Clinical trial results:
A randomised placebo-controlled trial of anti-ST2 in COPD (COPD-ST2OP)

Summary

EudraCT number	2018-000919-24
Trial protocol	GB
Global end of trial date	31 December 2020

Results information

Result version number	v1 (current)
This version publication date	28 January 2022
First version publication date	28 January 2022

Trial information

Trial identification

Sponsor protocol code	0671

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03615040
WHO universal trial number (UTN)	U1111-1210-1335
Other trial identifiers	IRAS ID: 244758, REC reference: 18/EM/0189, Funder reference: GB40568

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Ethics, Governance and Integrity Office, Leicester General Hospital, Leicester, United Kingdom, LE5 4PW
Public contact	COPD-ST2OP Trial Manager, Leicester Clinical Trials Unit, University of Leicester, COPD-ST2OP@leicester.ac.uk
Scientific contact	Prof Christopher Brightling, Chief Investigator, Department of Respiratory Sciences, University of Leicester, +44 (0)116 250 2704 , ceb17@leicester.ac.uk

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	17 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the efficacy of anti-ST2 versus placebo on frequency of moderate-to-severe exacerbations (health care utilisation resulting in treatment with systemic corticosteroids and/or antibiotics) in 48 weeks as an add-on to standard of care.

2) To assess the safety and tolerability of subcutaneous doses of anti-ST2 compared to placebo in adult patients with moderate to very severe COPD.

3) To assess the effects of anti-ST2 versus placebo both during stable visits and at the exacerbation events on the following:
(a) Symptoms
(b) Health status
(c) Lung function
(d) Inflammatory cell differentials: (i) Sputum cell count and (ii) Blood cell count
(e) Airway morphometry
(f) Pharmacogenomics

Protection of trial subjects:

Eligibility criteria for this trial were carefully considered to ensure the safety of the participants. Patients with active or unstable recent cardiovascular disease (CVD) were excluded from the trial. Cardiac safety was evaluated with monitoring of vital signs, ECG assessments, the collection of relevant AEs, and other assessments described in the protocol. Lastly, to monitor other factors that may impact upon cardiovascular risk, HbA1c, fasting glucose, and lipid panels were monitored to observe for indication of possible atherogenic and metabolic effects of MSTT1041A exposure. In populations at high risk for pre-existing CVD, additional monitoring strategies including echocardiography and cardiac biomarkers (e.g., NTproBNP) were also used.

Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs) and deaths were subject to expedited reporting by the site to the Sponsor. Leicester CTU and the Sponsor provided monthly safety updates to the Data Safety Monitoring Committee (DSMC) and Genentech (funder and supplier of the trial drug and placebo), who reviewed the trial data periodically. In order to comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, an accurate record of all Adverse Events (AEs) reported was maintained throughout the trial. Safety reviews occurred at monthly Trial Management Group (TMG) meetings and quarterly meetings with Genentech.

Safety and tolerability (i.e. SAE/AE rate in the 48 weeks of the trial from first dose) was a key secondary outcome.

Participants were evaluated for an additional 12 weeks following completion of the efficacy endpoint (visit 13, week 48).

A procedure for unblinding was available 24/7 via a validated web-based randomisation system (Sealed Envelope).

Background therapy:

Standard-of-care drug therapy as per British Thoracic Society (BTS) guidance for Chronic Obstructive Pulmonary Disease (COPD).

Evidence for comparator:

Interleukin-33 (IL-33) is an alarmin released from the epithelium following damage. IL-33 is an IL-1 family alarmin cytokine constitutively expressed at epithelial barrier surfaces where it is rapidly released from cells during tissue injury. IL-33 signals through a receptor complex of IL-1 receptor-like 1 (IL1RL1)

(known as ST2) and IL-1 receptor accessory protein (IL1RAcP) to initiate MyD88-dependent inflammatory pathways. The role of the IL33/ST2 axis in COPD is uncertain. IL33 has been implicated in eosinophil recruitment to the airway and maturation in the bone marrow largely via its effects upon innate lymphoid cells. IL33 increased following experimental cold in asthma and thus might play a role in the consequent inflammatory response and possible susceptibility to secondary bacterial infection in obstructive lung disease.

MSTT1041A (official USAN name now astegolimab) 490mg subcutaneous or matched placebo was given every 4 weeks for a total of 12 doses. Participants were followed up for 60 weeks (i.e. 48 week treatment period and 12 week follow-up), with secondary outcome measures at baseline, 4, 12, 24, 36, 48 and 60 weeks and at exacerbations events presenting prior to treatment initiation. The dose and dosing interval was derived from an earlier PK/PD modelling and was the highest dose included in a phase IIb asthma study. The primary outcome measure was exacerbation frequency. Exacerbation events are relatively infrequent and can be affected by season, therefore a 48 week treatment duration with follow-up out to 12 months was chosen.

Astegolimab has been investigated in 3 completed phase I studies. Additionally, a phase IIb study in patients with severe asthma and a phase II study in patients with atopic dermatitis have been completed. One phase II study in patients with severe COVID-19 pneumonia is ongoing, with patients having completed dosing. Astegolimab has been generally well tolerated and its safety profile remains favourable at this time.

Actual start date of recruitment	11 October 2018
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	United Kingdom: 81
Worldwide total number of subjects	81
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment at a single centre. Potential participants were identified by the research team using a variety of methods: database of previous COPD trial participants who consented to be contacted for future trials; respiratory outpatient clinics/acute admission unit; self-referrals; GP practices. Recruitment ran between 11 Oct 2018 and 05 Jul 2019.

Pre-assignment

Screening details:

Potential participants were assessed according to eligibility criteria at initial screening and provided written informed consent before commencing any trial-related procedures. Participants then entered a screening period for 7-14 days before randomisation. Those eligible were randomised into a 48-week treatment period (anti-ST2/placebo).

Pre-assignment period milestones

Number of subjects started	97[1]
Intermediate milestone: Number of subjects	Subjects consented: 97
Intermediate milestone: Number of subjects	Subjects randomised: 81
Number of subjects completed	81

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 16

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 97 patients consented to the trial and completed a screening visit (week 0). However, 16 of these were screen fails. Therefore, 81 participants were randomised (and thus enrolled) in the trial.

Period 1

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

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 1	Anti-ST2	Placebo
Started	42	39
Completed	42	39

Period 2

Period 2 title	Week-4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes

Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 2	Anti-ST2	Placebo
Started	42	39
Completed	42	39

Period 3

Period 3 title	Week-12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial

monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 3	Anti-ST2	Placebo
Started	42	39
Completed	41	38
Not completed	1	1
Death	-	1
Clinical diagnosis of lung cancer	1	-

Period 4

Period 4 title	Week-24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 4	Anti-ST2	Placebo
Started	41	38
Completed	40	38
Not completed	1	0
Participant decision	1	-

Period 5

Period 5 title	Week-36
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 5	Anti-ST2	Placebo
Started	40	38
Completed	40	36
Not completed	0	2
Participant decision	-	2

Period 6

Period 6 title	Week-48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, the trial management team and those involved in trial conduct remained blinded to treatment allocations until after database lock. Unblinded personnel included the trial statistician; pharmacy team; personnel responsible for trial drug preparation and reconstitution; trial monitor/Sponsor (one entity); and the DSMC in order to periodically review trial data. No emergency unblinding was required during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-ST2

Arm description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Arm type	Experimental
Investigational medicinal product name	MSTT1041A
Investigational medicinal product code	
Other name	Astegolimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

MSTT1041A was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses). We therefore estimate a cumulative maximum exposure per participant of approximately 5.88g, with a total study cumulative maximum exposure across all participants (n=81) of 445.9g. This calculation takes into account the 14 participants withdrawn from the trial treatment.

Arm title	Placebo

Arm description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

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

Dosage and administration details:

Placebo was administered by the blinded research personnel in the form of a 490mg subcutaneous infusion over 48 weeks (every 4 weeks for 12 months – maximum 12 doses).

Number of subjects in period 6	Anti-ST2	Placebo
Started	40	36
Completed	37	33
Not completed	3	3
Clinical diagnosis of Oesophageal cancer	1	-
Physician decision	2	2
Death	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Anti-ST2
Reporting group description:	
Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.	
Reporting group title	Placebo
Reporting group description:	
Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.	

Reporting group values	Anti-ST2	Placebo	Total
Number of subjects	42	39	81
Age categorical			
Units: Subjects			
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)	12	4	16
From 65-84 years	30	35	65
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	67.6	70.8	
standard deviation	± 8.2	± 6.2	-
Gender categorical			
Units: Subjects			
Female	17	13	30
Male	25	26	51
Smoking status			
Units: Subjects			
Current smoker	10	6	16
Ex smoker	32	33	65
Ethnicity			
Units: Subjects			
White	41	39	80
Indian	1	0	1
COPD GOLD stage			
Units: Subjects			
COPD GOLD stage I	1	0	1
COPD GOLD stage II	18	16	34
COPD GOLD stage III	14	16	30
COPD GOLD stage IV	9	7	16

Subject analysis sets	
Subject analysis set title	Over 48 Week (repeated measures)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat will be comprised all the participants randomised to the trial (regardless of whether they received trial drug), analysed in their allocated group, where data is available. Therefore participants with missing outcome data will be excluded from the analysis (i.e complete case analysis). No imputation will be carried out for the missing data.
Measurements are taken at week-4, week-12, week-24, week-36 and week-48

Reporting group values	Over 48 Week (repeated measures)		
Number of subjects	81		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.1		
standard deviation	± 7.5		
Gender categorical Units: Subjects			
Female Male			
Smoking status Units: Subjects			
Current smoker Ex smoker			
Ethnicity Units: Subjects			
White Indian			
COPD GOLD stage Units: Subjects			
COPD GOLD stage I COPD GOLD stage II COPD GOLD stage III COPD GOLD stage IV			

End points

End points reporting groups

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Subject analysis set title	Over 48 Week (repeated measures)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat will be comprised all the participants randomised to the trial (regardless of whether they received trial drug), analysed in their allocated group, where data is available. Therefore participants with missing outcome data will be excluded from the analysis (i.e complete case analysis). No imputation will be carried out for the missing data.
Measurements are taken at week-4, week-12, week-24, week-36 and week-48

Primary: Exacerbation rate in 48 weeks

End point title	Exacerbation rate in 48 weeks

End point description:

End point type	Primary

End point timeframe:

The rate of moderate to severe exacerbations each participant had over the course of observed time period for each participant (maximum trial duration for a patient was 49 weeks (48 weeks + 7 days))

End point values	Anti-ST2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: Exacerbation rate in 48 weeks				
arithmetic mean (standard deviation)	2.21 (± 2.04)	2.67 (± 2.14)		

Statistical analyses

Statistical analysis title	ITT analysis of exacerbation frequency in 48 weeks

Statistical analysis description:

A generalised linear model (assuming neg. binomial distribution) was used. The model includes the number of exacerbations during the 48 week treatment as an outcome with explanatory variables of treatment arm & number of exacerbations in the 12 months prior to the trial (stratification factor), and log-time on trial (in weeks) as an offset. The offset, allows for different lengths of time in the trial. Only observed exacerbations were used alongside the corresponding time period in the offset.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	t-test, 2-sided
Parameter estimate	Incidence Rate Ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.14
Variability estimate	Standard error of the mean
Dispersion value	0.15

Secondary: Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point title	Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point description:

End point type	Secondary

End point timeframe:

0-60 weeks (i.e. at any point during trial post randomisation)

End point values	Anti-ST2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: Individuals at least 1 (non-serious) AE				
At least one (non-serious) AE	34	28		
No (non-serious) AEs	8	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point title	Serious Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point description:

End point type	Secondary

End point timeframe:

0-60 weeks (i.e. at any point during trial post randomisation)

End point values	Anti-ST2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: Individuals with at least 1 SAE in trial				
At least 1 SAE during trial	12	16		
No SAEs during trial	30	23		

Statistical analyses

No statistical analyses for this end point

Secondary: St George’s Respiratory Questionnaire for COPD Patients (SGRQ-C)

End point title	St George’s Respiratory Questionnaire for COPD Patients (SGRQ-C)

End point description:

SGRQ-c total score

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-12, Week-24, Week-36 & Week-48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	60.1 (± 13.7)	58.4 (± 17.6)	56.7 (± 13.5)	58.9 (± 16.5)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	40	36
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	56.9 (± 15.2)	59.9 (± 18.2)	56.6 (± 15.3)	59.6 (± 17.9)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	59.5 (± 14.6)	59.5 (± 17.0)	57.7 (± 15.7)	63.3 (± 17.2)

Statistical analyses

Statistical analysis title	SGRQ-c total score - mixed effect linear model

Statistical analysis description:

Mixed effect linear model with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation). Analysed using the modified intention-to-treat population (all the participants randomised to the trial analysed in their allocated group, where data is available).

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	-0.2

Secondary: COPD Assessment Test (CAT) (Questionnaire)

End point title	COPD Assessment Test (CAT) (Questionnaire)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-12, Week-24, Week-36, Week-48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: CAT score				
arithmetic mean (standard deviation)	22.1 (± 6.6)	22.6 (± 5.7)	22.2 (± 5.5)	21.7 (± 5.8)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	36	40	36
Units: CAT score				
arithmetic mean (standard deviation)	22.0 (± 5.1)	22.3 (± 6.9)	22.7 (± 6.9)	22.1 (± 5.5)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: CAT score				
arithmetic mean (standard deviation)	22.7 (± 5.0)	22.4 (± 6.0)	23.4 (± 6.0)	23.6 (± 7.8)

Statistical analyses

Statistical analysis title	CAT score-mixed effect linear model

Statistical analysis description:

CAT score was analysed using mixed effect linear model with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical

variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation). The modified ITT population was used (i.e. the available data the the outcomes for individuals in the ITT population)

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.469
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	2

Secondary: Modified Medical Research Council (mMRC) Dyspnea Scale

End point title	Modified Medical Research Council (mMRC) Dyspnea Scale
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Weeks 4, 12, 24, 36, 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: mMRC dyspnoea score				
median (inter-quartile range (Q1-Q3))	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	36	40	36
Units: mMRC dyspnoea score				
median (inter-quartile range (Q1-Q3))	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (1.0 to 3.0)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: mMRC dyspnoea score				

median (inter-quartile range (Q1-Q3))	2.0 (2.0 to 3.0)	3.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (1.5 to 3.5)

Statistical analyses

Statistical analysis title	mMRC dyspnoea score Wilcoxon rank sum test Week 4
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	mMRC dyspnoea score Wilcoxon rank sum test Week 12
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	mMRC dyspnoea score Wilcoxon rank sum test Week 24
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	mMRC dyspnoea score Wilcoxon rank sum test Week 36
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	mMRC dyspnoea score Wilcoxon rank sum test Week 48

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Secondary: Visual Analogue Score (VAS) Total

End point title	Visual Analogue Score (VAS) Total
End point description:	
End point type	Secondary
End point timeframe: (Week 0 and) Weeks 4, 12, 24, 36, 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: Visual Analogue Score (VAS) Total				
arithmetic mean (standard deviation)	142.7 (± 54.6)	143.8 (± 53.8)	129.3 (± 45.7)	148.5 (± 61.2)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	40	36
Units: Visual Analogue Score (VAS) Total				
arithmetic mean (standard deviation)	139.5 (± 50.3)	140.0 (± 65.1)	131.0 (± 57.9)	146.6 (± 55.1)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: Visual Analogue Score (VAS) Total				
arithmetic mean (standard deviation)	146.9 (± 51.9)	147.6 (± 59.6)	140.7 (± 58.0)	146.5 (± 70.0)

Statistical analyses

Statistical analysis title	VAS Total mixed effects model

Statistical analysis description:

Using mixed effect linear model with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation). In the modified ITT population.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.9
upper limit	6.2

Secondary: Sputum Purulence Colour Card

End point title	Sputum Purulence Colour Card

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	36
Units: sputum purulence colour card score				
median (inter-quartile range (Q1-Q3))	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	36	38	36
Units: sputum purulence colour card score				
median (inter-quartile range (Q1-Q3))	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.5)

End point values	Anti-ST2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	21		
Units: sputum purulence colour card score				
median (inter-quartile range (Q1-Q3))	4.0 (2.0 to 6.0)	4.0 (2.0 to 6.0)		

Statistical analyses

Statistical analysis title	sputum purulence colour card Week 12
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sputum purulence colour card Week 24
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sputum purulence colour card Week 36
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sputum purulence colour card Week 48
Comparison groups	Anti-ST2 v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)

Secondary: Post BD Forced Expiratory Volume in 1 Second

End point title	Post BD Forced Expiratory Volume in 1 Second

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: FEV1,litre(s)				
arithmetic mean (standard deviation)	1.21 (± 0.46)	1.14 (± 0.48)	1.21 (± 0.46)	1.09 (± 0.46)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	34	37	35
Units: FEV1,litre(s)				
arithmetic mean (standard deviation)	1.22 (± 0.48)	1.14 (± 0.52)	1.17 (± 0.43)	1.10 (± 0.50)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	33	15	13
Units: FEV1,litre(s)				
arithmetic mean (standard deviation)	1.23 (± 0.47)	1.09 (± 0.52)	1.30 (± 0.50)	1.09 (± 0.57)

Statistical analyses

Statistical analysis title	Post-BD FEV1 mixed effects model

Statistical analysis description:

A mixed effect linear model with explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), visit time point (as categorical variable), baseline

score and patient identification as a random effect to account for repeated measures over time was fitted for each outcome. Adjusted mean difference between treatment arms with 95% confidence interval and p-value were reported. In the modified ITT population.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.09

Secondary: White Blood Cell Count

End point title	White Blood Cell Count
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week 4, 12, 24, 36, 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	37
Units: 10^9/L				
geometric mean (standard error)	8.2 (± 0.045)	8.0 (± 0.046)	7.5 (± 0.035)	7.5 (± 0.037)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	40	36
Units: 10^9/L				
geometric mean (standard error)	8.0 (± 0.043)	7.7 (± 0.047)	7.8 (± 0.047)	7.6 (± 0.050)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	20	16
Units: 10^9/L				

geometric mean (standard error)	8.0 (± 0.046)	7.3 (± 0.048)	7.5 (± 0.058)	8.0 (± 0.065)

Statistical analyses

Statistical analysis title	White Blood Cell Count

Statistical analysis description:

A mixed effect linear model was fitted on the log transformed outcome with explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), log baseline value, visit time point (as categorical variable) and patient identification as a random effect to account for repeated measures over time. As a result adjusted geometric mean ratio alongside two sided 95%CI and p-value were reported

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.07

Secondary: Eosinophil Count

End point title	Eosinophil Count

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	37
Units: 10^9/L				
geometric mean (standard error)	0.21 (± 0.107)	0.20 (± 0.111)	0.15 (± 0.105)	0.22 (± 0.111)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	38	36
Units: 10^9/L				
geometric mean (standard error)	0.13 (± 0.105)	0.20 (± 0.116)	0.12 (± 0.096)	0.21 (± 0.099)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	20	16
Units: 10^9/L				
geometric mean (standard error)	0.11 (± 0.106)	0.20 (± 0.111)	0.10 (± 0.143)	0.17 (± 0.160)

Statistical analyses

Statistical analysis title	Eosinophil Count mixed effects model

Statistical analysis description:

A mixed effect linear model was fitted on the log transformed outcome with explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), log baseline value, visit time point (as categorical variable) and patient identification as a random effect to account for repeated measures over time. As a result adjusted geometric mean ratio alongside two sided 95%CI and p-value were reported.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.69

Secondary: Neutrophil Count

End point title	Neutrophil Count

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	36
Units: 10^9/L				
geometric mean (standard error)	5.6 (± 0.062)	5.1 (± 0.064)	4.9 (± 0.046)	4.9 (± 0.049)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	39	36
Units: 10^9/L				
geometric mean (standard error)	5.4 (± 0.053)	5.2 (± 0.059)	5.4 (± 0.059)	5.0 (± 0.061)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	20	16
Units: 10^9/L				
geometric mean (standard error)	5.6 (± 0.056)	4.9 (± 0.059)	5.3 (± 0.079)	5.5 (± 0.089)

Statistical analyses

Statistical analysis title	Neutrophil Count mixed effects model

Statistical analysis description:

A mixed effect linear model was fitted on the log transformed outcome with explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), log baseline value, visit time point (as categorical variable) and patient identification as a random effect to account for repeated measures over time. As a result adjusted geometric mean ratio alongside two sided 95%CI and p-value were reported

Comparison groups	Placebo v Anti-ST2
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.668
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.13

Secondary: Macrophage count in sputum

End point title	Macrophage count in sputum

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	34	29	30
Units: Macrophage count (%)				
geometric mean (standard error)	8.9 (± 0.205)	9.6 (± 0.196)	8.6 (± 0.211)	11.0 (± 0.208)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	24	24	20
Units: Macrophage count (%)				
geometric mean (standard error)	9.0 (± 0.190)	9.8 (± 0.216)	9.2 (± 0.222)	12.3 (± 0.244)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	21	11	10
Units: Macrophage count (%)				
geometric mean (standard error)	8.1 (± 0.213)	9.7 (± 0.237)	6.9 (± 0.286)	11.4 (± 0.300)

Statistical analyses

Statistical analysis title	Macrophage count in sputum mixed effects model

Statistical analysis description:

A mixed effect linear model of the log outcome with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and log baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation)

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.114
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.07

Secondary: Epithelium count in sputum

End point title	Epithelium count in sputum

End point description:

End point type	Secondary

End point timeframe:
(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	34	29	30
Units: Epithelium count (%)				
geometric mean (standard error)	1.51 (± 0.255)	1.59 (± 0.243)	1.34 (± 0.257)	2.06 (± 0.253)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	24	24	20
Units: Epithelium count (%)				
geometric mean (standard error)	1.14 (± 0.243)	1.91 (± 0.276)	1.56 (± 0.284)	1.44 (± 0.311)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	21	11	10
Units: Epithelium count (%)				
geometric mean (standard error)	1.03 (± 0.266)	1.26 (± 0.296)	1.56 (± 0.435)	1.21 (± 0.456)

Statistical analyses

Statistical analysis title	Epithelium count in sputum mixed effects model
Comparison groups	Anti-ST2 v Placebo

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.15

Secondary: Eosinophil count in sputum

End point title	Eosinophil count in sputum

End point description:

End point type	Secondary

End point timeframe:
(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	34	29	30
Units: Eosinophil count (%)				
geometric mean (standard error)	1.42 (± 0.254)	1.63 (± 0.242)	0.43 (± 0.188)	1.69 (± 0.185)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	24	24	20
Units: Eosinophil count (%)				
geometric mean (standard error)	0.41 (± 0.168)	1.67 (± 0.190)	0.44 (± 0.191)	1.69 (± 0.209)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	21	11	10
Units: Eosinophil count (%)				
geometric mean (standard error)	0.47 (± 0.212)	1.94 (± 0.236)	0.33 (± 0.232)	1.24 (± 0.243)

Statistical analyses

Statistical analysis title	Eosinophil count in sputum mixed effects model

Statistical analysis description:

A mixed effect linear model with dependent variable of the log outcome at baseline and follow-up time points; explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), visit time point (as categorical variable), log baseline score; an interaction term between treatment and visit as fixed effects; and patient identification as a random effect.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.33

Secondary: Pre BD FEV1 (litres)

End point title	Pre BD FEV1 (litres)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	8	5
Units: litre(s)				
arithmetic mean (standard deviation)	1.43 (± 0.43)	0.94 (± 0.33)	1.43 (± 0.49)	0.86 (± 0.15)

Statistical analyses

Statistical analysis title	Pre BD FVC (litre)
Statistical analysis description:	
Analysis of covariance (ANCOVA) adjusting for the baseline value	
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.35

Secondary: Pre BD FEV1 predicted (%)	
End point title	Pre BD FEV1 predicted (%)
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	8	5
Units: FEV1 predicted (%)				
arithmetic mean (standard deviation)	55.9 (± 17.1)	39.6 (± 10.4)	56.5 (± 19.9)	38.2 (± 8.3)

Statistical analyses

Statistical analysis title	Pre BD FEV1 predicted
Statistical analysis description:	
Analysis of covariance (ANCOVA) adjusting for the baseline value	
Comparison groups	Placebo v Anti-ST2

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.63
upper limit	12.2

Secondary: Pre BD FVC (litre)

End point title	Pre BD FVC (litre)

End point description:

End point type	Secondary

End point timeframe:
(Week 0 and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	8	5
Units: litre(s)				
arithmetic mean (standard deviation)	2.97 (± 0.89)	2.17 (± 0.34)	2.88 (± 0.94)	2.20 (± 0.36)

Statistical analyses

Statistical analysis title	Pre BD FVC (litre)

Statistical analysis description:
Analysis of covariance (ANCOVA) adjusting for the baseline value

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.713
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.44

Secondary: Pre BD FVC predicted

End point title	Pre BD FVC predicted
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	8	5
Units: FVC predicted (%)				
arithmetic mean (standard deviation)	88.5 (± 16.6)	75.6 (± 16.7)	85.8 (± 22.8)	79.2 (± 28.5)

Statistical analyses

Statistical analysis title	Pre BD FVC predicted
Statistical analysis description:	
Analysis of covariance (ANCOVA) adjusting for the baseline value	
Comparison groups	Placebo v Anti-ST2
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.214
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.9
upper limit	7.1

Secondary: Pre BD FEV1/FVC ratio

End point title	Pre BD FEV1/FVC ratio

End point description:

End point type	Secondary

End point timeframe:
(Week 0 and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	8	5
Units: FEV1/FVC ratio				
arithmetic mean (standard deviation)	49.0 (± 14.1)	46.6 (± 18.6)	51.0 (± 15.5)	40.2 (± 9.6)

Statistical analyses

Statistical analysis title	Pre BD FVC1/FVC ratio

Statistical analysis description:
Analysis of covariance (ANCOVA) adjusting for the baseline value

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	18.97

Secondary: Body Plethysmography TLC

End point title	Body Plethysmography TLC

End point description:

End point type	Secondary

End point timeframe:
(Baseline and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	16	19	16
Units: litre(s)				
arithmetic mean (standard deviation)	7.5 (± 1.6)	7.5 (± 1.4)	7.6 (± 1.5)	7.6 (± 1.5)

Statistical analyses

Statistical analysis title	Body plethysmography TLC

Statistical analysis description:

To compare change from baseline to 48 weeks (pre and post treatment measurements), analysis of covariance (ANCOVA) model with baseline value as a covariate was fitted. Adjusted mean difference with 95% confidence interval and p-value were reported.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.905
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.52

Secondary: Body Plethysmography RV

End point title	Body Plethysmography RV

End point description:

End point type	Secondary

End point timeframe:

(Baseline and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	16	19	16
Units: litre(s)				
arithmetic mean (standard deviation)	4.5 (± 1.5)	4.7 (± 1.5)	4.8 (± 1.6)	5.0 (± 1.4)

Statistical analyses

Statistical analysis title	Body plethysmography RV

Statistical analysis description:

To compare change from baseline to 48 weeks (pre and post treatment measurements), analysis of covariance (ANCOVA) model with baseline value as a covariate was fitted. Adjusted mean difference with 95% confidence interval and p-value were reported.

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.47

Secondary: Body Plethysmography RV/TLC (%)

End point title	Body Plethysmography RV/TLC (%)

End point description:

End point type	Secondary

End point timeframe:

(Baseline and) Week 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	16	19	16
Units: RV/TLC ratio (%)				
arithmetic mean (standard deviation)	59.8 (± 9.5)	61.3 (± 11.5)	61.1 (± 11.2)	65.2 (± 9.7)

Statistical analyses

Statistical analysis title	Body plethysmography RV/TLC

Statistical analysis description:

To compare change from baseline to 48 weeks (pre and post treatment measurements), analysis of covariance (ANCOVA) model with baseline value as a covariate was fitted. Adjusted mean difference with 95% confidence interval and p-value were reported.

Comparison groups	Anti-ST2 v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.53
upper limit	1.65

Secondary: VAS dyspnoea score	
End point title	VAS dyspnoea score
End point description:	

End point type	Secondary
End point timeframe:	
(Week 0 and) Week 4, 12, 24, 36, 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: VAS score				
arithmetic mean (standard deviation)	60.1 (± 13.7)	58.4 (± 17.6)	56.7 (± 13.5)	58.9 (± 16.5)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	40	36
Units: VAS score				
arithmetic mean (standard deviation)	56.9 (± 15.2)	59.9 (± 18.2)	56.6 (± 15.3)	59.6 (± 17.9)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: VAS score				
arithmetic mean (standard deviation)	59.5 (± 14.6)	59.5 (± 17.0)	57.7 (± 15.7)	63.3 (± 17.2)

Statistical analyses

Statistical analysis title	VAS Dyspnoea mixed effects model
Statistical analysis description:	
A number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation)	
Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	0.7

Secondary: VAS Cough	
End point title	VAS Cough
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week 4, 12, 24, 36, 48	

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: VAS score				
arithmetic mean (standard deviation)	49.7 (± 23.7)	47.5 (± 22.7)	41.3 (± 19.6)	45.9 (± 25.5)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	36	40	35
Units: VAS score				
arithmetic mean (standard deviation)	44.2 (± 22.3)	45.1 (± 24.6)	47.6 (± 23.7)	45.2 (± 21.9)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: VAS score				
arithmetic mean (standard deviation)	48.4 (± 20.4)	46.0 (± 25.1)	40.4 (± 24.7)	47.0 (± 29.6)

Statistical analyses

Statistical analysis title	VAS Cough mixed effects model

Statistical analysis description:

A mixed effect linear model with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation)

Comparison groups	Anti-ST2 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	4.7

Secondary: VAS Sputum production

End point title	VAS Sputum production

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week 4, 12, 24, 36, 48

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	39	42	38
Units: VAS score				
arithmetic mean (standard deviation)	40.5 (± 25.5)	42.8 (± 24.5)	37.9 (± 24.5)	44.7 (± 27.0)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	35	40	36
Units: VAS score				
arithmetic mean (standard deviation)	40.1 (± 25.7)	40.2 (± 28.7)	36.9 (± 26.3)	43.5 (± 24.3)

End point values	Anti-ST2	Placebo	Anti-ST2	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	35	20	16
Units: VAS score				
arithmetic mean (standard deviation)	42.6 (± 27.3)	44.0 (± 26.2)	41.5 (± 26.5)	39.0 (± 27.6)

Statistical analyses

Statistical analysis title	VAS Sputum production mixed effects model

Statistical analysis description:

A mixed effect linear model with explanatory variables treatment, number of exacerbations in the 12 months prior to the trial (stratification), visit time point (as categorical variable) and baseline score as fixed effects. Participant ID as a random effect to take in to account the repeated measurement (i.e inter-class correlation)

Comparison groups	Placebo v Anti-ST2
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.527
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: recorded at each study timepoint
SAEs/SUSARs: reported to Sponsor and Leicester CTU within 24 hours of research staff learning of the event
AEs of special interest: reported to Sponsor within 24 hours of research staff learning of the event

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Anti-ST2

Reporting group description:

Participants randomised to 490mg MSTT1041A via subcutaneous infusion every 4 weeks for 12 visits.

Reporting group title	Placebo

Reporting group description:

Participants randomised to 490mg matched placebo via subcutaneous infusion every 4 weeks for 12 visits.

Serious adverse events	Anti-ST2	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 42 (28.57%)	16 / 39 (41.03%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Descending aorta thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right thrombosed popliteal aneurysm			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncopal episode			

subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood transfusion (anaemia)			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma of the bowel			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal symptoms			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal cancer			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymo-orchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
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			
Chest infection/infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clinical diagnosis of lung cancer			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Community acquired pneumonia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu-like illness (viral infection)			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital acquired pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	4 / 39 (10.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia and type 2 respiratory failure			

subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Right pneumothorax			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 respiratory failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Elective surgery (transurethral resection of the prostate)			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Resection of prostate			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel obstruction			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected UTI			

subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fractured neck of femur			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left scaphoid fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	
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: 3 %

Non-serious adverse events	Anti-ST2	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 42 (80.95%)	28 / 39 (71.79%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 42 (7.14%)	1 / 39 (2.56%)	
occurrences (all)	3	1	

Nervous system disorders			
Headache			
subjects affected / exposed	10 / 42 (23.81%)	5 / 39 (12.82%)	
occurrences (all)	20	9	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 42 (11.90%)	4 / 39 (10.26%)	
occurrences (all)	5	4	
Lethargy			
subjects affected / exposed	2 / 42 (4.76%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Malaise			
subjects affected / exposed	2 / 42 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	1 / 42 (2.38%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 42 (11.90%)	1 / 39 (2.56%)	
occurrences (all)	7	1	
Dyspepsia			
subjects affected / exposed	1 / 42 (2.38%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	2 / 42 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Oral pain			
subjects affected / exposed	1 / 42 (2.38%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	4 / 42 (9.52%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	5 / 42 (11.90%)	1 / 39 (2.56%)	
occurrences (all)	5	2	

Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	2	2	
Pulmonary mass			
subjects affected / exposed	3 / 42 (7.14%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	4 / 42 (9.52%)	3 / 39 (7.69%)	
occurrences (all)	5	4	
Neck pain			
subjects affected / exposed	4 / 42 (9.52%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
Pain in extremity			
subjects affected / exposed	1 / 42 (2.38%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Skin infection			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	6 / 42 (14.29%)	1 / 39 (2.56%)	
occurrences (all)	11	2	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 42 (7.14%)	4 / 39 (10.26%)	
occurrences (all)	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2019	1. Amendment to CTU trial manager and trial statistician contact details. 2. Change to Genentech (funder) main contact. 3. Nasal epithelial sample changed to optional. Differentiation between epithelial sample and nasosorption. 4. Reduction of duration for visit 0. 5. Addition of transfer factor to lung function tests (Sponsor request for comprehensive overview of tests). 6. Research team to contact GP to obtain additional information/clarification related to medical history, COPD exacerbations and medications if required. 7. GP questionnaire withdrawn from use as not viable document. 8. Extension of recruitment period from 7 months to up to 9 months. 9. Addition of process for CT scans, lung nodules and follow-up. 10. Update to secondary outcomes (removal of physical examination, medical history, current medications and pregnancy testing) as these are descriptors rather than outcomes. 11. Clarification of LCTU's data management responsibilities. 12. Amendment to recording and reporting of SAEs/SUSARs (from point of randomisation rather than from point of consent) and clarification on AESI reporting. 13. Clarification of withdrawal criteria. 14. Clarification of unblinded personnel and their roles. 15. Removal of FBC, U&Es, LFTs, CRP, RNA, serum/plasma inflammatory biomarkers, pharmacogenetics SNPs, and NTproBNP blood tests from visit 1. 16. Addition of participant identification centres (GP surgeries) with support from CRN East Midlands.
11 March 2020	1. Update to Sponsor's email address. 2. Removal of reference to interim analysis throughout. This was agreed following discussions with Leicester CTU Statistics Team who did not feel an interim analysis was justified or warranted. No data will be made available until after final data lock and the end of trial report is finalised ahead of publication. 3. Removal of week 60 washout (visit 14). This will be superseded by a new observational follow-up study (REC ref: 20/LO/0268, IRAS ID: 275215). 4. Update to Schematic of Trial Design for anti-ST2, schedule of procedures and participant trial flow chart to reflect removal of week 60. 5. Clarification of secondary endpoints (text re-arranged in more logical manner but endpoints themselves have not changed). These endpoints were clarified to ensure consistency with the statistical analysis plan (SAP). 6. Clarification of subgroup objectives and analyses. 7. Addition of full BEAT-COPD study name for clarification purposes. 8. Update of wording in relation to the Investigator's Brochure (IB) and Reference Safety Information (RSI) to be generic, to avoid further protocol amendments if the IB version changes.
11 May 2020	1. Week 60 washout (visit 14) reinstated following MHRA non-acceptance of its removal on medical grounds (Notice of Non-Acceptance dated 01/05/2020). 2. Original schematic of trial design and participant trial flow chart reinstated in accordance with the above. 3. Adaptions made to schedule of procedures as part of an Urgent Safety Measure (USM) due to COVID-19 restrictions (see footnote on page 50 for further information). 4. Clarification of time point of 12 week follow-up [12 weeks from visit 13 (week 48) rather than 12 weeks from end of treatment (visit 12, week 44)]. This was an error in the original protocol.

09 June 2020	1. Adaptions made to schedule of procedures. During the COVID-19 restriction period, participants will not be seen at the research clinic for unscheduled and withdrawal visits. 2. Update to Sponsor's email address. 3. Removal of reference to interim analysis throughout. This was agreed following discussions with Leicester CTU Statistics Team who did not feel an interim analysis was justified or warranted. No data will be made available until after final data lock and the end of trial report is finalised ahead of publication. 4. Treatment groups will remain blinded until the 60 week follow-up period is completed and the trial database lock. This was originally stated as '48 week follow-up period' which was an error in the original protocol. 5. Clarification of secondary outcomes, exploratory outcomes and subgroup objectives/analyses. The text has been re-arranged in a more logical manner to ensure consistency with the statistical analysis plan (SAP). The outcomes themselves have not changed. 6. Addition of full BEAT-COPD study name for clarification purposes. 7. Update of wording in relation to the Investigator's Brochure (IB) and Reference Safety Information (RSI) to be generic, to avoid further protocol amendments if the IB version changes.
07 July 2020	1. Pharmacogenomics response analysis in subgroups determined by single nucleotide polymorphism (SNP) for alleles associated with the IL33/ST2 axis and baseline thoracic CT-derived % wall area are to be changed from subgroup objectives to exploratory outcomes for the following reasons: • Due to COVID-19 there was a delay in transporting SNP samples to Genentech (San Francisco, California) and there were limitations for undertaking analyses in California and alternatively in Leicester. • From March-June 2020, California was on a mandated shelter-in-place and shipment of samples to the USA was restricted. Genentech was only accepting samples for projects predetermined to be business critical, and COPD-ST2OP samples were not deemed business critical. • Genentech was operating with a skeleton crew and therefore did not have adequate staff resource in place for sample testing and analysis, therefore causing a delay in obtaining the SNP data for the subgroup analyses. • A large proportion of participants were unable to undergo their visit 13 CT scan due to COVID-19, therefore the CT scan data will take a smaller role in the analysis than originally planned and analysis of the baseline CT scan is affected by access to the University of Leicester campus due to COVID-19. 2. The list of secondary and exploratory outcomes in the study summary has been tidied up to ensure consistency with the list of outcomes in section 3. 3. The Trial Statistician and Senior Trial Manager have been added to the list of protocol contributors. 4. For the subgroup objectives, it has been specified that the patient-reported outcome (PRO) and the lung function variable will be the St George's Respiratory Questionnaire for COPD patients (SGRQ-c) and forced expiratory volume in one second (FEV1) respectively.

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.

Small sample size at a single site, therefore not powered to detect a reduction in exacerbation frequency that was observed. Collection of secondary/exploratory outcomes reduced and spirometry & sputum induction discontinued due to COVID-19.

Notes: