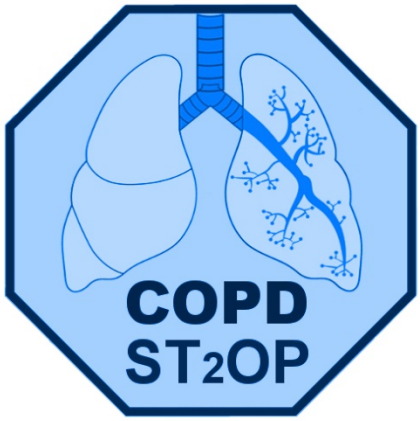
A randomised placebo-controlled trial of anti-ST2 in COPD (COPD-ST$_2$OP)



NCT03615040

Statistical analysis plan

V3.0, 11th January 2021

STATISTICAL ANALYSIS PLAN

A randomised placebo-controlled trial of anti-ST2 in COPD

(COPD-ST$_2$OP)

SAP Version: *V3.0*
Date: *11-Jan-2021*

Based on protocol: Anti-ST2 in COPD Protocol V7.0 07-July-2020
Trial registration: ClinicalTrials.gov Identifier: NCT03615040

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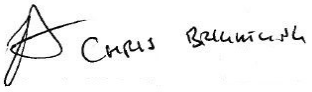
Revision History

Version	Date	Author(s) and Role	Summary of Changes/Comments
0.1	15-Oct-2018	Seid Mohammed	Initial version
0.2	14-Mar-2019	Seid Mohammed	After the whole document was reviewed by CLB
0.3	29-Mar-2019	Seid Mohammed	• After the whole document was reviewed by CEB • Detailed information added on the subgroup analysis based on the COPD-ST2OP Biomarker Research Proposal
0.4	06-Nov-2019	Seid Mohammed	• After the whole document was updated using the COPD-ST2OP mock paper and also updated based on the amended protocol 3.1 dated 11-Sep-2019
1.0	28-May-2020	Seid Mohammed	• After the whole document was updated based on the substantial amendment 02. This includes removal of reference to interim analysis, removal of week 60 washout period, updates to schematic of trial design and clarification of secondary endpoints. • COPD-ST$_2$OP Protocol version 5.0; 11 May 2020
1.1	09-July-2020	Seid Mohammed	• After the whole document was reviewed by NQ, AY, and CLB. • After the whole document was updated based on NQ, AY and CLB comments and suggestions
1.2	27-July-2020	Seid Mohammed	• After the whole document was reviewed by CLB. • Clarification of the sub group analysis
1.3	10-Aug-2020	Seid Mohammed	• After the whole document was updated based on Protocol version 7.0, 07 July 2020 • After the whole document was reviewed by AY, CEB and NQ. • Schedule visit table was updated based on the current protocol
2.0	18-Aug-2020	Seid Mohammed	• Sign off version
2.1	02-Dec-2020	Seid Mohammed	• Following database lock and review of the draft statistical analysis report *post hoc*, i) in addition to the

			median eosinophil count the clinically important cut-off 300 cells/µL was added to the subgroup analyses and ii) SGRQ-c domain scores (Symptoms, Activity and Impacts) were added and provided by the study team as an excel file rather than entered in the MACRO database.
3.0	11-Jan-2021	Seid Mohammed	• Sign off version

SAP approval for finalised version:

Trial Statistician	***Seid Mohammed***	
		11-01-2021
	Signature	**Date**
Chief Investigator	***Prof Chris Brightling***	
		11-01-2021
	Signature	**Date**
Principal Statistician	***Cassey Brookes***	
		11.01.2021
	Signature	**Date**

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of covariance
BMI	Body Mass Index
CAT	COPD Assessment Test
CI	Confidence Interval
CONSORT	Consolidated Standard of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DSMC	Data Safety Monitoring Committee
EudraCT	European Clinical Trials Database
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-33	Interleukin-33
ITT	Intention-to-treat
LFT	Lung Function Test
MAR	Missing at Random
MI	Multiple imputation
mMRC	Modified Medical Research Council
OR	Odds Ratio
QoL	Quality of life
RR	Rate Ratio
RV	Residual volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SUSAR	Suspected unexpected serious adverse reaction
TLC	Total lung capacity
VAS	Visual Analogue Scale

Contents

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for **a randomised placebo-controlled trial of anti-ST2 in COPD (COPD-ST$_2$OP)**. The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP follows internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This SAP should be read in conjunction with the most recent version of the clinical trial protocol.

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the Clinical Study Report (CSR). The SAP will be amended if there are substantial changes to the planned analyses, and in any case will be finalised before the database lock for this study. Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the CSR.

1.1 Study Objectives

1.1.1 Primary Objectives

The primary objective of the trial is 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 add-on to standard of care.

1.1.2 Secondary Objectives

The secondary objectives are to assess:

1. Safety and tolerability
2. Health status and respiratory symptoms
3. Lung function
4. Inflammatory cell differentials
    i. Sputum cell count
    ii. Blood cell count

1.1.3 Exploratory Objectives

The exploratory objectives are to assess:

1. Systemic inflammation
2. Upper airway inflammation
3. Airway infection and ecology

4. Breath volatile organic compound profiling
5. Quantitative airway geometry and densitometry
6. Pharmacogenomics
7. Pharmacokinetics and ADA level
8. Pharmacogenomics response analysis in subgroups determined by SNPs for alleles associated with the IL33/ST2 axis.

1.1.4 Subgroup Objectives

To evaluate the efficacy of anti-ST2 versus placebo on the outcome rate of protocol defined COPD exacerbations, change in St George's Respiratory Questionnaire for COPD patients (SGRQ-C), and FEV1 through 48 weeks treatment period, in subgroups defined by baseline blood eosinophil count (dichotomised about median value).

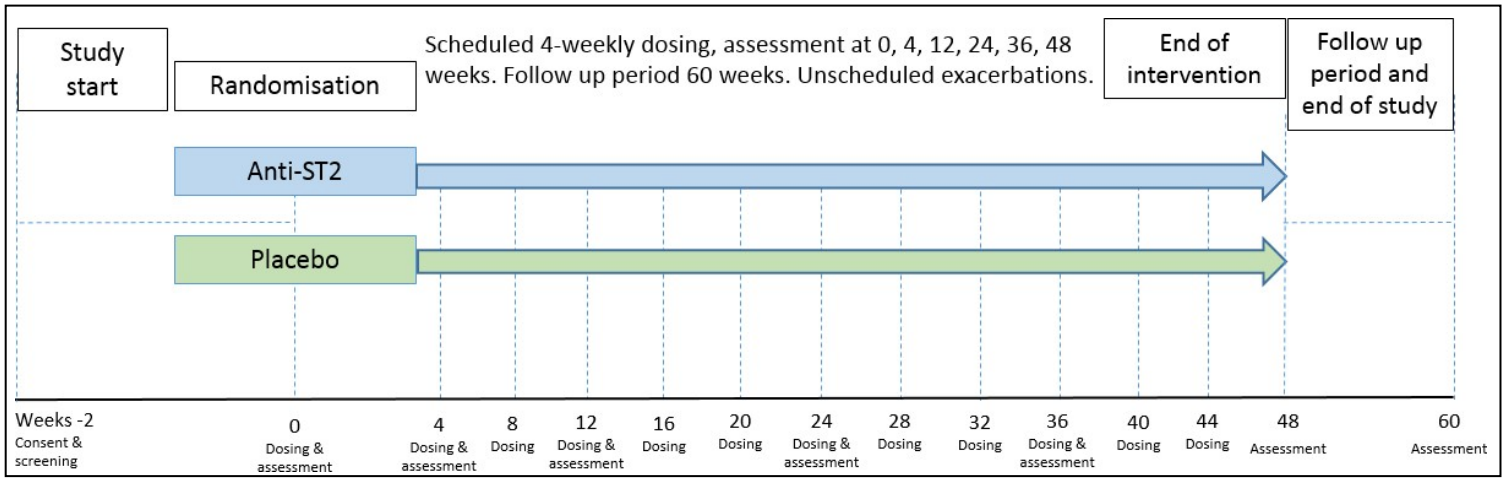
1.2 Trial Design

1.2.1 Overview

This is a single-centre, double-blind, placebo-controlled, parallel group, randomised trial to assess the efficacy and safety of anti-ST2 compared to placebo, in patients with moderate to very severe COPD (GOLD II-IV). Anti-ST2/placebo will be administered via subcutaneous injection once every 4 weeks (Week 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44) during the 48-week treatment period. The treatment period will followed by a 12-week follow-up period (i.e washout period). An overview of the trial design is presented in

.

Figure 1: Schematic of Trial Design for COPD-ST2OP



1.2.2 Participants

Participants will have a diagnosis of moderate to very severe COPD (GOLD II to IV). For further details please refer to the complete inclusion/exclusion criteria in section 6 of the trial protocol.

1.2.3 Treatment groups

1.2.3.1 Intervention group

The intervention is MSTT1041A (anti-ST2). It is a first-in-class, fully human, IgG2 monoclonal antibody (mAb) being developed for use in the treatment of asthma and COPD. Anti-ST2 binds with high affinity to the human receptor for IL-33/ST2, and blocks IL-33 binding, thus inhibiting association with the IL-1R accessory protein (AcP) co-receptor and formation of an activated receptor complex.

Anti-ST2 is presented as sterile, clear, and colourless to slightly yellow liquid. Each sterile vial is filled with a 1 mL deliverable volume of 70 mg/mL. It is formulated with 15 mM sodium acetate, 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 20, pH 5.2.

1.2.3.2 Placebo

Placebo for Anti-ST2 (MSTT1041A) is formulated with 10 mM sodium acetate, 9.0% (w/v) sucrose, 0.004% (w/v) polysorbate 20, pH 5.2, and is supplied in an identical vial configuration.

1.2.4 Sample size

Recruitment of 80 participants with a drop-out rate of 10% will be sufficient to give 80% power at the 5% level assuming either a 48 week exacerbation frequency 2 or 2.5 per year in the placebo group to observe a 50% or 40% reduction in exacerbation frequency in those receiving anti-ST2 respectively.

This sample size estimate is based upon a negative binomial model. The estimation of the over-dispersion was derived from the BEAT-COPD (Biomarkers to Target Antibiotic and Systemic Corticosteroid Therapy in COPD Exacerbations) [ISRCTN92422949] data and was 1.3 with a mean exacerbation frequency of 2.85.

1.2.5 Randomisation and blinding

Participants, investigators, the trial management team and everyone involved in trial conduct will remain blinded with regard to the allocation sequence and randomised treatment assignments until after database lock.

Unblinded personnel will include:

- The trial statistician, in order for the unblinded DSMC to make safety decisions
- The Pharmacy team, to take receipt of and dispense the IMP/placebo
- The designated individuals from the Respiratory BRC responsible for reconstituting the IMP/placebo.

- The trial monitor, in order to perform drug accountability and reconciliation. The Sponsor and the trial monitor are one entity; therefore it will not be possible to maintain the blind of the Sponsor.

Leicester Clinical Trials Unit (LCTU) will supply a web-based randomisation system from a third party (Sealed Envelope Ltd). Participants will be randomised in a 1:1 ratio to anti-ST2 or placebo. This will be set up as a blinded randomisation process, whereby a blinded randomisation code is allocated to a participant which corresponds to either the anti-ST2 or placebo. Decoding lists are held by unblinded personnel and available via Sealed Envelope for emergency unblinding. Randomisation will be stratified by frequency of moderate to severe exacerbation in the previous 12 months (i.e Low [2 or 3] and High [4 or more]).

1.2.6 Emergency unblinding

If it is deemed necessary by the clinical or research team to unblind the patient to the allocated treatment the Chief Investigator must be contacted. Only the Chief Investigator or delegated individual on the delegation log can decide to unblind. Emergency unblinding will be available to the investigator / pharmacist / Sponsor via the web-based Sealed Envelope system. The Sealed Envelope system will be fully audit traceable until the end of the trial to ensure that blinding has not been compromised. Unblinding will only occur in the case of a medical emergency or if a patient experiences an unexpected serious reaction such as a suspected unexpected serious adverse reaction (SUSAR).

Unblinding of all subjects will take place when the last patient has completed their final visit assessments and data collection and validation is complete.

To test the validity of the blinding both the participants and researchers will be asked if they were aware of treatment allocation; this will be recorded on the visit 14 CRF.

1.3 Visit schedule

Table 1: Schedule of Procedures

Trial assessment	Screen	Randomised treatment (visit window +/- 7 days)												Efficacy end point (visit window +/- 7 days)	3 month post-trial follow-up	Withdrawal	Unscheduled visit (e.g. exacerbation)
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 +/- 14 days		
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 60		
Consent	x																
Review Inclusion & Exclusion	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x♦	x♦
Randomisation		x															
Dosing		x	x	x	x	x	x	x	x	x	x	x	X				
Demographics (age, gender, BMI, ethnicity, smoking status)	x																
Vital signs (pulse, BP, temp, O_2 sats)	x	x	x	x	x	x	x	x	x	x	x	x	X	x^	x^	x♦	x♦
Medical history	x																
Concomitant Med	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x♦	x♦
Physical examination	x	x													x^		x♦
Safety AE/SAE		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x♦	x♦
COPD $^{++}$ Exacerbation frequency			x	x	x	x	x	x	x	x	x	x	X	x	x		x♦
SGRQ-c		x	x		x			x			x			x^	x^	x♦	x♦
mMRC	x	x	x		x			x			x			x^	x^	x♦	x♦
CAT		x	x		x			x			x			x^	x^	x♦	x♦
VAS (dyspnoea, cough, sputum)		x	x		x			x			x			x^	x^	x♦	x♦
Sputum Purulence Colour Card	x				x			x			x			x^	x^	x♦	x♦

Trial assessment	Screen	Randomised treatment (visit window +/- 7 days)												Efficacy end point (visit window +/- 7 days)	3 month post-trial follow-up	Withdrawal	Unscheduled visit (e.g. exacerbation)
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 +/- 14 days		
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 60		
VOC (PTRMS & ADVION)	x				x			x			x			x^	x^		x♦
Post- BD spirometry	x		x		x			x			x			x^	x^	x♦	x♦
Pre and post BD spirometry		x												x^			
'Body box'	x$^+$													x^			
HbA$_1$C	x		x		x			x			x			x^	x^		x♦
FBC	x		x		x			x			x			x^	x^	x♦	x♦
U&Es	x		x		x			x			x			x^	x^	x♦	x♦
LFTs	x		x		x			x			x			x^	x^	x♦	x♦
CRP	x		x		x			x			x			x^	x^	x♦	x♦
RNA (PAXgene)	x		x		x			x			x			x^	x^	x♦	x♦
DNA (PAXgene)	x																
Total IgE & RAST (HDM, pollen, cat, dog)	x																
Serum/plasma inflam biomarkers	x		x		x			x			x			x^	x^	x♦	x♦
Lipid profile	x													x^			
Pharmacokinetics PK$^{\$}$		x	x					x						x^			x♦
ADA		x	x					x						x^			x♦
Pharmacogenetics SNPs	x													x^			
NTproBNP	x		x		x			x			x			x^	x^	x♦	x♦
Participant Diary		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x♦	x♦

Trial assessment	Screen	Randomised treatment (visit window +/- 7 days)												Efficacy end point (visit window +/- 7 days)	3 month post-trial follow-up	Withdrawal	Unscheduled visit (e.g. exacerbation)
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 +/- 14 days		
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 60		
Urine sample (10-20ml) for Inflam Biomarker	x	x	x		x			x			x			x^	x^	x♦	x♦
Sputum for Biomarkers Differential cell count, qPCR and Microbiome		x	x		x			x			x			x^	x^		x♦
Nasal epithelial sampling & nasosorption	x				x			x			x			x^	x^		x♦
Pregnancy Testing **	x	x	x	x	x	x	x	x	x	x	x	x	X	x^	x^	x♦	x♦
ECG£	x													x^			x♦
ECHO*		x															x♦
CXR																	x♦
Non-contrast CT chest$$	x													x^			

***** For clinically meaningful increase in NTproBNP ***OR*** new symptoms/signs concerning for HF or cardiac dysfunction ***OR*** clinically significant ECG changes from baseline

+ Body plethysmography ('body box') will be done anytime between screening and week 12, unless patient has had the test within 12 months prior to screening

$ Pk samples should be taken pre-dose

£ 12 lead ECG. If, in the opinion of investigator, the ECG is grossly abnormal (e.g. LBBB, prolonged QTc), it will be compared to old ECGs. If there are no old ECGs for comparison, the investigator will make a clinical judgement about the suitability of the patients to take part in trial.

$$ CT scan. Patients who are claustrophobic or unable to lie flat won't be offered CT scan.

++ COPD Exacerbation frequency where a COPD exacerbation is defined by symptomatic worsening of COPD requiring use of systemic corticosteroids for at least 3 days, a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or Use of antibiotics; and/or An inpatient hospitalisation or death due to COPD.

** Pregnancy testing (blood and urine) can be at any trial visit for WOCBP (i.e.fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy) or if they have missed a menstrual cycle.

^ During the COVID-19 restriction period, these assessments will not be completed at Visit 13 (week 48) and Visit 14 (week 60). All remaining assessments will be competed as per the protocol remotely via a telephone consultation (i.e. participants will not be required to attend the research clinic). Should the restrictions be lifted, participants can attend the research clinic and complete all procedures.

♦ During the COVID-19 restriction period, participants will not be seen at the research clinic for unscheduled and withdrawal visits. Should the restrictions be lifted, participants can attend the research clinic and complete all procedures.

2 Outcomes and other variables

2.1 Primary Outcome

2.1.1 Definition and Derivation of Primary Outcome

The primary outcome is the frequency of moderate to severe exacerbation (defined as requiring treatment with systemic corticosteroids and/or antibiotics in the community of hospital or hospitalisation) in the 48 weeks. COPD exacerbations is defined by symptomatic worsening of COPD requiring:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids;
  and/or
- Use of antibiotics;
  and/or
- An inpatient hospitalisation or death due to COPD

The total number of moderate to severe exacerbation over 48 weeks is defined as a count outcome. This will be derived using the number of moderate to severe exacerbations each participant had over the course of 48 weeks. The outcome will have a minimum value of zero.

Maximum study time for a patient is approximately 49 weeks (48 weeks + 7 days); defined as the time from randomisation to the date of visit 13 (week 48). This will be calculated; (visit-13 date – randomisation date + 1).

2.1.2 Hypothesis to be investigated

COPD patients treated with anti-ST2 therapy will have reduced COPD exacerbation frequency after 48 weeks treatment compared to placebo treated patients.

2.2 Secondary Outcomes

2.2.1 Definition and Derivation of Secondary Outcomes

Note: ** indicates this data is held on Macro database; ^ indicates this data is held externally to the Macro database and will be provided by the team at NIHR Leicester Biomedical Research Centre – Respiratory.*

The secondary endpoints/outcomes are:

1. **Safety and tolerability (All visits)**

- AE event rate in the 48 weeks of the trial from first dose*
- SAE event rate in the 48 weeks of the trial from first dose*

2. **Patient related outcomes (PROs) (Weeks 0, 4, 12, 24, 36 and 48)***

- St George's Respiratory Questionnaire for COPD patients (SGRQ-c)
    - Total score*
    - Domains (*post hoc*):
        i. Symptoms score^
        ii. Activity score^
        iii. Impacts score^
- COPD Assessment Test (CAT)
- mMRC Dyspnoea Scale
- Visual analogue score (VAS)
    - Total
    - Dyspnoea
    - Cough
    - Sputum production
- Sputum purulence colour card

3. **Lung function (Weeks 0 and 48)**

- Pre and post BD Spirometry*
    - FEV1
    - FEV1 % predicted
    - FVC
    - FEV1/FVC %
    - BD reversibility %
- Whole body plethysmography (body box)*
    - TLC
    - RV
    - RV/TLC %

4. **Inflammation (Weeks 0, 4, 12, 24, 36, 48)**

- Cell count
    - Blood inflammatory cell differentials*
        - WBC
        - Eosinophils
        - Neutrophils
    - Sputum inflammatory cell differentials
        - Eosinophils
        - Neutrophils
        - Macrophages
        - Lymphocytes
        - Epilthelial cells
        - Total

2.2.2 Hypotheses to be investigated

All secondary outcomes measures are hypothesised to benefit from the anti-ST2 intervention.

2.3 Exploratory Outcomes

2.3.1 Definition and Derivation of Exploratory Outcomes

- Quantitative measures of airway geometry and densitometry – Contrast thoracic CT-derived outcomes (Weeks 0 and 48)
    - MLD E/I (small airway)
    - % WA
    - LA (Larger airways)
- Mediators
    - Sputum mediator profiling (biomarkers)
    - Blood biomarkers
- Cell subset analysis including but not restricted to exploration of ILC2 cells
- Urine biomarkers of inflammation
- Mediator profiling (biomarkers)
- Upper airway inflammation:
    - nasosorption
    - nasal epithelial sampling (optional)
- Airway infection and ecology:
    - targeted qPCR (bacteria and viruses) for common airway pathogens
    - microbiomics
- Breath volatile organic compound (VOC) profiling (PTRMS and ADVION) – breathomics
- Pharmacogenomics response analysis in subgroups determined by SNPs for alleles associated with the IL33/ST2 axis

2.4 Subgroups and/or interactions

There will be a subgroup analysis of the primary outcome, rate of protocol-defined moderate to severe COPD exacerbations through 48 weeks treatment period and secondary outcomes SGRQ-C and FEV1 by baseline blood eosinophil count (dichotomised about median value).

2.5 Treatment Compliance

All doses of the trial treatment will be administered subcutaneously (SC) at the research site by blinded research staff. The prescribed dosage, and mode of administration should not be changed. If a participant misses a dose, the missed dose can be given within 1 week. Any changes from the intended regimen will be recorded in the CRF.

A summary of the treatment received will be provided by treatment arms. This will include information in terms of dosing, administration, changes and delays from Visit 1

(week 0) to Visit 13 (week 48). Any treatment compliance will be presented by treatment arm and deviations from protocol including loss to follow-up, withdrawal by clinician and withdrawal of consent will be included.

3 Analysis Sets/Populations

3.1 Protocol deviations

3.1.1 Major deviations

Protocol deviations that will affect inclusion in trial populations are:

- Participants found to be ineligible after randomisation
- Participants who receive the wrong study treatment
- Participants who miss greater than one dose of study treatment
- Participants who delay a scheduled study visit greater than 4 weeks

3.1.2 Minor deviations

All other (non-major) protocol deviations will be reported but will not affect analysis populations. e.g. Missing one dose of study treatment, visit assessments delays less than 4 weeks, visit assessments earlier than scheduled (refer to Table 2 in Appendix 1).

3.2 Intention-to-treat Population

The intention-to-treat population will be comprised all the participants randomised in to the trial (regardless of whether they received trial drug) analysed in their allocated group, outcome data obtained from all participants will be included in the data analysis (i.e regardless of study completion or data completeness). All data up to the time of study discontinuation will be included for participants who withdrew prematurely.

3.3 Modified intention-to-treat population

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.

3.4 Per-protocol Population

The per-protocol population will comprise all participants recruited in to the trial who had their intervention administered and who do not have major protocol deviations.

3.5 Safety Population

The safety population will be comprised of the all individuals that received at least one injection of either the anti-ST2 or placebo, with individuals that received any injections of the active dose being analysed in the Anti-ST2 arm, regardless of randomised allocation.

3.6 Other Analysis Populations

None

4 General Issues for Statistical Analysis

4.1 Derived/ Computed Variables

Body mass index (BMI): This will be derived as per WHO Guidelines, BMI measures as Kg/m^2.

Age: Age will be measured in years and will be derived from the date of birth at the randomisation date.

COPD Assessment Tool (CAT) score: The CAT consists of 8 items with scores ranging from 0 to 5 (0= no impairment). An overall score will be calculated by adding the score from each item with total scores ranging from 0 to 40, higher scores indicating a more severe health status impairment or a poorer control of COPD.

St George's Respiratory Questionnaire for COPD patients (SGRQ-C): The SGRQ-C is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is then produced. Each questionnaire response has a unique empirically derived `weight'. The lowest possible weight is zero and the highest is 100. A **Total** and three component scores are calculated: **Symptoms**; **Activity**; **Impacts**.

The **Symptoms** component consists of all the questions in Part 1. The weights for Questions 1-7 are summed. A single response is required to each item. If multiple responses are given to an item, then average weight should be calculated.
The **Activity** component is calculated from the summed weights for the positive responses to items Questions 9 and 12 in Part 2 of the questionnaire.
The **Impacts** component is calculated from Questions 8, 10, 11, 13, 14 in Part 2 of the questionnaire.
Then the **Total** score is calculated by summing the weights to all the positive responses in each component.

FEV1/FVC ratio: FEV1 is the volume of air exhaled in 1 second, FVC is FVC is the full amount of air that can be exhaled with effort in a complete breath. FEV1/FVC ratio is a measure of airflow obstruction, with values <0.7 (70%) indicating airflow obstruction.

BD Reversibility percentage: this will be computed as % Reversibility = (post-BD FEV1- pre-BD FEV1) × 100/pre-BD FEV1

RV/TLC ratio: this is the residual volume (RV) to total lung capacity (TLC). It is calculated using $\frac{RV}{TLC}\ x\ 100\%$

4.2 Multiple Testing

There will be no adjustment for multiple comparisons as there will be only one primary analysis.

4.3 Interim Analysis and Data Review

There is no interim analysis planned. The DSMC will receive report three monthly during recruitment period, then six monthly thereafter during 12 month follow-up period. The report will contain tables on recruitment, disposition of participants, trial and data quality, adverse events, and protocol deviations. There will be open and closed sessions. The open sessions will involve presentation of data relating to recruitment and retention based on pooled data and data quality (e.g data return dates, treatment compliance) blind to treatment allocation. The closed session will involve presentation of efficacy and safety data unblinded by treatment group.

Recruitment and disposition will also be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram.

4.4 Analysis Software

It is anticipated that the analysis will be done in STATA, R or SAS statistical software (versions will be recorded in the statistical report). The University of Leicester holds the relevant licences for this software.

5 Statistical Methodology

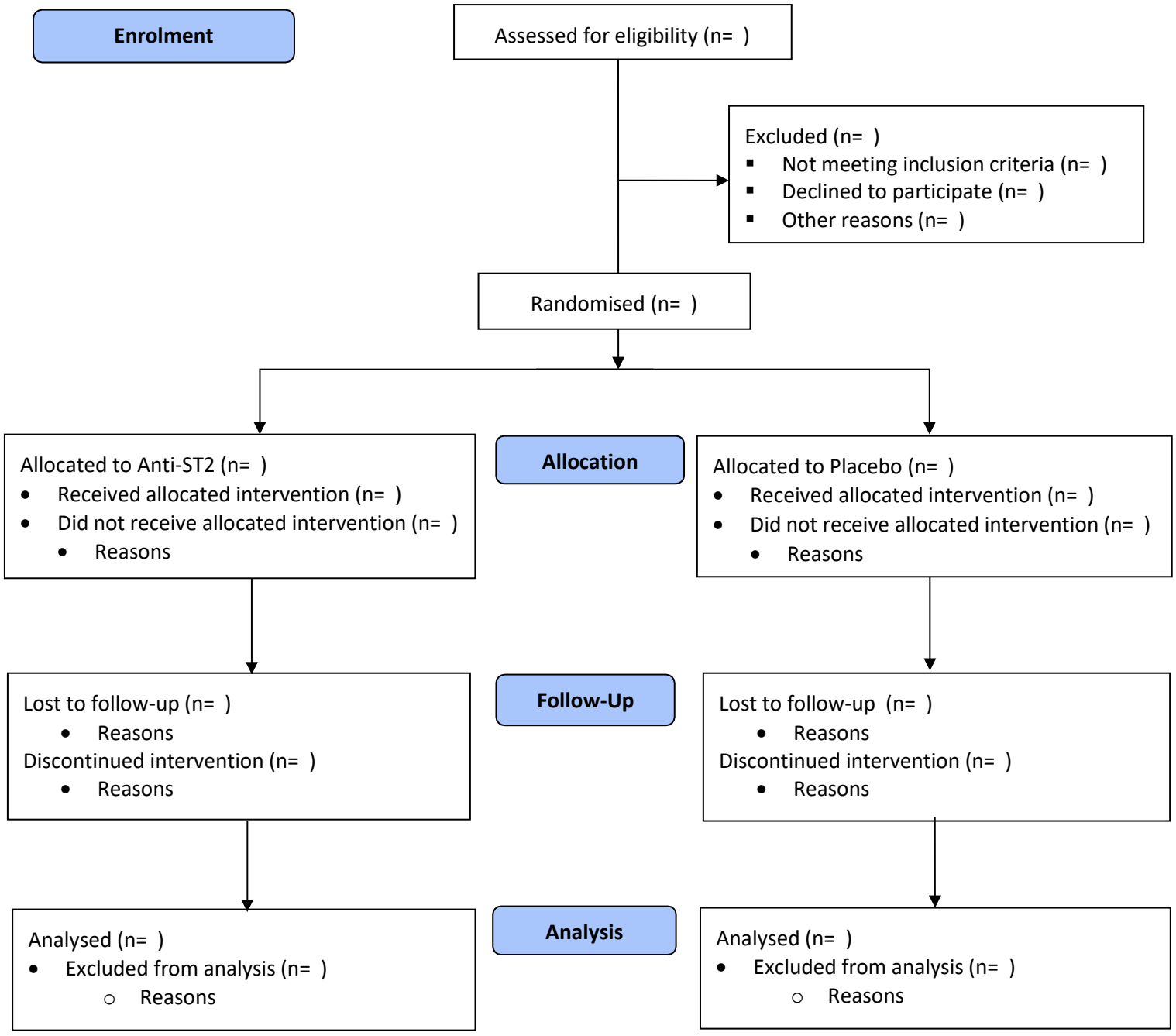
The statistical analysis will be based on relevant guidelines (e.g. ICH E3 and E9 statistical principles for clinical trials). The date of data extraction from the database will be included in each report.

5.1 Disposition of Patients

Patient disposition will be presented with respect to trial completion status, reason for non-completion, protocol deviations, primary outcome data completeness and length of stay in the trial (Figure 3). Results will be tabulated and summarised over time by intervention arm.

A CONSORT [1] diagram will display the flow of patients through the trial. A graph of cumulative recruitment will be presented in addition to summaries of recruitment (e.g. start and end date).

Figure 2: CONSORT Diagram



For detailed information on the reasons for exclusion criteria please refer to Table 3 in Appendix-1.

5.2 Demographic and Baseline Characteristics

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), and medians (with lower and upper quartiles) for continuous variables will be presented. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

The stratification variable will be summarised by treatment arm in order to check the balance of the low and high frequency of moderate to severe exacerbation in the previous 12 months prior to the study between the two randomised arms.

The baseline variables that will be summarised are included in Table 4 in Appendix-1.

5.3 Comparison of losses to follow-up

The numbers (with percentages) of losses to follow-up, withdrawals and discontinuation of study treatment will be reported descriptively between the intervention and placebo arms. Any deaths (and their causes) will be reported separately.

5.4 Primary Outcome Analysis

5.4.1 Primary Analysis of Primary Outcome

The main approach to primary analyses will be an intention-to-treat (ITT), where the ITT population consist of all randomised participants into the trial (regardless of whether they received trial drug). Descriptive statistics of the estimated exacerbations rates in the 48 week treatment period will be presented by treatment arm and overall (Table 5 in Appendix-1). Histogram of the number of exacerbations in the 48 week period by patient will be drawn to check the distribution of the number of exacerbations during treatment (Figure 5). Cumulative number of exacerbations will be plotted by treatment arm (Figure 6).

A generalised linear model (assuming a negative binomial distribution, which accounts for variability among patients in the number of and frequency of exacerbation) will be fitted for the primary outcome of COPD exacerbations during the 48 week treatment period as an outcome with explanatory variables of treatment arm and number of exacerbation in the 12 months prior to the trial (stratification factor), and log-time on study as an offset. The offset (log-time), allows for different lengths of time on treatment for each participant [2]. This assumes that missing data is missing at random (MAR), and will be applied where all of the available observed data are analysed without deletion nor imputation.

The primary outcome data is assumed to follow a negative binomial distribution with the over dispersion estimated to be 1.3. The primary analysis of the primary outcome will give an estimate of the significance of the dispersion parameter. If the dispersion is found to be non-significant (i.e no evidence of over-dispersion) we will consider the simpler Poisson model where the dispersion parameter equals to zero. The ratio of the exacerbation rates (RR) on the anti-ST2 relative to the placebo, associated two-sided 95% confidence interval (CI) and p-value will be reported (Table 5 in Appendix-1). A value of 1.0 would indicate the same rate as placebo; the lower the ratio the greater reduction in exacerbations compared with placebo. A two-sided p-value ≤ 0.05 will be considered as a significant difference in the number of COPD exacerbations in 48 weeks between the two treatment arms.

5.4.2 Secondary Analyses of Primary Outcome

The secondary analysis of the primary outcome will be carried out on the per-protocol population. In this analysis participants with major protocol deviations (as defined in section 3.1.1) will be excluded from the analysis. All other methods regarding the model construction and presentation will remain the same.

5.4.3 Sensitivity Analyses

To examine the sensitivity of the result of the primary analysis to departures from the underlying assumptions (i.e MAR), additional analysis will be performed using the controlled multiple imputation method [3].

5.5 Secondary Outcome Analyses

5.5.1 Primary Analysis of Secondary Outcomes

All secondary end-points will be analysed using the modified intention-to-treat population, with the exception of adverse events, for which we will analyse the safety population, consisting of all participants who received at least one dose of trial medication.

Descriptive statistics of all the secondary outcomes listed in section 2.2 will be presented by treatment arms and overall by assessment time points (i.e by visit). Numbers (with percentages) for binary and categorical variables and means (and standard deviations), and medians (with lower and upper quartiles) for continuous variables will be presented.

All binary secondary outcomes will be compared between treatment groups using logistic regression. Odd ratio (OR) with two-side 95% CI and P-value will be reported for those outcomes.

All continuous longitudinal outcomes (repeated measurements i.e week 0, 4, 12, 24, 36 and 48) will be compared using mixed effects model with explanatory variables of treatment arm, number of exacerbations in the 12 months prior to the trial (stratification factor), visit number in weeks (categorical) and patient identification as a random effect to account for repeated measures over time. This method will able to handle missing data happening during the follow-up measurements. Adjusted mean differences alongside two sided 95% CI and P-value will be reported for these outcomes. If the distribution of the variable found to be far from normal distribution, a log transformation will be used to modify the non-normality. Adjusted geometric mean difference alongside two sided 95% CI and P-value will be reported.

To compare change from baseline to 48 weeks (pre and post treatment measurements), analysis of covariance (ANCOVA) model with baseline value as a covariate will be used. Adjusted mean differences with 95% confidence interval will be reported if the data are normally distributed. If there is severe departure from normality the first approach will be data transformation with the above technique applied to the transformed data. Adjusted geometric mean difference with 95% CI and P-value will be reported. If the data cannot be transformed to normality then the Mann-Whitney U test will be used and in this case no baseline adjustment will be made.

All safety data will be analysed as described in section 7 of this SAP.

5.5.2 Secondary analysis of the Secondary outcome

Per-protocol population analysis will be carried out for key secondary outcomes. These are FEV_1 post-bronchodilator, SGRQ-C and CAT. All other methods regarding the model construction and presentation will remain the same.

5.5.3 Sensitivity Analyses

There will be no sensitivity analyses carried out for any secondary outcome measures.

6 Exploratory Outcome Analyses

The accumulation of the exploratory outcome data will take several months following completion of the week 60 follow-up period. Therefore the exploratory outcome analyses will not form part of initial data lock and analysis of this data will occur after the primary and secondary outcomes have been completed and reported. All exploratory end-points will be analysed at a later stage outside the remit of Leicester CTU. Therefore those analyses may not bound by this SAP, though they are expected to follow the broad principles laid out within this document.

6.1 Subgroup Analyses

A subgroup analysis of the primary outcome will be carried out based on baseline blood eosinophil, dichotomised by the median value. The primary outcome of COPD exacerbations in 48 weeks will be summarised by low or high eosinophil count and analysed as described in section 5.4.1. An indicator variable to specify the eosinophil group (low or high) will be added to the analysis model. The additional of an interaction term between eosinophil indicator variable and treatment group will assess the difference in treatment efficacy between low and high eosinophil groups. *Post hoc* the clinically important eosinophil cut-off (>300 eosinophils/µL) was included as an additional subgroup analysis.

Additional subgroup analyses of the SGRQ-C and FEV_1 will also be carried out based on the baseline blood eosinophil, dichotomised by the median value. The SGRQ-C sore and FEV_1 will be summarised by low or high eosinophil count and analysed as described in section 5.4.1. An indicator variable to specify the eosinophil group (low or high) will be added to the analysis model. The addition of an interaction term between eosinophil indicator variable and treatment group will assess the difference in SGRQ-C score and FEV1 between the low and high eosinophil groups.

6.2 Changes to the Planned Analysis

All changes to the original planned analysis will be noted in the statistical report alongside the reasons and justifications.

7 Safety and Adverse Events

All safety data will be presented according to the safety population. Any adverse events and serious adverse events occurring from the first dose throughout the trial period will be recorded on the AE CRF, Sponsor's SAE form and SAE tracking log.

An Adverse Event (AE) is any untoward medical occurrence in a patient, associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic condition (except COPD)
- New conditions detected or diagnosed after trial treatment administration even though it may have been present prior to the start of the trial
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of trial treatment
- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social admission to a hospital)
- COPD exacerbation, progression, signs and symptoms (unless they are considered to be related to the trial drug by the investigator; then they would constitute a reaction)

An adverse reaction (AR) is an untoward and unintended response(s) related to the study treatment. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study treatment qualify as adverse reactions.

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is defined as any adverse event or adverse reaction in a trial participant that:

- Results in death
- Is life threatening (the subject was at risk of death at the time of event)

- Requires hospitalisation or prolongation of an existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other serious Important Medical Event - an event that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed above should be considered.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an adverse reaction that is both unexpected (not consistent with the Reference Safety Information) and also meets the definitions of a Serious Adverse Reaction.

All adverse events will be listed including, seriousness, duration, relatedness, severity, action taken, outcome, and treatment arm and overall.

For detailed information on the ways of reporting AEs and SAEs please refer to Table 7 and Table 8 in Appendix-1.

8 References

1, Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010;152. Epub 24 March.

2, Keene ON, Calverley PM, Jones PW, Vestbo J, Anderson JA. Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. *Eur Respir J* 2008; **32:** 17–24.

3, Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics 2014;13:258-64.

9 Appendices

9.1 Appendix 1: Templates for Tables, Listings and Figures

Table 2: Protocol deviations by treatment arm and overall

Deviation Type		**Anti-ST2 (n =) n (%)**	**Placebo (n =) n (%)**	**Total (n=) n (%)**
Major deviations				
	ineligible after randomisation			
	received the incorrect trial treatment			
	missed greater than one dose of trial treatment			
	delayed a scheduled trial visit > 4 weeks			
Minor				
Total				

Table 3: Expansion of reasons for exclusion from the COPD-ST2OP trial

		N	**%[1]**
Patients assessed for eligibility and consent			
Eligible and recruited to the trial			
Excluded from the trial			
	Did not meet inclusion criteria		
	Reason 1		
	Reason 2		
	Reason 3		
	Refused to participate		
	Reason 1		
	Reason 2		
	Reason 3		
	Other reasons		

[1]Percentage calculated over the total of assessed patients (n=)

Figure 3: Time to study drug discontinuation or withdrawal

Table 4: Demographic and Baseline Clinical Characteristics

Characteristics	**Anti-ST2 (n =)**	**Placebo (n =)**	**Total (n =)**
Age (years), Mean (SD)			
Male sex, n (%)			
Ethnicity, n (%)			
White			
Asian			
BMI (kg/m^2), Mean (SD)			
Smoking status, n (%)			
Current			
Former			
Pack- years, mean (SD)			
Number of exacerbations in the previous 12 months, Mean (SD)			
Number of exacerbations in the previous 12 months, n (%)			
1			
2			
3			
≥4			
Number of exacerbations in the previous 12 months, n (%)			
Low [2 or 3]			
High [4 or more]			
Baseline eosinophil count, cells/µL, Mean (SD)			
Sputum eosinophils (%)			
Post-BD FEV1, % predicted normal, mean (SD)			
Post-BD FVC, % predicted normal, mean (SD)			
Post-BD FEV1/FVC, % mean (SD)			
GOLD status			
II			
III			
IV			
Previous diagnosis of asthma, n (%)			
Participants questionnaires, mean (SD)			
VAS dyspnoea score			
VAS sputum score			
VAS cough score			
mMRC dyspnoea score			
SGRQ-C total score			
CAT score			

Data are n (%), mean (SD), or median (IQR), unless otherwise stated.

Table 5: Summary of estimated exacerbation rates

		Anti-ST2	Placebo	Total
Number of exacerbations	N			
Exacerbation rate in 48 weeks	Mean (SD)			
	Median (IQR)			
	Min, Max			
Patients experienced an exacerbation	n (%)			
Patients did not experience any exacerbations	n (%)			

Abbreviations: SD= Standard deviation; IQR= Inter-quartile range, Min=Minimum; Max=Maximum; N= number of observations
Data are n (%), mean (SD), or median (IQR), unless otherwise stated.

Figure 4: Distribution of the number of moderate to severe exacerbation among subjects (overall)

Figure 5: Distribution of the number of moderate to severe exacerbation among subjects (by treatment arm)

Figure 6: Cumulative number of moderate to severe exacerbations occurred in each trial arm over the course of 48 weeks plotted over time by treatment arm

Table 6: Summary of treatment comparisons

	Anti-ST2 versus placebo		
	RR*	95% CI	p-value^
Frequency of Exacerbations in Anti-ST2 relative to Placebo			

*Adjusted for the number of exacerbation in the 12 months prior to the trial
^A two-sided p-value ≤ 0.05 will be considered as a significant difference in the number of COPD exacerbations in 48 weeks between the two treatment arms.
Abbreviations: RR= Rate Ratio; CI=Confidence interval

Table 7: Adverse events

		Anti-ST2 (n =)	Placebo (n =)	Total (n =)
Number of treatment-emergent adverse events				
Adverse events leading to deaths				
Patient reporting one or more treatment-emergent adverse event				
Number of treatment-emergent serious adverse events				
Patients reporting one or more treatment-emergent serious adverse event				
Patient with treatment-emergent adverse events leading to discontinuation				
Treatment-emergent adverse events by system organ				
	Respiratory, thoracic and mediastinal disorders			
	Upper respiratory tract infection			
	Lower respiratory tract infection			
	Musculoskeletal and connective tissue disorders			
	General disorders and administration-site disorders			
	Nervous system disorders			
	Gastrointestinal disorders			
	Skin and subcutaneous-tissue disorders			
	Injury, and procedural complications			
	Cardiac disorders			
	Vascular disorders			
	Metabolic disorders			
	Renal and urinary tract disorders			
	Reproductive system and breast disorders			

Figure 7: Frequency of AE term by treatment arm

Figure 8: Number of adverse events per patient by treatment arm

Table 8: Prevalence of AEs and SAEs by relatedness and severity

		Anti-ST2 (n =) n (%)	Placebo (n =) n (%)	Overall (n =) n (%)
Total AEs				
By severity				
	Mild			
	Moderate			
	Severe			
By relatedness to IMP				
	Unrelated			
	Unlikely			
	Possibly			
	Probably			
	Definitely			
	Unknown			
Total SAEs				
By Severity				

		Anti-ST2 (n =) n (%)	Placebo (n =) n (%)	Overall (n =) n (%)
	Mild			
	Moderate			
	Severe			
By relatedness to IMP				
	Unrelated			
	Unlikely			
	Possibly			
	Probably			
	Definitely			
	Unknown			

9.2 Appendix 2: Line listing of the adverse events

Preferred AE term	AE system	Seriousness	Start date	End date	Relatedness	Severity	Outcome	Treatment arm