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 (NOTUS)

Summary

EudraCT number	2018-001954-91
Trial protocol	DE LV NL LT BG GB FR PT PL ES GR BE HU CZ SK RO
Global end of trial date	27 May 2024

Results information

Result version number	v1 (current)
This version publication date	06 April 2025
First version publication date	06 April 2025

Trial information

Trial identification

Sponsor protocol code	EFC15805

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04456673
WHO universal trial number (UTN)	U1111-1211-8837

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	01 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2024
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) every 2 weeks (q2w) in participants with moderate or severe COPD as measured by annualized rate of acute moderate or severe COPD exacerbation (AECOPD).

Protection of trial subjects:

Participants 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 participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant 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	06 July 2020
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: 125
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Bulgaria: 130
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 53
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Czechia: 26
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Greece: 40
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Latvia: 24
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Mexico: 48

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Peru: 37
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Serbia: 20
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 79
Worldwide total number of subjects	935
EEA total number of subjects	415

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)	409
From 65 to 84 years	525
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 329 centers in 29 countries. A total of 2769 participants were screened between 06 July 2020 to 19 April 2023, of which 1834 participants were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 935 participants were randomized in a 1:1 ratio to receive either dupilumab 300 mg q2w or matching placebo. Randomization was stratified by country, inhaled corticosteroid (ICS) dose (high-dose ICS [yes/no]) at baseline, and smoking status at screening (current smokers or not).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to dupilumab 300 mg SC injection q2w up to 52 weeks.

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 for dupilumab was provided in identically matched glass pre-filled syringe to deliver 2 mL which matched dupilumab 300 mg. SC injection sites were 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 injections.

Arm title	Dupilumab 300 mg q2w

Arm description:

Participants received dupilumab 300 mg SC injection q2w up to 52 weeks.

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

Dosage and administration details:

Dupilumab was supplied as 150 milligram per milliliter (mg/mL) solution in a pre-filled glass syringe to deliver 300 mg in 2 mL injection. SC injection sites were 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 injections.

Number of subjects in period 1	Placebo	Dupilumab 300 mg q2w
Started	465	470
Randomized and treated	465	468
Safety Population	464	469
Completed	422	428
Not completed	43	42
Consent withdrawn by subject	31	23
Adverse event, non-fatal	7	14
Not related to Coronavirus Disease-2019 (COVID-19)	4	5
Poor compliance to protocol	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab 300 mg SC injection q2w up to 52 weeks.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Participants received dupilumab 300 mg SC injection q2w up to 52 weeks.	

Reporting group values	Placebo	Dupilumab 300 mg q2w	Total
Number of subjects	465	470	935
Age categorical Units: Subjects			
From 18 - 64 years	213	196	409
From 65 - 84 years	251	274	525
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	64.9	65.2	
standard deviation	± 8.5	± 8.1	-
Sex: Female, Male Units: Participants			
Female	153	150	303
Male	312	320	632
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	26	22	48
Asian	3	7	10
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	8	4	12
White	416	422	838
More than one race	8	12	20
Unknown or Not Reported	4	2	6

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab 300 mg SC injection q2w up to 52 weeks.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
Participants received dupilumab 300 mg SC injection q2w up to 52 weeks.	

Primary: Annualized Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Over the 52-week Treatment Period

End point title	Annualized Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Over the 52-week Treatment Period
End point description:	
Moderate exacerbations were recorded by the Investigator and defined as AECOPD event 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 event that required hospitalization or observation for >24 hours in an emergency department/urgent care facility or resulted 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 events that occurred during the 52-week treatment period divided by the total number of participant-years followed in the 52-week treatment period. The Intent-to-treat (ITT) population included all randomized participants 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	465	470		
Units: Exacerbation per participant-year				
number (confidence interval 95%)	1.295 (1.048 to 1.600)	0.859 (0.699 to 1.057)		

Statistical analyses

Statistical analysis title	Placebo versus Dupilumab 300 mg q2w
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	Dupilumab 300 mg q2w v Placebo

Number of subjects included in analysis	935
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0002
Method	Negative binomial model
Parameter estimate	Risk difference (RD)
Point estimate	-0.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.682
upper limit	-0.188

Notes:

[1] - A hierarchical testing procedure was used to control type I error and handle primary and first 4 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) to Week 12

End point title	Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) to Week 12

End point description:

The FEV1 was defined as 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. Baseline was defined as the last available value up to randomization but prior to the first dose of study treatment. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization. Only those participants with data collected are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	464		
Units: Liters				
least squares mean (standard error)	0.057 (± 0.017)	0.139 (± 0.017)		

Statistical analyses

Statistical analysis title	Placebo versus Dupilumab 300 mg q2w

Statistical analysis description:

Derived from mixed-effect model with repeated measures (MMRM) model with the change from baseline in pre-bronchodilator 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-bronchodilator FEV1, and FEV1 baseline-by-visit interaction as covariates.

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0001
Method	MMRM model
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.124

Notes:

[2] - A hierarchical testing procedure was used to control type I error and handle primary and first 4 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Percentage of Participants With Saint George's Respiratory Questionnaire Improvement ≥4 Points at Week 52

End point title	Percentage of Participants With Saint George's Respiratory Questionnaire 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. Percentage of participants who achieved a clinically meaningful response in SGRQ total score (improvement by ≥4 points)/responders are reported. SGRQ is 50-item self-administered questionnaire. Scores by dimension were calculated for 3 domains:symptoms(respiratory symptoms: frequency and severity), activity(activities that cause or are limited by breathlessness) and impacts(social functioning and psychological disturbances due to airway disease). Each question's response had unique empirically derived weight where lowest possible weight was 0 and highest was 100. Total score was obtained by summing all positive responses. Total and domain score was derived from relevant items and converted to a score of 0 to 100; higher score indicating worse health status/health related quality of life. Analysis was performed in ITT population with an opportunity to

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	362		
Units: Percentage of participants				
number (not applicable)	46.5	51.4		

Statistical analyses

Statistical analysis title	Placebo versus Dupilumab 300 mg q2w

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.

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	721
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3329
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.856
upper limit	1.581

Notes:

[3] - A hierarchical testing procedure was used to control type I error and handle primary and first 4 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

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

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

End point description:

SGRQ measures 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 (respiratory symptoms: frequency and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). Each question's response had a unique empirically derived weight; lowest possible weight: 0 and highest: 100. Total score: summing all positive responses. Total and domain score derived from relevant items and converted to a score of 0 to 100; higher score indicating worse health status/health related quality of life. Baseline: last available value up to randomization but prior to first dose of study treatment. ITT population with opportunity to reach Week 52: participants who had an opportunity to reach Week 52 assessments. Only those participants with data collected are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	350		
Units: score on a scale				
least squares mean (standard error)	-6.444 (± 0.922)	-9.816 (± 0.920)		

Statistical analyses

Statistical analysis title	Placebo versus Dupilumab 300 mg q2w

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.

Comparison groups	Placebo v Dupilumab 300 mg q2w
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0068
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	-3.371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.811
upper limit	-0.931

Notes:

[4] - A hierarchical testing procedure was used to control type I error and handle primary and first 4 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second to Week 52

End point title	Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second to Week 52

End point description:

The FEV1 was defined as 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. Baseline was defined as the last available value up to randomization but prior to the first dose of study treatment. The ITT population with an opportunity to reach Week 52 included participants who had an opportunity to reach Week 52 assessments and were analyzed for the continuous and proportion type endpoints at Week 52. Only those participants with data collected are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	359		
Units: Liters				
least squares mean (standard error)	0.054 (± 0.020)	0.115 (± 0.021)		

Statistical analyses

Statistical analysis title	Placebo versus Dupilumab 300 mg q2w

Statistical analysis description:

Derived from MMRM model with the change from baseline in pre-bronchodilator 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-bronchodilator FEV1, and FEV1 baseline-by-visit interaction as covariates.

Comparison groups	Placebo v Dupilumab 300 mg q2w

Number of subjects included in analysis	715
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0182
Method	MMRM model
Parameter estimate	LS Mean Difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.113

Notes:

[5] - A hierarchical testing procedure was used to control type I error and handle primary and first 4 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second to Weeks 2, 4, 8, 24, 36, and 44

End point title	Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second to Weeks 2, 4, 8, 24, 36, and 44

End point description:

The FEV1 was defined as 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. Baseline was defined as the last available value up to randomization but prior to the first dose of study treatment. The ITT population with an opportunity to reach Week 52 included participants who had an opportunity to reach Week 52 assessments and were analyzed for all weeks up to Week 52. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and 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	356	359		
Units: Liters				
least squares mean (standard error)				
Week 2	0.072 (± 0.018)	0.108 (± 0.018)		
Week 4	0.077 (± 0.018)	0.132 (± 0.019)		
Week 8	0.069 (± 0.019)	0.133 (± 0.020)		
Week 24	0.064 (± 0.020)	0.154 (± 0.021)		
Week 36	0.068 (± 0.021)	0.117 (± 0.021)		
Week 44	0.065 (± 0.020)	0.154 (± 0.021)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in 1 Second to Weeks 2, 4, 8, 12, 24, 36, and 52

End point title	Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in 1 Second 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-bronchodilator FEV1 referred to the spirometry performed consistent with the mechanism of action of reliever (30 minutes for albuterol or another short-acting beta agonists). Baseline was defined as the last available value up to randomization but prior to the first dose of study treatment. The ITT population with an opportunity to reach Week 52 included participants who had an opportunity to reach Week 52 assessments and were analyzed for all weeks up to Week 52. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and 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	356	358		
Units: Liters				
least squares mean (standard error)				
Week 2	0.082 (± 0.018)	0.101 (± 0.018)		
Week 4	0.098 (± 0.018)	0.126 (± 0.018)		
Week 8	0.083 (± 0.019)	0.147 (± 0.020)		
Week 12	0.064 (± 0.020)	0.136 (± 0.020)		
Week 24	0.081 (± 0.020)	0.152 (± 0.020)		
Week 36	0.070 (± 0.020)	0.131 (± 0.021)		
Week 52	0.059 (± 0.020)	0.127 (± 0.021)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Flow (FEF) 25 to 75 Percent (%) to Weeks 2, 4, 8, 12, 24, 36, 44, and 52

End point title	Change From Baseline in Forced Expiratory Flow (FEF) 25 to 75 Percent (%) to Weeks 2, 4, 8, 12, 24, 36, 44, and 52

End point description:

FEF is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEF 25-75% was defined as the FEF at 25% to 75% of forced vital capacity (FVC), where

FVC was defined as the volume of air 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. Baseline was defined as the last available value up to randomization but prior to the first dose of study treatment. The ITT population with an opportunity to reach Week 52 included participants who had an opportunity to reach Week 52 assessments and were analyzed for all weeks up to Week 52. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and 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	356	359		
Units: Liters per second				
least squares mean (standard error)				
Week 2	0.057 (± 0.018)	0.103 (± 0.018)		
Week 4	0.056 (± 0.018)	0.114 (± 0.018)		
Week 8	0.059 (± 0.019)	0.134 (± 0.019)		
Week 12	0.066 (± 0.021)	0.137 (± 0.021)		
Week 24	0.051 (± 0.019)	0.147 (± 0.020)		
Week 36	0.073 (± 0.021)	0.128 (± 0.022)		
Week 44	0.053 (± 0.021)	0.154 (± 0.021)		
Week 52	0.065 (± 0.020)	0.122 (± 0.020)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Severe Chronic Obstructive Pulmonary Disease Exacerbations Over the 52-week Treatment Period

End point title	Annualized Rate of Severe Chronic Obstructive Pulmonary Disease Exacerbations Over the 52-week Treatment Period

End point description:

Severe exacerbations were recorded by the Investigator and defined as AECOPD event that required hospitalization or observation for >24 hours in an emergency department/urgent care facility or resulted 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 events that occurred during the 52-week treatment period divided by the total number of participant-years followed in the 52-week treatment period. The ITT population included all randomized participants 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	465	470		
Units: Exacerbation per participant-year				
number (confidence interval 95%)	0.124 (0.072 to 0.215)	0.070 (0.039 to 0.123)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Moderate or Severe Chronic Obstructive Pulmonary Disease Exacerbation Event During the 52-week Treatment Period

End point title	Time to First Moderate or Severe Chronic Obstructive Pulmonary Disease Exacerbation Event 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. Moderate exacerbations were recorded by the Investigator and defined as AECOPD event that required either systemic corticosteroids (such as intramuscular, intravenous, or oral) and/or antibiotics. Severe exacerbations were recorded by the Investigator and defined as AECOPD event that required hospitalization or observation for >24 hours in an emergency department/urgent care facility or resulted in death. For both moderate and severe events to be counted as separate events, they were separated by at least 14 days. Median time as well as 95% confidence interval was calculated using Kaplan-Meier estimates. The ITT population included all randomized participants analyzed according to the treatment group allocated by randomization.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and 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	465	470		
Units: Weeks				
median (confidence interval 95%)				
Week 12	0.172 (0.139 to 0.207)	0.108 (0.081 to 0.138)		
Week 24	0.265 (0.225 to 0.306)	0.206 (0.170 to 0.244)		
Week 36	0.342 (0.298 to 0.387)	0.292 (0.250 to 0.335)		
Week 52	0.424 (0.375 to 0.471)	0.361 (0.315 to 0.407)		

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)

End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An SAE was defined as 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 disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed or worsened or became serious during TE period (between the first administration of study treatment to the last administration of the study treatment + 98 days). The Safety population included 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:

From the first dose of study treatment (Day 1) up to the last dose of the study treatment + 98 days, up to 506 days

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	469		
Units: Participants				
Any TEAE	330	322		
Any TESAE	79	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Hematology

End point title	Percentage of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Hematology

End point description:

Blood samples were collected to determine PCSA in hematology. PCSA values were defined as abnormal values considered medically important by Sponsor according to pre-defined criteria/thresholds based on literature review and defined by Sponsor for clinical laboratory tests. Criteria for PCSA: Hemoglobin

(Hb): ≤115 grams per liter (g/L) (Male[M]); ≤95 g/L (Female[F]), ≥185 g/L (M); ≥165 g/L (F), Decrease from baseline ≥20 g/L; Hematocrit: ≤0.37 volume per volume (v/v) (M); ≤0.32 v/v (F), ≥0.55 v/v (M); ≥0.5 v/v (F); Erythrocyte Count: ≥6 Tera/L; Platelet count: <100 Giga/L, ≥700 Giga/L; Leukocytes: <3 Giga/L (Non-Black [NB]); <2 Giga/L (Black [B]), ≥16 Giga/L; Neutrophils: <1.5 Giga/L (NB); <1 Giga/L (B); Lymphocytes: >4 Giga/L; Monocytes: >0.7 Giga/L; Basophils: >0.1 Giga/L; Eosinophils: >0.5 Giga/L or >upper limit of normal (ULN) (if ULN ≥0.5 Giga/L). Safety population. n=number of participants with data collected for each specified category.

End point type	Secondary

End point timeframe:

From the first dose of study treatment (Day 1) up to the last dose of the study treatment + 98 days, up to 506 days

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	459	464		
Units: Percentage of participants				
number (not applicable)				
Hb: ≤115 g/L (M); ≤95 g/L (F) (n=459,464)	6.1	5.0		
Hb: ≥185 g/L (M); ≥165 g/L (F) (n=459,464)	3.7	4.7		
Hb: Decrease from baseline ≥20 g/L (n=459,464)	9.8	11.4		
Hematocrit:≤0.37 v/v(M);≤0.32 v/v(F)(n=459,464)	6.1	5.0		
Hematocrit:≥0.55 v/v(M);≥0.5 v/v(F)(n=459,464)	23.1	26.5		
Erythrocyte Count: ≥6 Tera/L (n=459,464)	4.4	6.0		
Platelet count: <100 Giga/L (n=459,464)	0.2	0.6		
Platelet count: ≥700 Giga/L (n=459,464)	0.7	0.4		
Leukocytes:<3 Giga/L(NB);<2 Giga/L(B)(n=459,464)	0.7	0.6		
Leukocytes: ≥16 Giga/L (n=459,464)	5.2	4.1		
Neutrophils:<1.5Giga/L(NB);<1 Giga/L(B)(n=447,456)	2.7	1.5		
Lymphocytes: >4 Giga/L (n=459,464)	5.9	8.2		
Monocytes: >0.7 Giga/L (n=459,464)	65.8	64.9		
Basophils: >0.1 Giga/L (n=459,464)	28.1	29.5		
Eosinophils: >0.5 Giga/L or >ULN (n=458,464)	15.3	21.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Potentially Clinically Significant Abnormalities in Clinical Chemistry

End point title	Percentage of Participants With Potentially Clinically Significant Abnormalities in Clinical Chemistry

End point description:

PCSA criteria: Sodium: ≤129 millimoles (mmol)/L, ≥160 mmol/L; Potassium: <3 mmol/L, ≥5.5 mmol/L; Chloride: <80 mmol/L, >115 mmol/L; Glucose: ≤3.9 mmol/L and <lower limit of normal (LLN), ≥11.1 mmol/L (unfasted [UF]); ≥7 mmol/L (fasted [F]);Total cholesterol: ≥7.74 mmol/L; Creatinine kinase: >3 ULN, >10 ULN; Creatinine: ≥150 micromoles (µmol)/L (adults), ≥30% change from baseline (CFB), ≥100% CFB, Creatinine Clearance (CG): ≥60 - <90 milliliter per minute (mL/min), ≥30 - <60 mL/min, ≥15 - <30 mL/min, <15 mL/min; Urea nitrogen: ≥17 mmol/L; Uric acid: <120 µmol/L, >408 µmol/L; Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST): >3 ULN, >5 ULN, >10 ULN; Alkaline phosphatase (ALP): >1.5 ULN; Total bilirubin (TB): >1.5 ULN, >2 ULN; ALT and TB: ALT >3 ULN and Bilirubin (B) > 2 ULN; Direct bilirubin (DB) and TB: DB >35% B and B >1.5 ULN; Albumin: ≤25 g/L. Safety population. n=number of participants with data collected for each specified category.

End point type	Secondary

End point timeframe:

From the first dose of study treatment (Day 1) up to the last dose of the study treatment + 98 days, up to 506 days

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	459	464		
Units: Percentage of participants				
number (not applicable)				
Sodium: ≤129 mmol/L (n=459,464)	1.7	1.9		
Sodium: ≥160 mmol/L (n=459,464)	0	0.2		
Potassium: <3 mmol/L (n=459,464)	0.4	0.4		
Potassium: ≥5.5 mmol/L (n=459,464)	11.3	10.8		
Chloride: <80 mmol/L (n=459,464)	0	0.2		
Chloride: >115 mmol/L (n=459,464)	0	0.2		
Glucose: ≤3.9 mmol/L and <LLN (n=459,464)	7.0	6.5		
Glucose:≥11.1 mmol/L(UF); ≥7 mmol/L(F) (n=459,464)	7.6	8.8		
Total cholesterol: ≥7.74 mmol/L (n=459,464)	6.1	4.3		
Creatinine kinase: >3 ULN (n=459,464)	2.2	3.9		
Creatinine kinase: >10 ULN (n=459,464)	0	0		
Creatinine: ≥150 µmol/L (n=459,464)	2.6	3.0		
Creatinine: ≥30% CFB (n=459,464)	20.3	19.2		
Creatinine: ≥100% CFB (n=459,464)	0.7	2.4		
CG: ≥60 - <90 mL/min (n=459,464)	36.4	39.0		
CG: ≥30 - <60 mL/min (n=459,464)	18.5	16.8		
CG: ≥15 - <30 mL/min (n=459,464)	0	0.9		
CG: <15 mL/min (n=459,464)	0.2	0.4		
Urea nitrogen: ≥17 mmol/L	0.2	0.4		
Uric acid: <120 µmol/L (n=459,464)	0	0.4		
Uric acid: >408 µmol/L (n=459,464)	37.7	39.7		
ALT: >3 ULN (n=459,464)	1.5	0.4		
ALT: >5 ULN (n=459,464)	0.2	0		
ALT: >10 ULN (n=459,464)	0	0		
AST: >3 ULN (n=459,464)	0.2	0.4		
AST: >5 ULN (n=459,464)	0	0.2		
AST: >10 ULN (n=459,464)	0	0		

ALP: >1.5 ULN (n=459,464)	3.9	2.8		
TB: >1.5 ULN (n=459,464)	0.9	2.2		
TB: >2 ULN (n=459,464)	0.2	0		
ALT and TB: ALT >3 ULN and B> 2 ULN (n=459,464)	0.2	0		
DB and TB: DB >35% B and B >1.5 ULN (n=22,36)	4.5	5.6		
Albumin: ≤25 g/L (n=459,464)	0.2	0.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Abnormal Results for Urine Protein in Urinalysis

End point title	Percentage of Participants With Abnormal Results for Urine Protein in Urinalysis

End point description:

Urine dipstick samples were collected to determine the significant abnormalities in urine protein. The Safety population included 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. Only those participants with data collected are reported. Here, n=number of participants with data collected for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 24, 36, 52 and 64

End point values	Placebo	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	469		
Units: Percentage of participants				
number (not applicable)				
Baseline (Day 1) (n=462,469)	5.0	6.2		
Week 4 (n=452,456)	4.1	4.9		
Week 8 (n=443,452)	3.7	5.3		
Week 12 (n=440,450)	4.5	6.4		
Week 24 (n=444,447)	3.9	4.5		
Week 36 (n=434,436)	3.9	4.5		
Week 52 (n=421,422)	5.0	6.6		
Week 64 (n=384,403)	4.5	5.5		

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:

Plasma samples were collected to evaluate antibodies to dupilumab. Pre-existing immunoreactivity is defined as an ADA positive response in the assay at baseline with all post-treatment ADA results negative, or an ADA positive response at baseline with all post-treatment ADA responses less than 4-fold over baseline titer levels. Treatment-emergent response is defined as a positive response in the ADA assay post first dose, when baseline results are negative or missing. Treatment-boosted response is defined as an ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive. The ADA population included all participants in the safety population who had at least 1 reportable ADA result 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	452	461		
Units: Participants				
Pre-existing immunoreactivity	6	4		
Treatment-emergent ADA response	11	47		
Treatment-boosted ADA response	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs, SAEs, all-cause mortality (deaths) were collected from the first dose of study treatment (Day 1) up to the last dose of the study treatment + 98 days, up to 506 days.

Adverse event reporting additional description:

Analysis was performed on the Safety population. 1 participant was exposed to different treatment other than planned (was allocated to placebo arm but inadvertently received dupilumab 300 mg q2w on Day 113). 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	27.0

Reporting groups

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

Participants received dupilumab 300 mg SC injection q2w up to 52 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo matched to dupilumab 300 mg SC injection q2w up to 52 weeks.

Serious adverse events	Dupilumab 300 mg q2w	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 469 (13.86%)	79 / 464 (17.03%)	
number of deaths (all causes)	14	8	
number of deaths resulting from adverse events	13	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Myelomonocytic Leukaemia			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			

subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary Thyroid Cancer			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Lung			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity Necrosis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			

subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Vascular Disorder			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden Death			
subjects affected / exposed	2 / 469 (0.43%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	2 / 2	2 / 2	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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			
Benign Prostatic Hyperplasia			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (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			
Hypoxia			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	25 / 469 (5.33%)	40 / 464 (8.62%)	
occurrences causally related to treatment / all	0 / 35	0 / 47	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Tibia Fracture			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal Burn			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella Fracture			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 469 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	0 / 469 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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	0 / 469 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	2 / 469 (0.43%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ventricular Arrhythmia			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postinfarction Angina			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Incompetence			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor Pulmonale			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular Disorder			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Lacunar Stroke			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			

subjects affected / exposed	0 / 469 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral Infarction			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Paralysis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron Deficiency Anaemia			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical Fistula			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Stenosis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
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	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Stenosis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 469 (0.43%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Soft Tissue Necrosis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal Abscess			

subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Colitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (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	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	3 / 469 (0.64%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Covid-19 Pneumonia			
subjects affected / exposed	6 / 469 (1.28%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Influenza			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Bacterial			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Candidiasis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal Candidiasis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 469 (1.92%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pneumonia Klebsiella			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia Pneumococcal			

subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pseudomonal			
subjects affected / exposed	0 / 469 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Streptococcal			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (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	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected Covid-19			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 469 (0.43%)	0 / 464 (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	2 / 469 (0.43%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 469 (0.21%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 464 (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	Dupilumab 300 mg q2w	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 469 (26.65%)	120 / 464 (25.86%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	31 / 469 (6.61%)	33 / 464 (7.11%)	
occurrences (all)	34	35	
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 469 (7.89%)	29 / 464 (6.25%)	
occurrences (all)	72	46	
Infections and infestations			
Covid-19			
subjects affected / exposed	45 / 469 (9.59%)	36 / 464 (7.76%)	
occurrences (all)	45	38	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	32 / 469 (6.82%) 39	28 / 464 (6.03%) 31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2020	To decrease the study burden on participants, to minimize COVID-19 pandemic-related risks in this vulnerable and elderly population of COPD participants, and to update the adverse event of special interest with the updated Sponsor safety information related to eye disorders.
16 December 2021	To provide flexibility for participant enrollment criteria while maintaining the favorable benefit risk profile and scientific objectives of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported