Clinical trial results:
A Phase 2, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of MEDI3506 in Adult Participants with Uncontrolled Moderate-to-severe Asthma

Summary

EudraCT number	2020-000789-40
Trial protocol	HU DE
Global end of trial date	06 February 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2023
First version publication date	28 December 2023

Trial information

Trial identification

Sponsor protocol code	D9181C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04570657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, 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	06 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the effect of tozorakimab (MEDI3506) compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 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: 87
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	235
EEA total number of subjects	81

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)	235
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled and randomised in 52 study centres in 7 countries including Argentina, Germany, Hungary, Poland, South Africa, the United Kingdom, and the United States from 17 September 2020. The last participant completed their last study visit on 06 February 2023.

Pre-assignment

Screening details:

Adult participants with uncontrolled moderate to severe asthma were randomised in a 1:1:1 ratio to receive tozorakimab Dose A (lower dose), tozorakimab Dose B (higher dose), or placebo. Of the 478 participants screened, 250 were enrolled, and of these 15 were excluded from analysis due to invalidity of data.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tozorakimab Dose A

Arm description:

Participants were randomised to receive tozorakimab Dose A by SC injection.

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:

Tozorakimab Dose A by subcutaneous (SC) injection.

Arm title	Tozorakimab Dose B

Arm description:

Participants were randomised to receive tozorakimab Dose B by SC injection.

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:

Tozorakimab Dose B by SC injection.

Arm title	Placebo

Arm description:

Participants were randomised to receive placebo by SC injection.

Arm type	Placebo

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

Dosage and administration details:

Placebo by SC injection.

Number of subjects in period 1	Tozorakimab Dose A	Tozorakimab Dose B	Placebo
Started	77	77	81
Intent to Treat (ITT) Population	77	77	81
As-treated Population	77	77	81
Pharmacokinetic (PK) Population	75 [1]	77	0 [2]
Completed	76	74	77
Not completed	1	3	4
Consent withdrawn by subject	1	2	2
Physician decision	-	1	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	-	-	1

Notes:

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

Justification: Two participants in the tozorakimab Dose A arm were not included in the PK population due to no post-baseline PK results.

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

Justification: Participants in the placebo arm were not included in the PK population.

Baseline characteristics

Reporting groups	
Reporting group title	Tozorakimab Dose A
Reporting group description:	
Participants were randomised to receive tozorakimab Dose A by SC injection.	
Reporting group title	Tozorakimab Dose B
Reporting group description:	
Participants were randomised to receive tozorakimab Dose B by SC injection.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomised to receive placebo by SC injection.	

Reporting group values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo
Number of subjects	77	77	81
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)	77	77	81
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	42.1	43.1	48.3
standard deviation	± 11.97	± 12.37	± 10.41
Gender Categorical Units: participants			
Female	53	54	43
Male	24	23	38
Race Units: Subjects			
Asian	0	0	1
Black or African American	4	8	7
White	71	67	72
Other	2	2	1
Ethnicity Units: Subjects			
Hispanic or Latino	26	24	33
Not Hispanic or Latino	51	53	48

Reporting group values	Total		
Number of subjects	235		

Age Categorical Units: participants			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	235		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: participants			
Female	150		
Male	85		
Race Units: Subjects			
Asian	1		
Black or African American	19		
White	210		
Other	5		
Ethnicity Units: Subjects			
Hispanic or Latino	83		
Not Hispanic or Latino	152		

End points

End points reporting groups

Reporting group title	Tozorakimab Dose A
Reporting group description:	
Participants were randomised to receive tozorakimab Dose A by SC injection.	
Reporting group title	Tozorakimab Dose B
Reporting group description:	
Participants were randomised to receive tozorakimab Dose B by SC injection.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomised to receive placebo by SC injection.	

Primary: Change from Baseline to Week 16 in Pre-bronchodilator (Pre-BD) Forced Expiratory Volume in the First Second (FEV1) as Measured in the Study Clinic

End point title	Change from Baseline to Week 16 in Pre-bronchodilator (Pre-BD) Forced Expiratory Volume in the First Second (FEV1) as Measured in the Study Clinic
End point description:	
In-clinic spirometry measurements were taken prior to the administration of bronchodilators. Baseline was the last measurement prior to first injection of investigational product (IP). The least squares (LS) means, LS mean differences and 80% confidence intervals (CIs), and one-sided p-value results were based on a mixed model repeated measures (MMRM). The model included fixed effects for baseline, background medication, geographic region, baseline inhaled corticosteroids (ICS) total daily dose, visit, treatment, and the baseline by visit and treatment by visit interactions. Visits within participant were considered as repeated measurements. The ITT population included participants who were randomised and received any study intervention. Participants with data available are included.	
End point type	Primary
End point timeframe:	
Baseline and week 16	

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	77	81	
Units: litres				
least squares mean (standard error)	0.148 (± 0.047)	0.116 (± 0.048)	0.112 (± 0.046)	

Statistical analyses

Statistical analysis title	LS Mean Difference: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473 [1]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.004
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.071
upper limit	0.079

Notes:

[1] - One-sided p-value

Statistical analysis title	LS Mean Difference: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.267 [2]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.036
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.038
upper limit	0.111

Notes:

[2] - One-sided p-value

Secondary: Change from Baseline to Weeks 8 and 16 in Post-bronchodilator (Post-BD) FEV1 as Measured in the Study Clinic

End point title	Change from Baseline to Weeks 8 and 16 in Post-bronchodilator (Post-BD) FEV1 as Measured in the Study Clinic

End point description:

In-clinic spirometry measurements were taken following the use of bronchodilators. Bronchodilatation was induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose), and measurements were taken after up to a maximum of 4 inhalations. Baseline was the last measurement prior to first injection of IP.
The LS means, LS mean differences and 80% CIs, and one-sided p-value results were based on MMRM. The model included fixed effects for baseline, background medication, geographic region, baseline ICS total daily dose, visit, treatment, and the baseline by visit and treatment by visit interactions. Visits within participant were considered as repeated measurements. The ITT population included participants who were randomised and received any study intervention. Participants with data available are included.

End point type	Secondary

End point timeframe:

Baseline and weeks 8 and 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	35	
Units: litres				
least squares mean (standard error)				
Week 8	-0.062 (± 0.067)	0.008 (± 0.068)	-0.050 (± 0.060)	
Week 16	-0.064 (± 0.067)	-0.050 (± 0.068)	-0.026 (± 0.060)	

Statistical analyses

Statistical analysis title	Week 8 Difference: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437 [3]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.012
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.11
upper limit	0.086

Notes:

[3] - One-sided p-value

Statistical analysis title	Week 8 Difference: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221 [4]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.059
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.039
upper limit	0.157

Notes:

[4] - One-sided p-value

Statistical analysis title	Week 16 Difference: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 [5]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.038
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.136
upper limit	0.06

Notes:

[5] - One-sided p-value

Statistical analysis title	Week 16 Difference: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372 [6]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.025
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.122
upper limit	0.072

Notes:

[6] - One-sided p-value

Secondary: Serum Concentrations of Tozorakimab

End point title	Serum Concentrations of Tozorakimab[7]

End point description:

Tozorakimab serum concentrations were measured using a validated assay method. The PK population included participants who received at least one dose of tozorakimab and had at least one detectable serum concentration measurement post-first dose of study intervention. Participants with data available at each time point are presented.
99999 = Geometric mean (CV%) could not be calculated due to too many samples with tozorakimab concentrations below the limit of quantification.

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) samples were taken pre-dose (day 1) and at weeks 1, 4, 8, 12, 16, 20, and 24

Notes:

[7] - 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: It was pre-specified for serum concentrations of tozorakimab to be assessed in participants included in the tozorakimab Dose A and tozorakimab Dose B reporting arms only.

End point values	Tozorakimab Dose A	Tozorakimab Dose B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: µg/L				
geometric mean (geometric coefficient of variation)				
Pre-dose (n=74, 77)	99999 (± 99999)	99999 (± 99999)		
Week 1 (n=74, 76)	8939.24 (± 367.31)	18374.15 (± 239.89)		
Week 4 (n=72, 72)	2165.82 (± 180.17)	4102.04 (± 168.60)		
Week 8 (n=74, 70)	2680.07 (± 113.59)	4476.11 (± 109.27)		
Week 12 (n=74, 75)	2673.94 (± 121.08)	4646.57 (± 153.62)		
Week 16 (n=71, 72)	2742.93 (± 128.83)	5007.93 (± 117.76)		
Week 20 (n=75, 72)	356.56 (± 177.25)	761.75 (± 152.78)		
Week 24 (n=74, 72)	80.36 (± 170.34)	146.67 (± 214.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-drug Antibodies (ADAs)

End point title	Number of Participants with Anti-drug Antibodies (ADAs)

End point description:

ADA prevalence is the number of participants ADA positive (ADA+) at baseline (BL) and/or post-BL. Treatment-emergent ADA+ (TE-ADA +) positive is defined as being either of treatment-induced ADA+ (ADA negative [ADA-] at BL and at least one post-BL ADA+) and treatment-boosted ADA+ (ADA+ at BL and BL titre is boosted by ≥ 4-fold increase at ≥ 1 post-BL time point). Treatment-emergent ADA- (TE-ADA-) is defined as ADA+ but not fulfilling the definition of TE-ADA+. ADA persistently positive is defined as ADA- at BL and ADA+ at ≥ 2 post-BL assessment with ≥ 16 weeks between first and last positive assessments, or ADA+ at the last post-BL assessment. ADA transiently positive is defined as ADA- at BL, having at least one post-BL ADA+ assessment and not fulfilling the conditions of ADA persistently positive. BL is defined as the last ADA assessment prior to first injection of IP. The as-treated population included participants who were randomised and received any study intervention.

End point type	Secondary

End point timeframe:

Blood samples were taken pre-dose (day 1) and at weeks 1, 4, 8, 12, 16, and 24

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	81	
Units: participants				
ADA prevalence (n=77, 77, 81)	3	3	1	
TE-ADA+ (n=75, 77, 81)	3	2	1	

Treatment-induced ADA+ (n=75, 77, 81)	3	2	1	
TE-ADA- (n=75, 77, 81)	0	1	0	
Baseline and post-baseline + (n=74, 77, 81)	0	1	0	
ADA persistently positive (n=74, 77, 81)	3	1	0	
ADA transiently positive (n=74, 77, 81)	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in the Asthma Control Questionnaire-6 (ACQ-6) Score

End point title	Change from Baseline to Week 16 in the Asthma Control Questionnaire-6 (ACQ-6) Score

End point description:

In the ACQ-6, participants were asked to recall how their asthma has been during the previous week by responding to one BD-use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between >0.75 and <1.5 indicate partly controlled asthma, and scores ≥1.5 indicate not well-controlled asthma. Results were based on an MMRM which included fixed effects for baseline, background medication, geographic region, baseline ICS total daily dose, visit, treatment and the baseline by visit and treatment by visit interactions. Visits within participant were considered as repeated measurements. A negative change from baseline indicates an improvement in asthma control. The ITT population included participants who were randomised and received any study intervention. Participants with data available are included.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	77	81	
Units: score on a scale				
least squares mean (standard error)	-0.925 (± 0.117)	-0.942 (± 0.117)	-0.895 (± 0.112)	

Statistical analyses

Statistical analysis title	LS Mean Difference: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371 [8]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.047
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.231
upper limit	0.137

Notes:

[8] - One-sided p-value

Statistical analysis title	LS Mean Difference: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.416 [9]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.215
upper limit	0.154

Notes:

[9] - One-sided p-value

Secondary: Number of Participants with a Decrease in ACQ-6 Score ≥ 0.5 from Baseline to Week 16

End point title	Number of Participants with a Decrease in ACQ-6 Score ≥ 0.5 from Baseline to Week 16

End point description:

In the ACQ-6, participants were asked to recall how their asthma has been during the previous week by responding to one BD-use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between >0.75 and <1.5 indicate partly controlled asthma, and scores ≥1.5 indicate not well-controlled asthma. A decrease in ACQ-6 score baseline indicates an improvement in asthma control, and individual changes of at least 0.5 are considered clinically meaningful. The ITT population included participants who were randomised and received any study intervention. Participants with missing ACQ-6 scores were not included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	77	
Units: participants	53	56	53	

Statistical analyses

Statistical analysis title	Odds Ratio: Tozorakimab Dose B versus Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.41
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.88
upper limit	2.25

Statistical analysis title	Odds Ratio: Tozorakimab Dose A versus Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.612
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.76
upper limit	1.9

Secondary: Change from Baseline to Week 16 in St George's Respiratory Questionnaire (SGRQ) Domain and Total Scores

End point title	Change from Baseline to Week 16 in St George's Respiratory Questionnaire (SGRQ) Domain and Total Scores

End point description:

The SGRQ is a 50-item patient-reported outcome instrument to measure the health status of participants with airway obstruction diseases, giving a total score and 3 domain scores (symptoms,

activity, and impacts). The total score is expressed as a percentage of overall impairment, with 100 representing the worst possible health status and 0 the best possible health status. Each domain score ranges from 0 to 100, with higher scores indicating greater impairment. A negative change from baseline indicates an improvement in impairments. Results were based on an MMRM which included fixed effects for baseline, background medication, geographic region, baseline ICS total daily dose, visit, treatment and the baseline by visit and treatment by visit interactions. Visits within participant were considered as repeated measurements. The ITT population included participants who were randomised and received any study intervention. Participants with data available are included.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	77	80	
Units: score on a scale				
least squares mean (standard error)				
SGRQ Activity Total Score	-10.340 (± 2.477)	-11.706 (± 2.507)	-10.342 (± 2.390)	
SGRQ Impacts Total Score	-8.237 (± 1.750)	-8.509 (± 1.774)	-6.816 (± 1.689)	
SGRQ Symptoms Total Score	-15.290 (± 2.828)	-19.130 (± 2.873)	-15.981 (± 2.726)	
SGRQ Total Score	-10.133 (± 1.815)	-11.366 (± 1.838)	-9.470 (± 1.750)	

Statistical analyses

Statistical analysis title	SGRQ Activity Score: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [10]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.002
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.825
upper limit	3.828

Notes:

[10] - One-sided p-value

Statistical analysis title	SGRQ Activity Score: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324 [11]
Method	MMRM
Parameter estimate	Ls mean difference
Point estimate	-1.364
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.198
upper limit	2.47

Notes:

[11] - One-sided p-value

Statistical analysis title	SGRQ Impacts Score: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248 [12]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.421
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.103
upper limit	1.26

Notes:

[12] - One-sided p-value

Statistical analysis title	SGRQ Impacts Score: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [13]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.694
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.383
upper limit	0.996

Notes:

[13] - One-sided p-value

Statistical analysis title	SGRQ Symptoms Score: Tozorakimab Dose A - Placebo

Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42 [14]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.691
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.715
upper limit	5.096

Notes:

[14] - One-sided p-value

Statistical analysis title	SGRQ Symptoms Score: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.181 [15]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.15
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-7.579
upper limit	1.28

Notes:

[15] - One-sided p-value

Statistical analysis title	SGRQ Total Score: Tozorakimab Dose A - Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [16]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.663
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.454
upper limit	2.129

Notes:

[16] - One-sided p-value

Statistical analysis title	SGRQ Total Score: Tozorakimab Dose B - Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192 [17]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.896
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.694
upper limit	0.903

Notes:

[17] - One-sided p-value

Secondary: Number of Participants Achieving ACQ-6 Well Controlled Status at Week 16

End point title	Number of Participants Achieving ACQ-6 Well Controlled Status at Week 16

End point description:

In the ACQ-6, participants were asked to recall how their asthma has been during the previous week by responding to one BD-use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between >0.75 and <1.5 indicate partly controlled asthma, and scores ≥1.5 indicate not well-controlled asthma. The ITT population included participants who were randomised and received any study intervention. Participants with missing ACQ-6 scores were not included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	77	
Units: participants	17	18	21	

Statistical analyses

Statistical analysis title	Odds Ratio: Tozorakimab Dose B versus Placebo
Comparison groups	Tozorakimab Dose B v Placebo

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.53
upper limit	1.38

Statistical analysis title	Odds Ratio: Tozorakimab Dose A versus Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.5
upper limit	1.31

Secondary: Number of Participants with a Decrease in SGRQ Total Score of ≥ 4 Points from Baseline to Week 16

End point title	Number of Participants with a Decrease in SGRQ Total Score of ≥ 4 Points from Baseline to Week 16

End point description:

The SGRQ is a 50-item patient-reported outcome instrument to measure the health status of participants with airway obstruction diseases, giving a total score and 3 domain scores (symptoms, activity, and impacts). The total score is expressed as a percentage of overall impairment, with 100 representing the worst possible health status and 0 the best possible health status. A decrease in the SGRQ total score indicates an improvement in overall impairment. The ITT population included participants who were randomised and received any study intervention. Participants with missing SGRQ scores were not included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	77	
Units: participants	50	53	54	

Statistical analyses

Statistical analysis title	Odds Ratio: Tozorakimab Dose B versus Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.68
upper limit	1.7

Statistical analysis title	Odds Ratio: Tozorakimab Dose A versus Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.828
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.59
upper limit	1.46

Secondary: Asthma CompEx Annualised Event Rate

End point title	Asthma CompEx Annualised Event Rate

End point description:

The annualised rate of asthma CompEx events was calculated as the total number of asthma CompEx events / (date of last dose of IP + 28 - date of first dose of IP - recovery time + 1) / 365.25.
The rates, rate ratios, and one-sided p-values were estimated from a negative binomial regression, with the log(follow up time) included as an offset term. The dependent variable will be the number of

CompEx events during the on-treatment period (i.e., from baseline to last dose date +28 days), and the model will include treatment group, background medication, geographic region and baseline ICS total daily dose as covariates. The ITT population included participants who were randomised and received any study intervention.

End point type	Secondary

End point timeframe:

Baseline to week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	81	
Units: events per participant-treatment year				
number (confidence interval 80%)	0.86 (0.58 to 1.28)	0.69 (0.44 to 1.07)	0.99 (0.68 to 1.44)	

Statistical analyses

Statistical analysis title	Rate Ratio: Tozorakimab Dose B versus Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.166 [18]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.7
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.43
upper limit	1.12

Notes:

[18] - One-sided p-value

Statistical analysis title	Rate Ratio: Tozorakimab Dose A versus Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.346 [19]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.87

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.56
upper limit	1.36

Notes:

[19] - One-sided p-value

Secondary: Number of Participants for Time to First Asthma CompEx Event

End point title	Number of Participants for Time to First Asthma CompEx Event

End point description:

Asthma CompEx is a combination of exacerbations of asthma and diary events (i.e., a combination of electronic diary [eDiary] variables). eDiary events are defined by criteria using morning/evening diary variables of PEF, symptoms, and use of rescue medication. A participant was considered to have a CompEx event if they had one or both of an asthma exacerbation or diary event. For participants who did not experience an on-treatment CompEx event, date of censoring was the minimum between the date of last dose + 28 days, and the last day of eDiary recording during the on-treatment period. Time to first Asthma CompEx event was calculated as [start date of first event or censoring - date of first dose] + 1. The ITT population included participant who were randomised and received any study intervention.

End point type	Secondary

End point timeframe:

Baseline to week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	81	
Units: participants	19	15	15	

Statistical analyses

Statistical analysis title	Hazard Ratio: Tozorakimab Dose B versus Placebo
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.6
upper limit	1.7

Notes:

[20] - One-sided p-value estimated using a Cox regression model with treatment group, background medication, geographic region, and ICS total daily dose as covariates.

Statistical analysis title	Hazard Ratio: Tozorakimab Dose A versus Placebo
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239 [21]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.8
upper limit	2

Notes:

[21] - One-sided p-value estimated using a Cox regression model with treatment group, background medication, geographic region, and ICS total daily dose as covariates.

Secondary: Percent Change from Baseline to Week 16 in Concentration of Fractional Exhaled Nitric Oxide (FeNO) in Exhaled Breath

End point title	Percent Change from Baseline to Week 16 in Concentration of Fractional Exhaled Nitric Oxide (FeNO) in Exhaled Breath

End point description:

A standardised single-breath FeNO test was performed to evaluate airway inflammation. Results were based on MMRM on log-transformed change from baseline. Log-transformed change from baseline is calculated as the visit value in log minus the baseline value in log. The results from the model were then back transformed. The model included fixed effects for baseline (in log), background medication, geographic region, baseline ICS total daily dose, visit, treatment and the baseline by visit and treatment by visit interactions. Visits within subject were considered as repeated measurements.

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	77	81	
Units: percent change				
least squares mean (confidence interval 80%)	-17.429 (-23.423 to -10.965)	-16.500 (-22.548 to -9.981)	-5.007 (-11.612 to 2.091)	

Statistical analyses

Statistical analysis title	Geometric LS Mean Ratio
Comparison groups	Tozorakimab Dose B v Placebo

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [22]
Method	MMRM
Parameter estimate	Geometric LS mean ratio
Point estimate	0.879
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.8
upper limit	0.966

Notes:

[22] - One-sided p-value

Statistical analysis title	Geometric LS Mean Ratio
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [23]
Method	MMRM
Parameter estimate	Geometric LS Mean Ratio
Point estimate	0.869
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.791
upper limit	0.956

Notes:

[23] - One-sided p-value

Secondary: Eosinophil Count

End point title	Eosinophil Count

End point description:

The eosinophil count at baseline and week 16 are presented. Baseline was defined as the last measurement prior to first injection of IP.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	81	
Units: 10^9 cells/L				
geometric mean (geometric coefficient of variation)				

Baseline (N=77, 77, 81)	0.187 (± 80.4)	0.200 (± 88.4)	0.178 (± 83.3)	
Week 16 (N=65, 70, 73)	0.122 (± 82.9)	0.136 (± 77.6)	0.185 (± 93.2)	

Statistical analyses

Statistical analysis title	Week 16 Geometric LS Mean Ratio
Statistical analysis description: Tozorakimab Dose B versus Placebo	
Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	Geometric LS Mean Ratio
Point estimate	0.675
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.599
upper limit	0.76

Notes:

[24] - One-sided p-value

Statistical analysis title	Week 16 Geometric LS Mean Ratio
Statistical analysis description: Tozorakimab Dose A versus Placebo	
Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.001 [26]
Method	MMRM
Parameter estimate	Geometric LS Mean Ratio
Point estimate	0.63
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.559
upper limit	0.71

Notes:

[25] - A total of 156 participants were included in this analysis.

[26] - One-sided p-value

Other pre-specified: Change from Baseline to Week 16 in Pre-BD FEV1 as Measured in the Study Clinic: Analysis per Number of Exacerbations in Last 12 Months

End point title	Change from Baseline to Week 16 in Pre-BD FEV1 as Measured in the Study Clinic: Analysis per Number of Exacerbations in

	Last 12 Months

End point description:

In-clinic spirometry measurements were taken prior to the administration of bronchodilators. Baseline was the last measurement prior to first injection of IP.
The LS means, LS mean differences and 80% CIs, and one-sided p-value results were based on MMRM. The model included fixed effects for baseline, visit, treatment, and the baseline by visit and treatment by visit interactions. Visits within participant were considered as repeated measurements. Analysis is presented by the number of exacerbations experienced within the 12 months prior to baseline (1 or ≥ 2 exacerbations in the previous 12 months). The ITT population included participants who were randomised and received any study intervention.

End point type	Other pre-specified

End point timeframe:

Baseline and week 16

End point values	Tozorakimab Dose A	Tozorakimab Dose B	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	47	52	
Units: litres				
least squares mean (standard error)				
1 Exacerbation in Last 12 Months (N=45, 47, 52)	0.188 (± 0.065)	0.042 (± 0.070)	0.165 (± 0.062)	
≥ 2 Exacerbations in Last 12 Months (N=31, 30, 29)	0.059 (± 0.067)	0.194 (± 0.065)	-0.018 (± 0.069)	

Statistical analyses

Statistical analysis title	LS Mean Difference: Tozorakimab Dose A - Placebo

Statistical analysis description:

Analysis of treatment difference in participants with 1 exacerbation in the last 12 months.

Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385 [27]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.023
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.078
upper limit	0.124

Notes:

[27] - One-sided p-value; alpha = 0.1

Statistical analysis title	LS Mean Difference: Tozorakimab Dose A - Placebo

Statistical analysis description:

Analysis of treatment difference in participants with ≥ 2 exacerbations in the last 12 months.

Comparison groups	Tozorakimab Dose A v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.186 [29]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.077
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.034
upper limit	0.187

Notes:

[28] - A total of 90 participants were included in this analysis.

[29] - One-sided p-value; alpha = 0.1

Statistical analysis title	LS Mean Difference: Tozorakimab Dose B - Placebo

Statistical analysis description:

Analysis of treatment difference in participants with ≥ 2 exacerbations in the last 12 months.

Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.007 [31]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.212
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.102
upper limit	0.322

Notes:

[30] - A total of 90 participants were included in this analysis.

[31] - One-sided p-value; alpha = 0.1

Statistical analysis title	LS Mean Difference: Tozorakimab Dose B - Placebo

Statistical analysis description:

Analysis of treatment difference in participants with 1 exacerbation in the last 12 months.

Comparison groups	Tozorakimab Dose B v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [32]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.123

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.224
upper limit	-0.022

Notes:

[32] - One-sided p-value; alpha = 0.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to Week 24 (up to 24 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Tozorakimab Dose A
Reporting group description: Participants were randomised to receive tozorakimab Dose A by SC injection.	
Reporting group title	Tozorakimab Dose B
Reporting group description: Participants were randomised to receive tozorakimab Dose B by SC injection.	
Reporting group title	Placebo
Reporting group description: Participants were randomised to receive placebo by SC injection.	

Serious adverse events	Tozorakimab Dose A	Tozorakimab Dose B	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	2 / 81 (2.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Acid peptic disease			

subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tozorakimab Dose A	Tozorakimab Dose B	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 77 (32.47%)	20 / 77 (25.97%)	20 / 81 (24.69%)
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	4 / 77 (5.19%)	7 / 77 (9.09%)	2 / 81 (2.47%)
occurrences (all)	5	15	5
Injection site swelling			
subjects affected / exposed	0 / 77 (0.00%)	4 / 77 (5.19%)	1 / 81 (1.23%)
occurrences (all)	0	5	4

Injection site urticaria			
subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	0 / 81 (0.00%)
occurrences (all)	1	7	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	3 / 81 (3.70%)
occurrences (all)	4	2	3
COVID-19			
subjects affected / exposed	15 / 77 (19.48%)	10 / 77 (12.99%)	11 / 81 (13.58%)
occurrences (all)	17	12	12
Nasopharyngitis			
subjects affected / exposed	6 / 77 (7.79%)	5 / 77 (6.49%)	4 / 81 (4.94%)
occurrences (all)	6	6	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2020	- Removal of references to the interim analysis for the study. - Removal of airway volume and airway resistance computed tomography (CT) scan measures from airway remodelling endpoint. - Addition of study stopping criteria. - Removal of reference of relatedness of serious adverse events as a reason to discontinue participants from the study and 'any SAE of ≥ Grade 4 severity' added. - Addition of new discontinuation criterion - Severity rating scale for adverse events updated to a Grade 1 to 5 based on Common Terminology Criteria for Adverse Events (CTCAE).
23 February 2021	- Addition of provision for increased flexibility during the screening period, for clinical laboratory testing due to practical limitation in receiving test results. - Addition of provision for increased flexibility for COVID-19 PCR testing during the screening period due to practical limitation in receiving test results. - Clarification that all female participants should have had a pregnancy test. - Addition of provision for retesting of interferon gamma release assay (IGRA). - Provision of clarification to investigators of the sponsor's approach to COVID-19 vaccination in this study. - Addition of provision for retesting of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP). - Adjustment to the periods to which the adherence criteria applied. - Addition of allowance that limited personnel that had responsibility for PK and ADA sample analysis could have access to the randomisation schedule. - Clarification that adenoviral vector vaccines were not considered live attenuated. - Addition of restriction on when vaccines against COVID-19 may have been administered, and clarification on the requirement to record COVID-19 vaccination.
25 May 2021	- To amend study endpoints as appropriate for the change to a 2-part study design. - To amend the study design to include 2 parts: Part A (main study) and Part B (airway hyperresponsiveness and remodelling study). - Specified that post-BD spirometry was to be performed if documented evidence of asthma was not already available. - Clarification that on days when IP was administered, all assessments should have been performed pre-dose unless otherwise specified. - Provision of clarity on pregnancy testing in female participants. - Clarification of provision for airwave oscillometry and in-clinic spirometry to be performed 4 hours post-administration of study intervention at randomisation. - Specified that the mean value of each parameter from the triplicate electrocardiogram was to be used as the baseline value. - Clarification of the doses of tozorakimab used in Part A. - Clarification of a positive IGRA test in the context of treated latent tuberculosis infection. - Clarification of eligibility criteria relating to history of asthma exacerbations and the use of systemic corticosteroids. - Clarified that assessment of injection site reactions after administration of study intervention was carried out by a blinded study team. - Updated list of medication withhold periods to be applied prior to scheduled spirometry, airway oscillometry, and FeNO measurement. - Updated information to be recorded if and when a participant received a COVID-19 vaccination. - Changed 'congenital abnormality' to 'congenital anomaly'. - Specified that ADA samples may have been tested for neutralising antibodies.

08 March 2022	- Removal of references to and text regarding Part B, and removal of occurrences of 'Part A' as Part B had been removed and Part A was the entirety of the study. - Addition of text to minimise any missing mandatory samples. - Updated rationale for risk of progression of heart failure. - Changes to the inclusion criteria to increase the permitted body mass index, and historic exacerbation requirement from one in 12 months to one in 24 months. - Changes to the exclusion criteria to remove the exclusion of all participants who tested positive for SARS-CoV-2 at the first screening visit, and all participants who tested positive at the second screening visit continued to be excluded; to remove the exclusion of participants with NT-proBNP above the upper limit of normal; and to remove reference to HbA1c in relation to the control of type 2 diabetes. - Removed dose from list of information to be recorded for COVID-19 vaccination. - Adjustment of requirements of acceptable documentation of historical asthma exacerbations. - Aligned with EU guidelines for data storage.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

15 participants at 1 study centre were excluded from the final analysis due to inability to confirm the validity of the data. This did not change the interpretation of the primary endpoint or for any other endpoint.

Notes: