participants with baseline FeNO >=20 ppb within the ITT population were included.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	195		
Units: exacerbation per participant-year				
number (confidence interval 95%)	1.117 (0.831 to 1.502)	0.699 (0.510 to 0.958)		

Statistical analyses

Statistical analysis title	Annualized rate-subgroup FeNO>=20 ppb: 52 weeks

Statistical analysis description:

Derived using negative binomial model with the total number of the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD

exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0052
Method	Negative binomial model
Parameter estimate	Risk difference (RD)
Point estimate	-0.418
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.728
upper limit	-0.109

Notes:

[9] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Threshold for significance at 0.049 level. Parameter estimate was derived using delta method.

Secondary: Change From Baseline in Pre-BD FEV1 to Weeks 2, 4, 8, 24, 36 and 44

End point title	Change From Baseline in Pre-BD FEV1 to Weeks 2, 4, 8, 24, 36 and 44

End point description:

The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed after a wash out period of bronchodilators according to their action duration. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 2, 4, 8, 24, 36 and 44

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	466		
Units: liters				
least squares mean (standard error)				
Week 2	0.075 (± 0.017)	0.159 (± 0.017)		
Week 4	0.069 (± 0.017)	0.163 (± 0.017)		
Week 8	0.069 (± 0.017)	0.149 (± 0.017)		
Week 24	0.068 (± 0.018)	0.170 (± 0.018)		
Week 36	0.072 (± 0.018)	0.155 (± 0.018)		
Week 44	0.089 (± 0.019)	0.176 (± 0.019)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-BD FEV1 to Weeks 2, 4, 8, 12, 24, 36 and 52

End point title	Change From Baseline in Post-BD FEV1 to Weeks 2, 4, 8, 12, 24, 36 and 52

End point description:

The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Post-BD FEV1 referred to the spirometry performed within 30 minutes after administration of bronchodilator. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 2, 4, 8, 12, 24, 36 and 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	467		
Units: liters				
least squares mean (standard error)				
Week 2	0.071 (± 0.017)	0.158 (± 0.017)		
Week 4	0.080 (± 0.017)	0.158 (± 0.017)		
Week 8	0.077 (± 0.018)	0.153 (± 0.018)		
Week 12	0.084 (± 0.018)	0.156 (± 0.018)		
Week 24	0.072 (± 0.019)	0.169 (± 0.019)		
Week 36	0.072 (± 0.019)	0.155 (± 0.019)		
Week 52	0.058 (± 0.019)	0.138 (± 0.019)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-BD Forced Expiratory Flow at 25 Percent (%) to 75% (FEF 25-75%) of Forced Vital Capacity (FVC) to Weeks 2, 4, 8, 12, 24, 36, 44, and 52

End point title	Change From Baseline in Pre-BD Forced Expiratory Flow at 25 Percent (%) to 75% (FEF 25-75%) of Forced Vital Capacity (FVC) to Weeks 2, 4, 8, 12, 24, 36, 44, and 52

End point description:

FEF is the amount of air (in liters) 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 (in liters) that can be forcibly blown out after full inspiration in the upright position. Spirometry was performed after a wash out period of bronchodilators according to their action duration. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 2, 4, 8, 12, 24, 36, 44 and 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	466		
Units: liters/second				
least squares mean (standard error)				
Week 2	0.065 (± 0.016)	0.110 (± 0.016)		
Week 4	0.066 (± 0.015)	0.115 (± 0.015)		
Week 8	0.069 (± 0.016)	0.114 (± 0.016)		
Week 12	0.076 (± 0.016)	0.137 (± 0.016)		
Week 24	0.080 (± 0.017)	0.142 (± 0.017)		
Week 36	0.087 (± 0.017)	0.132 (± 0.017)		
Week 44	0.091 (± 0.017)	0.162 (± 0.017)		
Week 52	0.088 (± 0.017)	0.135 (± 0.017)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-BD FEF 25-75% to Weeks 2, 4, 8, 12, 24, 36 and 52

End point title	Change From Baseline in Post-BD FEF 25-75% to Weeks 2, 4, 8, 12, 24, 36 and 52

End point description:

FEF is the amount of air (in liters) 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 (in liters) that can be forcibly blown out after full inspiration in the upright position. Spirometry was performed after a wash out period of bronchodilators according to their

action duration. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Weeks 2, 4, 8, 12, 24, 36 and 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	467		
Units: liters/second				
least squares mean (standard error)				
Week 2	0.074 (± 0.017)	0.135 (± 0.017)		
Week 4	0.087 (± 0.017)	0.144 (± 0.017)		
Week 8	0.083 (± 0.017)	0.144 (± 0.017)		
Week 12	0.089 (± 0.018)	0.161 (± 0.018)		
Week 24	0.093 (± 0.019)	0.169 (± 0.019)		
Week 36	0.093 (± 0.019)	0.161 (± 0.018)		
Week 52	0.093 (± 0.019)	0.153 (± 0.019)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Severe COPD Exacerbations Over the 52-Week Treatment Period

End point title	Annualized Rate of Severe COPD Exacerbations Over the 52-Week Treatment Period

End point description:

Moderate exacerbations were recorded by the Investigator and defined as AECOPD that required either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations were also recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they were separated by at least 14 days. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated. Events were adjudicated by independent third party. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	468		
Units: exacerbation per participant-years				
number (confidence interval 95%)	0.086 (0.050 to 0.147)	0.072 (0.040 to 0.132)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Moderate or Severe COPD Exacerbation During the 52-Week Treatment Period

End point title	Time to First Moderate or Severe COPD Exacerbation During the 52-Week Treatment Period

End point description:

The time to first moderate or severe exacerbation was defined as date of the first event minus randomization date +1. The median time to first severe exacerbation was derived from Cox regression model. Moderate exacerbations events were recorded by the investigator and defined as AECOPD that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations were recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they were separated by at least 14 days. The ITT population consisted of the randomized population analyzed according to the treatment group allocated by randomization.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Weeks 12, 24, 36 and 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	468		
Units: weeks				
median (confidence interval 95%)				
Up to Week 12	0.019 (0.009 to 0.035)	0.024 (0.013 to 0.041)		
Up to Week 24	0.039 (0.024 to 0.059)	0.034 (0.021 to 0.054)		
Up to Week 36	0.045 (0.029 to 0.067)	0.039 (0.024 to 0.059)		
Up to Week 52	0.061 (0.042 to 0.086)	0.043 (0.027 to 0.065)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)[10]

End point description:

An Adverse Event (AE):Any untoward medical occurrence in participant temporally associated with use of study treatment, whether or not considered related to study treatment. TEAEs:AEs that developed or worsened in grade or became serious during TE period which was defined as the period from time of first dose of study treatment until last visit in study. Serious adverse events (SAE):Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. The Safety population consisted of all participants who actually received at least 1 dose or partial of a dose of the study treatment, analyzed according to the treatment participants actually received.

End point type	Secondary

End point timeframe:

TEAEs were collected from the time from the first administration of study treatment to the last administration of the study treatment + 98 days, up to 491 days

Notes:

[10] - 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: One participant was exposed to different treatment other than planned (was randomized to placebo arm and received dupilumab on Day 40). The actual arm was considered as dupilumab 300 mg q2w. In safety analyses, the actual arms are used.

End point values	Placebo	Dupilumab 300 mg q2w-Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	470	469[11]		
Units: participants				
number (not applicable)				
Any TEAE	359	365		
Any TESAE	74	65		

Notes:

[11] - One participant exposed to different treatment other than planned.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibodies (ADA) to Dupilumab

End point title	Number of Participants With Anti-Drug Antibodies (ADA) to Dupilumab

End point description:

Number of participants with treatment-emergent response to dupilumab with peak post-baseline titers during the on-treatment period are reported. Treatment-emergent response was defined as a positive response in the ADA assay post first dose, when baseline results were negative or missing. Categories were based on titer values and included: low (Titer <1000); moderate (1000<=Titer<=10,000); and high (Titer >10,000). On-treatment period was defined as last study treatment administration plus 14 days; that is, Week 52. The ADA population consisted of all participants in the Safety population with at least 1 reportable ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment.

End point type	Secondary

End point timeframe:
Up to Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	462		
Units: participants				
number (not applicable)				
Low titer	7	27		
Moderate titer	0	1		
High titer	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from the time from the first administration of study treatment to the last administration of the study treatment + 98 days, up to 491 days

Adverse event reporting additional description:

Analysis was performed on the Safety population. One participant was exposed to different treatment other than planned (was randomized to placebo arm but received dupilumab on Day 40). The actual arm was considered as dupilumab 300 mg q2w. In safety analyses, the actual arms are used.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo matched to dupilumab 300 mg as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52).

Reporting group title	Dupilumab 300 mg q2w-Safety population

Reporting group description:

Participants received dupilumab 300 mg administered as SC injections q2w up to a maximum of 52 weeks (last dose administered at Week 50, EOT visit occurred 2 weeks after last administration of treatment i.e., at Week 52). One participant was exposed to different treatment other than planned (was randomized to placebo arm and received dupilumab on Day 40. The actual arm was considered as dupilumab 300 mg q2w. In safety analyses, the actual arms are used).

Serious adverse events	Placebo	Dupilumab 300 mg q2w-Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 470 (15.74%)	65 / 469 (13.86%)	
number of deaths (all causes)	9	8	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Glioblastoma			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ductal Adenocarcinoma Of Pancreas			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Carcinoma Cell Type Unspecified Stage Iv			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Adenocarcinoma			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate Cancer			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Cancer			

subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Lung			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Emergency			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Vascular Disorder			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Occlusion			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest Pain			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Distress Syndrome			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	2 / 470 (0.43%)	2 / 469 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atelectasis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Respiratory Failure			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	26 / 470 (5.53%)	28 / 469 (5.97%)	
occurrences causally related to treatment / all	0 / 34	0 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax Spontaneous			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			

subjects affected / exposed	3 / 470 (0.64%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax Traumatic			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	2 / 470 (0.43%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Abrasion			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	2 / 470 (0.43%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	2 / 470 (0.43%)	2 / 469 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	2 / 470 (0.43%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cor Pulmonale Acute			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			

subjects affected / exposed	1 / 470 (0.21%)	2 / 469 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal Rhythm			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Basal Ganglia Haemorrhage			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 470 (0.00%)	2 / 469 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	2 / 470 (0.43%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Loss Anaemia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			

subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Polyp			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Ischaemia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Failure			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal Syndrome			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic Kidney Disease			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hyperparathyroidism			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Bacterial			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Infective			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	5 / 470 (1.06%)	2 / 469 (0.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	

Covid-19			
subjects affected / exposed	4 / 470 (0.85%)	3 / 469 (0.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 470 (0.43%)	3 / 469 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 470 (2.55%)	6 / 469 (1.28%)	
occurrences causally related to treatment / all	0 / 13	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epiglottitis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			

subjects affected / exposed	2 / 470 (0.43%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subcutaneous Abscess			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 470 (0.21%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 470 (0.00%)	1 / 469 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 470 (0.21%)	0 / 469 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Placebo	Dupilumab 300 mg q2w-Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 470 (36.60%)	168 / 469 (35.82%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	30 / 470 (6.38%)	26 / 469 (5.54%)	
occurrences (all)	36	28	
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 470 (5.96%)	17 / 469 (3.62%)	
occurrences (all)	32	17	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 470 (7.02%)	38 / 469 (8.10%)	
occurrences (all)	39	57	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 470 (3.62%)	25 / 469 (5.33%)	
occurrences (all)	18	34	
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	16 / 470 (3.40%)	25 / 469 (5.33%)	
occurrences (all)	17	27	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	45 / 470 (9.57%)	45 / 469 (9.59%)	
occurrences (all)	60	55	
Upper Respiratory Tract Infection			
subjects affected / exposed	46 / 470 (9.79%)	37 / 469 (7.89%)	
occurrences (all)	66	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2019	The overall rationale for the changes implemented in the protocol amendment was to address feedback from Health authorities.
29 September 2020	This amendment was implemented to replace some on-site study visits and assessments by telephone visits to decrease the burden on participants, to minimize Coronavirus disease-2019 pandemic-related risks in this vulnerable and elderly population of participants with COPD, as well as to update the list of adverse events of special interest with the updated Sponsor safety information related to eye disorders, that is, addition of any severe type of conjunctivitis or blepharitis, and keratitis. Specified that self-injection of dupilumab required training and documentation and it also specifies with approved label. Correction on type of COPD exacerbations assessed by the EXACT. Update based on deleted assessments for FEV1 and FEF because of replacement of on-site visits to telephone visits. Allowed more flexibility for rescreening of participants. Provided further clarity for supply and administration of study treatment. Updated contraceptive guidance and collection of pregnancy information as per sponsor standard operating procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported