Clinical trial results:
A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of MEDI3506 in Participants with Moderate to Severe Chronic Obstructive Pulmonary Disease and Chronic Bronchitis (FRONTIER 4)

Summary

EudraCT number	2020-000571-20
Trial protocol	GB DE DK HU NL PL CZ
Global end of trial date	13 November 2023

Results information

Result version number	v2 (current)
This version publication date	24 January 2025
First version publication date	28 November 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D9180C00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04631016
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, Maryland, United States, 20878
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.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	24 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the effects of MEDI3506 compared with placebo on pulmonary function in participants with chronic obstructive pulmonary disease (COPD) and chronic bronchitis.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Participants who have a documented stable regimen of dual therapy or triple therapy for >= 3 months prior to enrollment; there should have been no change in treatment after the previous exacerbation prior to entering into the study. Where dual therapy consists of inhaled corticosteroids (ICS) + long-acting beta 2 agonist (LABA) or LABA + long-acting muscarinic receptor antagonist (LAMA), and triple therapy consists of ICS + LABA + LAMA. Both dual and triple therapy may be in the form of separate inhalers of fixed dose combination inhalers but may not be in nebulized form.

Evidence for comparator:

Itepekimab, a monoclonal antibody targeting IL-33, demonstrated clinical activity in asthma, with potential in chronic obstructive pulmonary disease (COPD). In the Phase 2 study, primary endpoint exacerbation rate was not met. Subgroup analysis showed that itepekimab reduced exacerbation rate and improved lung function in former smokers with COPD (Rabe et al. Lancet Respir Med 2021;9: 1288–98). Astegolimab, a selective ST2 IgG2 monoclonal antibody did not significantly reduce exacerbation rate in the Phase 2 study, but did improve health status compared with placebo (Yousuf et al. Lancet Respir Med 2022; 10: 469–77).

Actual start date of recruitment	14 December 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	Australia: 5
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Israel: 5

Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	135
EEA total number of subjects	101

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)	62
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 47 centers in 12 countries (Australia, Canada, Czech Republic, Denmark, Germany, United Kingdom, Hungary, Israel, Poland, South Africa, Spain, and USA).

Pre-assignment

Screening details:

A total of 137 participants were randomized, of which 135 participants received at least one dose of study drug.

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	Investigator, Monitor, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Tozorakimab

Arm description:

Participants received 7 doses of subcutaneous (SC) tozorakimab Dose Level 1 injection once every 4 weeks (Q4W).

Arm type	Experimental
Investigational medicinal product name	Tozorakimab
Investigational medicinal product code	MEDI3506
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Seven doses of SC tozorakimab Dose Level 1 injection once Q4W.

Arm title	Placebo

Arm description:

Participants received 7 doses of SC placebo injection matched to tozorakimab once Q4W.

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

Dosage and administration details:

Seven doses of SC placebo injection matched to tozorakimab once Q4W.

Number of subjects in period 1	Tozorakimab	Placebo
Started	67	68
Completed	58	63
Not completed	9	5
Consent withdrawn by subject	5	4
Failure to meet randomization criteria	-	1
Adverse event, non-fatal	3	-
Reason unspecified	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Tozorakimab
Reporting group description:	
Participants received 7 doses of subcutaneous (SC) tozorakimab Dose Level 1 injection once every 4 weeks (Q4W).	
Reporting group title	Placebo
Reporting group description:	
Participants received 7 doses of SC placebo injection matched to tozorakimab once Q4W.	

Reporting group values	Tozorakimab	Placebo	Total
Number of subjects	67	68	135
Age categorical			
Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	29	33	62
From 65-84 years	38	35	73
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	64.5	64.3	
standard deviation	± 8.3	± 6.1	-
Sex: Female, Male			
Units: Participants			
Female	26	27	53
Male	41	41	82
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	64	65	129
More than one race	0	0	0
Unknown or Not Reported	2	1	3
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	66	66	132
Unknown or Not Reported	0	0	0

End points

End points reporting groups	
Reporting group title	Tozorakimab
Reporting group description:	
Participants received 7 doses of subcutaneous (SC) tozorakimab Dose Level 1 injection once every 4 weeks (Q4W).	
Reporting group title	Placebo
Reporting group description:	
Participants received 7 doses of SC placebo injection matched to tozorakimab once Q4W.	

Primary: Change From Baseline to Week 12 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (Pre-BD FEV1) as Measured in Clinic	
End point title	Change From Baseline to Week 12 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (Pre-BD FEV1) as Measured in Clinic
End point description:	
The mean change from baseline in Pre-BD FEV1 at Week 12 (tozorakimab – placebo) estimated using a repeated measures mixed effects analysis of covariance measures was estimated. Data available from all visits up to and including Week 12, irrespective of whether the participant discontinued study drug or received reliever therapy was considered. FEV1 was measured by spirometry at clinic. Intent-to-treat (ITT) population included all participants who received any study drug and were analyzed according to the treatment they actually received.	
End point type	Primary
End point timeframe:	
Baseline (Day -35 to Day -28) through Week 12	

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Litre				
least squares mean (standard error)	0.019 (± 0.026)	-0.005 (± 0.025)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tozorakimab v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.216
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.024

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.015
upper limit	0.063

Secondary: Serum Tozorakimab Concentration

End point title	Serum Tozorakimab Concentration[1]

End point description:

Serum concentration of tozorakimab collected over time are reported. The lower limit of quantification (LLOQ) for tozorakimab was considered to be 10 µg/L. Pharmacokinetic (PK) evaluable population included participants who received at least 1 dose of tozorakimab and had at least 1 detectable post-treatment sample available. Number of participants analyzed (N) denotes the number of participants evaluated for this outcome measure. Number analyzed (n) denotes those participants who had adequate PK sample available at the specified time point.

End point type	Secondary

End point timeframe:

Post-dose at Study Weeks 2, 4, 12, 20, 24, 28, 32, and 36

Notes:

[1] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Tozorakimab			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: µg/L				
arithmetic mean (standard deviation)				
Week 2 (n=64)	24604.70 (± 43934.55)			
Week 4 (n=65)	8041.59 (± 22355.66)			
Week 12 (n=63)	7548.78 (± 6416.68)			
Week 20 (n=62)	10789.81 (± 31903.70)			
Week 24 (n=58)	6410.05 (± 4123.46)			
Week 28 (n=58)	7289.36 (± 5331.35)			
Week 32 (n=57)	1483.19 (± 1779.88)			
Week 36 (n=58)	420.13 (± 701.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) to

Tozorakimab

End point title	Number of Participants With Positive Anti-drug Antibodies (ADA) to Tozorakimab

End point description:

Number of participants with positive ADA to tozorakimab are reported. Treatment-induced ADA positive is defined as ADA negative at baseline and positive at post-baseline assessment. Treatment-boosted ADA positive is defined as ADA positive at baseline and boosted (>= 4 fold) the pre-existing titre during the study period. Persistent positive is defined as ADA negative at baseline and positive at >= 2 post-baseline assessments (with >= 16 weeks between first and last positive) or ADA positive at last post-baseline assessment. Transiently positive is defined as ADA negative at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who had at least one post-baseline ADA assessment.

End point type	Secondary

End point timeframe:

Pre-dose at Study Weeks 0 (baseline) and post-dose at Study Weeks 2, 4, 12, 20, 24, 28, 32, and 36

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	65		
Units: Participants				
Treatment-induced ADA	1	0		
Treatment-boosted ADA	0	0		
Persistently positive ADA	0	0		
Transiently positive ADA	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in 4-weekly Mean Evaluating Respiratory Symptoms of COPD (E-RS:COPD) Total Score

End point title	Change From Baseline to Week 12 in 4-weekly Mean Evaluating Respiratory Symptoms of COPD (E-RS:COPD) Total Score

End point description:

Change from baseline to Week 12 in 4-weekly mean E-RS:COPD total score is reported. The E-RS™:COPD is an 11-item electronic patient reported outcome (ePRO) questionnaires developed to evaluate the severity of respiratory symptoms of COPD including breathlessness (5 items; score range: 0 to 17), cough and sputum (3 items; score range: 0 to 11), and chest symptoms (3 items; score range: 0 to 12). The ePRO was completed every day at home and at site visits. Summation of E-RS:COPD item responses produced a total score ranging from 0 to 40, with higher scores indicating greater severity. The 4-weekly mean will be calculated as the sum of all non-missing daily scores over the 28-day evaluation period, divided by the number of non-missing daily scores. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Baseline (from evening of Study Day -14 to the morning of Study Day 1) through Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Units on a scale				
least squares mean (standard error)	-6.09 (± 1.004)	-6.06 (± 0.962)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing First Chronic Obstructive Pulmonary Disease Composite Exacerbations (COPDCompEx) Event

End point title	Number of Participants Experiencing First Chronic Obstructive Pulmonary Disease Composite Exacerbations (COPDCompEx) Event

End point description:

The COPDCompEx combines exacerbations with events defined from participant e-Diaries and peak expiratory flow (PEF). COPDCompEx defined exacerbations included episodes leading to one or more of the following: hospitalization, emergency room visit, treatment with systemic corticosteroids (injected and/or oral), or treatment with antibiotics. Diary COPDCompEx events are defined by threshold and slope criteria being met for >= 2 consecutive days using the following diary and home spirometry variables: overall symptom rating, night-time awakenings due to symptoms, reliever medication use, PEF. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Baseline (Day -35 to Day -28) through Week 28

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants	28	36		

Statistical analyses

Statistical analysis title	Hazard ratio
Comparison groups	Tozorakimab v Placebo

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.57
upper limit	1.11

Secondary: Change From Baseline to Week 12 in Mean Breathlessness, Cough and Sputum Scale (BCSS) Score (Over the Previous 4 Weeks)

End point title	Change From Baseline to Week 12 in Mean Breathlessness, Cough and Sputum Scale (BCSS) Score (Over the Previous 4 Weeks)

End point description:

Change from baseline to Week 12 in mean BCSS score (over the previous 4 weeks) is reported. The BCSS was a 3-item daily diary that assesses the severity of the 3 symptoms: breathlessness, sputum, and cough, each on a 5-point Likert scale ranging from 0 (no symptoms) to 4 (severe symptoms). Item scores were summed to yield a total score ranging from 0 to 12; wherein higher total score indicated more severe symptoms. The BCSS was captured each evening via eDiary. The 4-weekly mean BCSS score was calculated as the sum of all non-missing daily scores over the 28-dayevaluation period, divided by the number of non-missing daily scores. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Baseline (from evening of Study Day -14 to the morning of Study Day 1) through Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Units on a scale				
least squares mean (standard error)	-2.18 (± 0.313)	-2.18 (± 0.298)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Cough Visual Analogue Scale (VAS) Score

End point title	Change From Baseline to Week 12 in Cough Visual Analogue Scale (VAS) Score

End point description:

Change from baseline to Week 12 in cough VAS score is reported. Participants were asked to complete a cough severity VAS (100 mm linear scale marked with a horizontal line by the participant, with 0 mm representing ''no cough'' and 100 mm representing "worst cough") that measured subjective assessment by the participant of the prior 24 hrs for severity of cough symptoms. It was completed each evening in the eDiary. The 4-weekly mean cough VAS score was calculated as the sum of all non-missing daily scores over the 28-day evaluation period, divided by the number of non-missing daily scores. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Baseline (from evening of Study Day -14 to the morning of Study Day 1) through Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: mm				
least squares mean (standard error)	-17.21 (± 3.639)	-17.70 (± 3.483)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Saint George's Respiratory Questionnaire (SGRQ) Total Score

End point title	Change From Baseline to Week 12 in Saint George's Respiratory Questionnaire (SGRQ) Total Score

End point description:

The SGRQ was a 50-item ePRO instrument developed to measure health status of participants with airway obstruction diseases and is divided into 2 parts. Part 1: 8 items pertaining to severity of respiratory symptoms in preceding 4 weeks; Part 2: 42 items related to daily activity and psychosocial impacts of participant's respiratory condition. The SGRQ yielded a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicated impact of disease on overall health status, which was expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. The domain scores range from 0 to 100, with higher scores indicative of greater impairment. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 12.

End point type	Secondary

End point timeframe:

Baseline (from evening of Study Day -14 to the morning of Study Day 1) through Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: Units on a scale				
least squares mean (standard error)	-9.177 (± 2.116)	-8.273 (± 2.029)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Decrease in SGRQ Total score of >= 4 Points From Baseline to Week 12

End point title	Percentage of Participants With a Decrease in SGRQ Total score of >= 4 Points From Baseline to Week 12

End point description:

SGRQ: 50-item ePRO instrument developed to measure health status of participants with airway obstruction diseases and is divided into 2 parts. Part 1: 8 items pertaining to severity of respiratory symptoms in preceding 4 weeks; Part 2: 42 items related to daily activity and psychosocial impacts of participant's respiratory condition. The SGRQ yielded total score and 3 domain scores (symptoms, activity, impacts). Total score indicated impact of disease on overall health status, which was expressed as percentage of overall impairment, in which 100 represents worst possible health status and 0 indicates best possible health status. Domain scores range from 0 to 100, higher scores indicative of greater impairment. A change of 4 units/points is associated with a minimum clinically important difference. ITT population: participants who received any study drug and were analyzed according to treatment they actually received. Number of participants analyzed: participants evaluable at Week 12.

End point type	Secondary

End point timeframe:

Baseline (from evening of Study Day -14 to the morning of Study Day 1) through Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	65		
Units: Percentage of Participants				
number (not applicable)	61.3	61.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Airwave Oscillometry (AO) Parameters

End point title	Change From Baseline to Week 12 in Airwave Oscillometry (AO) Parameters

End point description:

Change from baseline to Week 12 in AO parameters including frequency dependence of resistance at 5-20 Hz (R5-R20) and respiratory resistance at 5 Hz (R5; total airway resistance) and 20 Hz (R20;

resistance of large airways) is reported. AO is a non-invasive lung function test assessed using an AO device. It is assessed during quiet, tidal breathing with no participant effort required, by superimposing a multi-frequency oscillation onto the participant's natural breathing. AO device uses a vibrating mesh to generate a multifrequency sinusoidal pseudorandom noise (PRN) signal. The AO markers; respiratory resistance at 5 Hz (R5) and 20 Hz (R20) and difference between resistance at 5 and 20Hz (R5-R20; resistance in small airways) are recorded. These markers measure peripheral airway resistance. ITT population: all participants who received any study drug and were analyzed according to received treatment. Number of participants analyzed: participants who were evaluable at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Study Day 1) and Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: kPa*s/L				
least squares mean (standard error)				
R5-R20	0.008 (± 0.013)	-0.014 (± 0.013)		
R5	0.015 (± 0.032)	-0.030 (± 0.030)		
R20	0.006 (± 0.024)	-0.017 (± 0.023)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in AO Parameter-Area Under the Reactance Curve (AX)

End point title	Change From Baseline to Week 12 in AO Parameter-Area Under the Reactance Curve (AX)

End point description:

Change from baseline to Week 12 in AO Parameter-Area Under the Reactance Curve (AX) is reported. AO is a non-invasive lung function test assessed using an AO device. It is assessed during quiet, tidal breathing with no participant effort required, by superimposing a multi-frequency oscillation onto the participant’s natural breathing. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Study Day 1) and Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: kPa/L				
least squares mean (standard error)	-0.081 (± 0.375)	-0.267 (± 0.360)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio to Baseline in Daily, Night-time, and Awake Time Cough Frequency at Week 12

End point title	Ratio to Baseline in Daily, Night-time, and Awake Time Cough Frequency at Week 12

End point description:

Ratio to baseline in daily, night-time, and awake time cough frequency at Week 12 is reported. Objective cough frequency was measured using an ambulatory cough monitoring (ACM) which was fitted and worn by the participants for approximately 24 hours after the visits. Daily cough frequency as full average hourly cough of the full duration of recording, night time cough frequency as sleep average hourly cough of the duration of recording at night, and awake time cough frequency as awake average hourly cough of the full duration of recording minus sleep recording will be derived from the recording. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Day -21 to Day -7) and Week 12

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: Ratio to baseline				
geometric mean (confidence interval 80%)				
Daily cough frequency	0.89 (0.74 to 1.07)	0.83 (0.70 to 0.99)		
Night time cough frequency	1.03 (0.62 to 1.70)	0.61 (0.38 to 0.98)		
Awake time cough frequency	0.89 (0.74 to 1.07)	0.84 (0.71 to 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-BD FEV1 and Post-BD FEV1 Through Week 28 in Participants With Extent of Emphysema < 10%

End point title	Change From Baseline in Pre-BD FEV1 and Post-BD FEV1 Through Week 28 in Participants With Extent of Emphysema < 10%

End point description:

Change from baseline in pre-BD FEV1 and post-BD FEV1 through Week 28 in participants with extent of emphysema < 10% is reported. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Week -5 to -4) through Week 28 post-dose

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	35		
Units: Litre				
least squares mean (standard error)				
Pre-BD FEV1 (n=31,35)	0.031 (± 0.057)	0.006 (± 0.049)		
Post-BD FEV1 (n=30,34)	-0.039 (± 0.071)	-0.018 (± 0.059)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-BD and Post-BD Forced Vital Capacity (FVC) Through Week 28 in Participants With Extent of Emphysema < 10%

End point title	Change From Baseline in Pre-BD and Post-BD Forced Vital Capacity (FVC) Through Week 28 in Participants With Extent of Emphysema < 10%

End point description:

Change from baseline in pre-BD and post-BD FVC through Week 28 in participants with extent of emphysema < 10% is reported. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Week -5 to -4) through Week 28 post-dose

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	35		
Units: Litre				
least squares mean (standard error)				
Pre-BD FVC (n=31,35)	-0.143 (± 0.105)	-0.056 (± 0.093)		

Post-BD FVC (n=30,34)	-0.121 (± 0.114)	0.046 (± 0.096)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-BD FEV1 and Post-BD FEV1 Through Week 28 in Participants With Extent of Emphysema >= 10%

End point title	Change From Baseline in Pre-BD FEV1 and Post-BD FEV1 Through Week 28 in Participants With Extent of Emphysema >= 10%

End point description:

Change from baseline in pre-BD FEV1 and post-BD FEV1 through Week 28 in participants with extent of emphysema >= 10% is reported. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Week -5 to -4) through Week 28 post-dose

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: Litre				
least squares mean (standard error)				
Pre-BD FEV1	-0.015 (± 0.036)	-0.068 (± 0.034)		
Post-BD FEV1	0.074 (± 0.044)	-0.053 (± 0.042)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-BD and Post-BD FVC Through Week 28 in Participants With Extent of Emphysema >= 10%

End point title	Change From Baseline in Pre-BD and Post-BD FVC Through Week 28 in Participants With Extent of Emphysema >= 10%

End point description:

Change from baseline in pre-BD and post-BD FVC through Week 28 in participants with extent of emphysema >= 10% is reported. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Week -5 to -4) through Week 28 post-dose

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: Litre				
least squares mean (standard error)				
Pre-BD FVC	0.089 (± 0.086)	-0.121 (± 0.084)		
Post-BD FVC	0.081 (± 0.081)	-0.094 (± 0.077)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), and TEAEs of Special Interest (TEAESIs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), and TEAEs of Special Interest (TEAESIs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Adverse event of special interest (AESI) are AEs of scientific and medical interest specific to understanding of tozorakimab and requires close monitoring. The TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 through 253 days (maximum observed duration)

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants				
Any TEAEs	53	50		
Any TESAEs	14	9		
Any TEAESIs	33	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point title	Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point description:

Number of participants with abnormal vital signs reported as TEAEs are reported. Abnormal vital signs are defined as any abnormal finding in the vital sign parameters (oral or tympanic temperature, diastolic blood pressure, systolic blood pressure, heart [pulse] rate, and respiratory rate). As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 through 253 days (maximum observed duration)

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants				
Hypertension	2	3		
Hypotension	1	0		
Dyspnoea	2	3		
Pyrexia	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point description:

Number of participants with abnormal clinical laboratory parameters reported as TEAEs are reported. Abnormal clinical laboratory parameters defined as any abnormal finding during analysis of clinical chemistry, hematology, endocrinology, and urinalysis. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 through 253 days (maximum observed duration)

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants				
Anaemia	0	1		
Hypercholesterolaemia	0	1		
Hyperuricaemia	0	1		
Hypertransaminasaemia	1	0		
Haematuria	2	0		
SARS-CoV-2 test positive	2	0		
Hyperthyroidism	0	1		
Hypothyroidism	1	0		
Urinary tract infection	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Electrocardiograms (ECGs) Reported as TEAEs

End point title	Number of Participants With Abnormal Electrocardiograms (ECGs) Reported as TEAEs

End point description:

Number of participants with abnormal ECGs reported as TEAEs are reported. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 through 253 days (maximum observed duration)

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants				
Left ventricular failure	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Level

End point title	Change From Baseline in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Level

End point description:

Change in NT-proBNP Level from baseline is reported. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Day -35 to Day -28) through Week 28

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: pmol/L				
arithmetic mean (standard deviation)				
Week 28	4.051 (± 17.937)	1.948 (± 14.280)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Left Ventricular Ejection Fraction (LVEF) as Measured by Echocardiogram

End point title	Change From Baseline in Left Ventricular Ejection Fraction (LVEF) as Measured by Echocardiogram

End point description:

Change from baseline in LVEF as measured by echocardiogram is reported. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes those participants who were evaluable at Week 28.

End point type	Secondary

End point timeframe:

Baseline (Week -3 to -1) through Week 28

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Ratio				
arithmetic mean (standard deviation)				
Week 28	0.9 (± 5.78)	0.2 (± 4.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Seropositive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

End point title	Number of Participants Seropositive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

End point description:

Number of participants who were seronegative at baseline and who had positive SARS-Cov-2 serology result at the end of study is reported. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of participants analyzed (N) denotes the number of participants who were SARS-CoV-2 serum negative at baseline and had at least one post-baseline result.

End point type	Secondary

End point timeframe:

Baseline (Week 0) through Week 28

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Participants	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Coronavirus Disease 2019 (COVID-19) Related AEs and SAEs

End point title	Number of Participants With Coronavirus Disease 2019 (COVID-19) Related AEs and SAEs

End point description:

The number of participants with COVID-19 related AEs and SAEs are reported. As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 through 253 days (maximum observed duration)

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Participants				
COVID-19 related AEs	17	14		
COVID-19 related SAEs	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Post-BD FEV1 To Weeks 12 and 28

End point title	Change From Baseline in Post-BD FEV1 To Weeks 12 and 28

End point description:

Change from baseline in post-BD FEV1 to Weeks 12 and 28 is reported. ITT population included all participants who received any study drug and were analyzed according to the treatment they actually received. Here, number of subjects analyzed (N) denotes those participants who were included in the analysis.

End point type	Other pre-specified

End point timeframe:

Baseline (Week -5 to -4) to Weeks 12 and 28 post-dose

End point values	Tozorakimab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Litre				
least squares mean (standard error)				
Week 12	0.041 (± 0.036)	-0.025 (± 0.033)		
Week 28	0.021 (± 0.036)	-0.049 (± 0.033)		

Statistical analyses

Statistical analysis title	MMRM analysis at Week 28

Statistical analysis description:

Results are based on the mixed model for repeated measures (MMRM) analysis.

Comparison groups	Tozorakimab v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.036 [3]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	0.07

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.02
upper limit	0.12

Notes:

[2] - Kenward-Roger correction has been used for degrees of freedom approximation in the generation of model.
[3] - One-sided p-value

Statistical analysis title	MMRM analysis at Week 12

Statistical analysis description:

Results are based on the Mixed model for repeated measures (MMRM) analysis.

Comparison groups	Tozorakimab v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.044 [5]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	0.067
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.017
upper limit	0.116

Notes:

[4] - Kenward-Roger correction has been used for degrees of freedom approximation in the generation of model.
[5] - One-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through 253 days (maximum observed duration)

Adverse event reporting additional description:

As-treated population included all participants who received any study drug and were analyzed according to the treatment they actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received 7 doses of SC placebo injection matched to tozorakimab once Q4W.

Reporting group title	Tozorakimab

Reporting group description:

Participants received 7 doses of subcutaneous (SC) tozorakimab Dose Level 1 injection once every 4 weeks (Q4W).

Serious adverse events	Placebo	Tozorakimab	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 68 (13.24%)	14 / 67 (20.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 68 (1.47%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 68 (8.82%)	6 / 67 (8.96%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
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	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 68 (1.47%)	0 / 67 (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	1 / 68 (1.47%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Tozorakimab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 68 (57.35%)	40 / 67 (59.70%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 68 (4.41%)	8 / 67 (11.94%)	
occurrences (all)	3	10	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 68 (0.00%)	10 / 67 (14.93%)	
occurrences (all)	0	25	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	27 / 68 (39.71%)	26 / 67 (38.81%)	
occurrences (all)	56	53	
Infections and infestations			
Covid-19			
subjects affected / exposed	14 / 68 (20.59%)	14 / 67 (20.90%)	
occurrences (all)	14	15	
Nasopharyngitis			
subjects affected / exposed	7 / 68 (10.29%)	3 / 67 (4.48%)	
occurrences (all)	12	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2020	Adjustments regarding timing of repeat attempts in case of failure to successfully obtain spontaneous and induced sputum samples. Added text regarding participants who met eligibility criteria for main study but not sub study and clarification regarding quantitative assessment of computerized tomography (CT) scan showing emphysema in Exclusion Criterion 4 (c). Criteria for discontinuation amended. Added detail regarding how the echocardiogram should be performed and urine specific gravity to Table 8 (Laboratory Safety Variables) in protocol. 'Hepatitis A' was removed from other safety tests. Intensity Rating Scale was replaced with Severity Rating Scale based on the common terminology criteria for adverse events (CTCAE) criteria.
08 February 2021	Exploratory induced sputum sub-study and exploratory capnography sub-study were removed, prior to inclusion of any participants in that sub-study. Added PK and immunogenicity samples at study visit (SV) 11. Added exploratory endpoints covering certain spirometry measures. Added instructions on when coronavirus disease 2019 (COVID-19) vaccination should be given to study participants. Added specific study stopping criteria (individual investigational product discontinuation criteria already present). Added clarification for exclusion criterion 15. Removed requirement for surveillance CT scans as exclusion for main study from exclusion criterion 9(g). Added need for future CT scans as exclusion for CT sub-study from exclusion criterion 43. Added clarification for vaccines with adenoviral vectors that are unable to replicate from exclusion criterion 34(d). Added clarification on recording of COVID-19 vaccination. New question added in Appendix J (Example of Patient COVID-19 Screening Questionnaire) for COVID-19 vaccination.
01 June 2021	Added clarification that pregnancy tests should have been carried out in women of childbearing potential only. Clarified urine pregnancy test at SV2 was not required if CT scan was not performed. Permitted local laboratories to perform severe acute respiratory syndrome coronavirus 2 (SARSCoV2) nucleic acid testing (nasopharyngeal swab), as well as the central laboratory and permitted less frequent testing dependent on prevalence of COVID-19 infection. In inclusion criterion 3, clarification of influenza and pneumococcal vaccine requirements added. Clarification of a positive interferon gamma release assay (IGRA) test in the context of treated latent tuberculosis (TB) infection added. To remove unnecessary effective prohibition on participants unsuccessfully screened for the Imaging Sub-study being rescreened for the Sub-study. In the case of re-screening, to permit echocardiogram and IGRA (TB test) results no more than 3 months old to be re-used. Included that the randomization schedule may be provided to limited personnel. Clarified information to be recorded in the event of a participant receiving a COVID-19 vaccine. Clarified that agreement to participate in the Study Participant Feedback Questionnaire would be included in the informed consent form (ICF). Congenital abnormality changed to congenital anomaly. Clarification of processing of pharmacokinetic (PK) samples from participants who received placebo. Included that neutralizing antibody may also be assessed.

23 July 2021	Removed Exclusion Criterion 4 (predominant emphysema). Section 2.2 (Background), Section 2.3.1 (Risk Assessment) and Section 5.2 (Scientific rationale for study design) updated with new emerging evidence and rationale for update. Added additional secondary and exploratory objective to assess response to tozorakimab by extent of emphysema on baseline CT scan. Reference to exclusion criteria for extent of emphysema removed. Added emphysema subgroup analysis for primary endpoint. Polymerase chain reaction (PCR) analysis changed to nucleic acid analysis. Added information that automated calculation of emphysema percentage was not possible. Changed timing of inclusion criterion 9 from >= 1 exacerbation of chronic obstructive pulmonary disease (COPD) in 12 months to >= 1 exacerbation in 24 months and updated rationale for study population to reflect this change. Changed BMI to 18-35 kg/m^2. Clarified wording on lung resection exclusion and testing. Clarification on testing for hepatitis C infection added.
16 February 2022	Amended participants randomization and number of evaluable participants. Updated new participant numbers, sample size justification in statistical method section. Clarified spirometry assessment timing. Added salivary sample as additional option for SARS-CoV-2 nucleic acid test. Updated risk assessment related to progression of heart failure. Revised CT risk mitigations. Removed Week 20 assessment of blood biomarkers and assessment of soluble receptor for advanced glycation end products (sRAGE) and fibronectin. mRNA nasal transcriptome exploratory biomarkers clarified as from nasal mucosal sampling. Week 36 assessment of serum biomarkers added. Updated number of participants to be randomized and expected percentage of participants in baseline and inhaled corticosteroids (ICS) strata removed. Added advice on ensuring adequate time for CT and echocardiogram assessments. Clarified use of eDiary and spirometry assessment timing. Reduced overall number of participants in the CT sub-study. Clarified when to perform echocardiogram in cases of suspected heart failure. Updated inclusion criterion 1, 3, 4, 5, 8, 9, 13, and exclusion criterions 1, 3a, 3c, 3e, 3f, 5, 9g, 24, 9e, 10, 15, 23, 34h, 34i, 34k, 41, and 43. Removed collection of spontaneous sputum samples from home. Phenotype monitoring details of participants removed. Reduced overall number of participants in CT sub-study to remain proportionate to reduced size of main study. Text around strata caps and safety alerts removed. Revised vaccination against influenza and pneumonia advice. Added baseline audiometry testing to be documented before randomization. Advice on spirometry assessment timing clarified. Dose of radiation in mSV removed. Revised text to add circumstances in which anti-drug antibody (ADA) samples could be collected after follow-up period. Reduced size of population in small CT exploratory sub-study to explore impact of tozorakimab on radiological biomarkers of airways inflammation and mucus plugging.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported