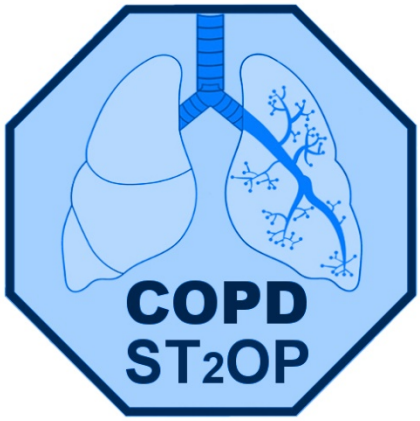
A randomised placebo-controlled trial of anti-ST2 in COPD (COPD-ST$_2$OP)



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Study protocol

V7.0, 7th July 2020

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

Trial Protocol Version 7.0; 07-July-2020

RESEARCH REFERENCE NUMBERS

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REC Reference Number:	18/EM/0189 (East Midlands-Leicester South)
SPONSOR:	University of Leicester (ref: 0671)
FUNDER:	Genentech

This protocol has regard for the HRA guidance and order of content, in line with Version 1.2 (March 2016) of the HRA CTIMP Protocol Development Tool.

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities and members of the Research Ethics Committee, by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Investigator and/or Sponsor.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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

VERSION: Version 7.0; 07/07/2020

For and on behalf of the Trial Sponsor:

Signature: .....

Date: 11 / 09 / 2020

Name (please print):

Dr Cat Taylor

Position:

Research Governance Manager

Chief Investigator:

Signature:

Date:10/09/2020

Name: (please print):

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ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LCTU	Leicester Clinical Trials Unit
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product

PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VOC	Volatile Organic Compound
WOCBP	Woman of Child Bearing Potential

iii. TRIAL SUMMARY

This will be a single-centre, double-blinded, placebo- controlled, parallel group, randomised controlled trial comparing MSTT1041A (anti-ST2 antibody) versus placebo in COPD. MSTT1041A 490mg subcutaneous (s/c) or matched placebo dosed every 4 weeks for a total of 12 doses. Patients will be 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. (Trial schedule and assessments are detailed in Appendix 1). The dose and dosing interval has been derived from an earlier PK/PD modelling and is the highest dose included in an ongoing phase 2b asthma study. The primary outcome measure is exacerbation frequency. Exacerbation events are relatively infrequent and can be affected by season, therefore we have chosen a 48 week treatment duration with follow-up out to 12 months.

Trial Title	A randomised placebo-controlled trial of anti-ST2 in COPD
Short Title	Anti-ST2 in COPD
Trial Acronym	COPD-ST_2OP
Clinical Phase	IIa
Trial Design	Single-centre, double-blinded, placebo-controlled, parallel group, randomised controlled trial
Trial Participants	Moderate to very severe COPD (GOLD II to IV)
Planned Sample Size	80
Treatment duration	48 weeks
Follow up duration	12 weeks
Planned Trial Period	60 weeks (+/- 2 weeks)
Planned Recruitment Period	Up to 9 months
Investigational Medicinal Product(s)	Anti-ST2
Formulation, Dose, Route of Administration	Injectable, 490mg, subcutaneous
Primary Objective	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
Primary Outcome Measures	Annual/48 week COPD exacerbation frequency where an 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
Secondary Objectives	Safety and tolerability, patient related outcomes (PROs), lung function and inflammatory cell differentials in sputum and blood.
Exploratory Objectives	Systemic inflammation, upper airway inflammation, airway infection and ecology, breath volatile organic compound profiling, quantitative airway geometry and densitometry, mediators, cell subset analysis and pharmacogenomics.
Subgroup Objectives	Rate of protocol defined COPD exacerbation through 48 week treatment period, SGRQ-c and FEV1 in subgroups defined by baseline blood eosinophil count.

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Genentech South San Francisco California USA	Financial support and provision of the drug and placebo
NIHR Biomedical Research Centre (BRC) and Clinical Research Facility (CRF)	Local infrastructure support

v. ROLE OF TRIAL SPONSOR AND FUNDER

The trial sponsor, University of Leicester, will be responsible for all aspects of the trial as per ICH-GCP, apart from where these duties have been delegated to the Leicester Clinical Trials Unit. The funder, Genentech, will be responsible for funding the trial, supplying the drug and placebo, performing certain sample analysis not available at Leicester. Data and samples will be shared between the Sponsor and Funder and the Funder will be provided with all Protocols and SOPs for their comment and input.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committees

The TMG will comprise of the trial Chief Investigator, Trial Clinical Co-ordinators, Trial Manager, Database Developer (as required), Trial Statistician and a Research Nurse. The TMG will be responsible for the day-to-day management of the trial. The TMG is responsible for all aspects of the trial (including recruitment rate, budget management, safety reporting, protocol compliance etc.) and for ensuring appropriate action is taken to safeguard trial participants and the quality of the trial.

Trial Steering Committee (TSC)

The TSC will comprise of an Independent Chairperson, Chief Investigator, Funder Representative and other Independent Members including Patient Representative. The TSC will provide oversight of the trial and monitor the progress of the trial to ensure it is being conducted in accordance with the protocol, relevant regulations and the principles of GCP.

Data Safety Management Committee (DSMC)

The DSMC will consist of independent experts who will assess the progress, conduct, participant safety and critical endpoints of a clinical trial. The DSMC will adopt a DAMOCLES charter to define its terms of reference and operation and will make recommendations to the TSC. The DSMC will meet on a regular basis as specified in the DSMC charter to review the

trial information and accruing data during the conduct of the trial and make recommendations to the TSC.

vii. Protocol contributors

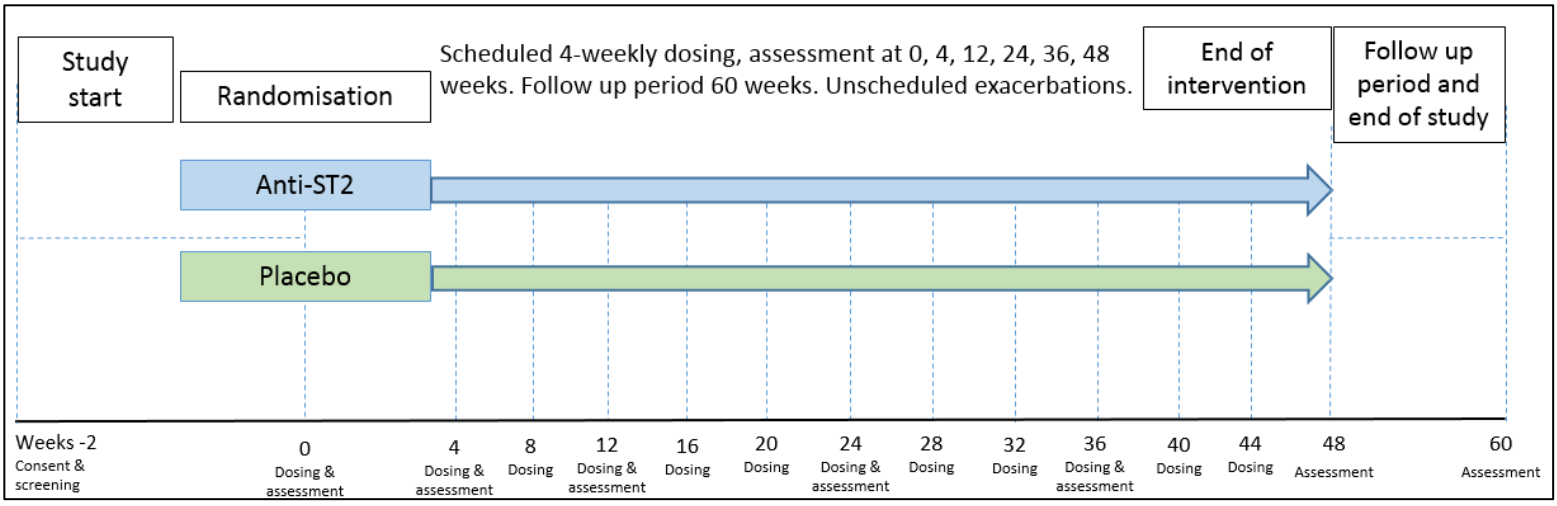
- Prof Chris Brightling and Dr Ahmed Yousuf, Respiratory BRC- trial design and protocol write up.
- Cassey Brookes, Dr Shaun Barber and Seid Mohammed, Leicester Clinical Trials Unit – sample size, statistical analysis & randomisation.
- Dr Sarah Edwards and Niamh Quann, Leicester Clinical Trials Unit – trial management, safety reporting & pharmacovigilance, randomisation, data management, quality assurance.

viii. KEY WORDS: anti-ST2, moderate to very severe COPD, safety and efficacy, randomised trial

ix.TRIAL FLOW CHART

(See Appendix 3)

Fig 1: Schematic of Trial Design for anti-ST2



1 BACKGROUND and rationale for conducting this trial

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide[1]. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third-leading cause of death and disability worldwide by 2030[2]. The costs to society for treating COPD are high, accounting for approximately 3.4% of the total health care budget of the European Union.

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. More than 500,000 hospitalisations and 100,000 deaths are attributed to AECOPD in the US each year [3]. In addition to a substantial economic burden, AECOPD is also responsible for much of the morbidity and mortality from COPD.

Interleukin-33 (IL-33) is an alarmin released from the epithelium following damage [4]. 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[5]. 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[6]. 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 [7]. Both eosinophilic inflammation and viral infection drive COPD exacerbations and therefore targeting the IL33/ST2 axis might reduce COPD exacerbations.

2 Assessment and management of risk

Beyond standard of care the participants will undergo additional blood tests, breathing tests, airway sampling, and a non-contrast CT scan and a SC IMP. These are all common routine tests. The blood, breath and airway sampling has minimal risk and mild discomfort. The non-contrast CT scan will involve radiation but the increased risk of cancer from radiation in an elderly population with a significant smoking history will have a high lifetime risk and therefore the radiation exposure will present a very small increase in this risk. The IMP both placebo and drug can potentially cause local reactions. Anti-ST2 has been tested in healthy volunteers and a phase 2b trial in asthma is currently ongoing. The target is anticipated to reduce exacerbation risk and symptoms and therefore might reduce risk in those individuals. Based on the three completed Phase I clinical trials and the ongoing Phase IIb trial in patients with uncontrolled severe asthma, the safety profile for anti-ST2 remains favourable at this time. We will also monitor and analyse all potential cases of anaphylaxis and major adverse cardiac events (MACE).

- **Risk Type C = Markedly higher than the risk of standard medical care**

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary objective

We hypothesise that anti-ST2 will impact on airway inflammation in COPD and consequently will reduce COPD exacerbation frequency.

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 or hospitalisation or death due to COPD, respectively) in 48 weeks as add-on to standard of care.

3.2 Secondary Objectives

Another key objective is to assess the safety and tolerability of SC doses of anti-ST2 compared to placebo in adult patients with moderate to very severe COPD.

Additionally, to assess the effects of anti-ST2 versus placebo both during stable visits and at the exacerbation events on the following:

1. Symptoms
2. Health status
3. Lung function
4. Inflammatory cell differentials
    i. Sputum cell count
    ii. Blood cell count
5. Airway morphometry
6. Pharmacogenomics

3.3 Exploratory Objectives

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.

3.4 Subgroup Objectives

- To evaluate the efficacy of anti-ST2 versus placebo on the outcome rate of protocol-defined COPD exacerbations through 48 weeks treatment period, patient reported outcomes (PROs) [SGRQ-c], and lung function [FEV1] in subgroups defined by baseline blood eosinophil count.

3.5 Outcome measures

3.5.1 Primary outcome

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

*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

For a detailed layout of the timeline for all visit procedures please refer to Appendix 1 Schedule of Procedures.

3.5.2 Secondary outcomes *(*indicates this data is held on Macro database)*

1. **Safety and tolerability**
   - 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
   - COPD Assessment Test (CAT)
   - mMRC Dyspnoea Scale
   - Visual analogue score (VAS)
     - 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)**
- Cell count
     - Blood inflammatory cell differentials*
       - WBC
       - Eosinophils
       - Neutrophils
     - Sputum inflammatory cell differentials
       - Eosinophils
       - Neutrophils
       - Macrophages
       - Lymphocytes
       - Epithelial cells
       - Total

3.5.3 Exploratory outcomes

- Quantitative measures of airway geometry and densitometry (Weeks 0 and 48, non-contrast thoracic CT-derived outcomes)
  - 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 (PTR-MS & ADVION) – breathomics
- Pharmacogenomics response analysis in subgroups determined by SNPs for alleles associated with the IL33/ST2 axis

4 TRIAL DESIGN

This is a single-centre, double-blind, placebo- controlled, parallel group, randomised controlled 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 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 be followed by a 12-week follow-up period (i.e washout period). An overview of the trial design is presented in Figure 1.

After signing the informed consent at the initial visit, patients will enter a screening period within 7-14 days of randomisation. Patients who qualify to participate in the trial will be randomised into a 48-week treatment period in which they will receive either 490 mg anti-ST2 or a matching placebo. Patients will be evaluated for an additional 12 weeks following completion of the efficacy endpoint (visit 13, week 48). Treatment groups will remain blinded until the 60-week follow-up period is completed, and trial database is locked. Visit procedures will be performed as shown in Appendix 1.

5 TRIAL SETTING

This trial will be a single centre RCT, sponsored by the University of Leicester and coordinated by the Leicester NIHR Respiratory BRC and Leicester Clinical Trials (LCTU).

6 PARTICIPANT ELIGIBILITY CRITERIA

Eligibility criteria for this trial have been carefully considered to ensure the safety of the patients included in the trial and that the results of the trial can be used. It is important the participants meet all the inclusion criteria and none of the exclusion criteria.

6.1 Inclusion criteria

1. Symptoms typical of COPD when stable (baseline mMRC dyspnoea score ≥ 2)
2. GOLD COPD stage 2-4
3. Smoking pack years ≥ 10 years
4. Age > 40 years
5. Receiving standard-of-care drug therapy as per BTS guidance for COPD
6. A history of ≥ 2 moderate-to-severe exacerbations in the last 12 months.
7. Be able to give valid written consent; compliant with trial procedures and trial visits.
8. Able to understand written and spoken English.

6.2 Exclusion criteria

1. Significant known respiratory disorders other than COPD that in the view of the investigator will affect the trial
2. Patients whose treatment is considered palliative (life expectancy <12 months)
3. Known hypersensitivity to the active substance of IMP or any of the excipients
4. Known history of anaphylaxis
5. Patients with a COPD exacerbation and/or pneumonia within the 4 weeks prior to visit 1
6. Have, in the opinion of investigator, uncontrolled co-morbid conditions, such as diabetes mellitus, hypertension and heart failure [e.g. NYHA class III (e.g. less than ordinary activity causes fatigue, palpitation, or dyspnoea) patients will be excluded if they have had exacerbation of their HF in previous 6 months, and class IV (e.g. Symptoms of heart failure at rest)] that will affect the trial.
7. Myocardial infarction, unstable angina or stroke within 12 month prior to screening
8. Diagnosis of malignancy within 5 years of visit 1 (except for excised localised carcinoma of skin not including malignant melanoma)
9. Clinically significant ECG changes, which in the opinion of investigator warrants further investigations
10. Laboratory abnormalities, which in the opinion of investigator warrants further investigations
11. Have, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse.
12. Pregnant, breastfeeding, or lactating women. Women of child-bearing potential (see protocol section 9.7)) must have a negative blood serum pregnancy test performed at the screening visit and must agree to use two methods of birth control, (one of which must be a barrier method).
13. Participation in an interventional clinical trial within 3 months of visit 1 or receipt of any investigational medicinal product within 3 months or 5 half-lives.
14. Upon questioning the patient has blood born infection (e.g. HIV, hepatitis B or C).

7 TRIAL PROCEDURES

See appendix 1 for detailed visit structure and trial procedures.

7.1 Participant Identification and Recruitment

The trial will recruit in a single centre (NIHR Leicester BRC Respiratory) that has a previous track record of delivering randomised designed studies. The participants will be identified from a database which has the details of patients who have taken part in previous COPD related trials and have consented to be contacted for future trials. They will also be identified from respiratory outpatient clinics and acute admission unit.

We will recruit members of the public who self-refer and who meet the inclusion/exclusion criteria. We will put posters advertising the study throughout the University Hospitals of Leicester NHS Trust and with permission in other community settings such as, pharmacies, GP practices and public notice boards. We will also make use of the NHS intranet, digital and social media (such as Facebook and Twitter) to help promote the study, whilst interest and patient feedback regarding the study will be generated via other media outlets (e.g. press releases, radio) where possible.

Patients will also be recruited from primary care. The Clinical Research Network (CRN) East Midlands will assist with identifying GP practices that are willing to identify potential participants for the trial. The practice will identify potential participants from the practice database for eligibility based on criteria supplied by the research team. Additionally, posters will be placed in the practice and clinical rooms, alerting staff and patients to the trial. The practice team will invite the patient to participate and the patient will respond to the research team if they wish to do so. Although this is a single centre trial, participants will be recruited from GP practices across Leicester, Leicestershire, Rutland (LLR) Clinical Commissioning Groups (CCGs).Once a participant has been identified as potentially eligible or requests further information, they will be sent a letter inviting them to express interest in the trial and return a reply slip which will contain the minimum amount of personal data. Alternatively they will be approached by a member of the clinical or research team and if interested their details passed onto the trial team for eligibility assessment. The trial team will contact the participant and arrange for a baseline screening visit (visit 0) and advise the participant to bring any concurrent medications with them.

They may also discuss halting any current medication such as inhalers that would affect the baseline measures. For participants with long acting inhalers, i.e. taken once a day (e.g. Spiriva) we would recommend these be halted 24 hours before the visit. For medium acting inhalers i.e. taken twice a day (e.g. symbicort, seretide, fostair, eklira, Anoro ellipta, Duaklir genuair, and Duoresp spiromax), we would recommend halting 12 hours before the visit. All other inhalers we would recommend halting 4 hours before the visit. This information would also be stated in the letter generated by the trial team with the appointment details.

Eligible participants will be offered trial entry at the baseline screening visit (visit 0) after they have had 24 hours to read the PIS and have understood the nature of trial.

7.1.2 Screening

Each potential participant will provide informed consent at screening before starting any trial related procedures. Participants will be assessed for eligibility as per inclusion/exclusion criteria at initial screening and at each subsequent follow up visit this will be checked for changes.

All potential participants who submit a reply or who agree to be contacted by the trial team, will be assigned a screening number and will be reviewed by a member of the research team who will screen for eligibility using pre-specified inclusion/exclusion criteria prior to or at the consent/screening visit. Participants who are deemed not to be eligible for the trial (even if this is prior to a screening visit 0), will be screen failed and their anonymised data (initials and year of birth) added to the screening log along with the details of their ineligibility. This will be maintained by the blinded trial staff with the Investigator Site File (ISF).

A log of all participants enrolled in the trial (i.e. who have been randomised) will also be created and kept securely with the unblinded staff as it will contain the treatment information.

7.1.3 Payment

Participants will be reimbursed for travel expenses at the usual NHS Trust rate (up to a maximum of £50 per visit) payable on production of original receipts (if taxis are not provided) at all trial visits (including screening and exacerbation visits). Once randomised participants will

receive an additional £25 per completed scheduled visit to compensate for any inconvenience. The payment schedule will depend on the participant's preference and will either be received after a series of visits have been completed, or at their final visit in a single lump sum.

7.2 Consent

Written version of the participant information sheet and consent form will be presented to the participants detailing the exact nature of the trial; what it will involve for the participant; the implication and constraints of the protocol; the potential side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason, without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be given a minimum of 24 hours to consider the information and have the opportunity to question the researcher, or other independent parties to decide whether they will participate in the trial. The participant will attend an initial screening visit, where written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent, which will contain information that conforms to current data sharing and handling requirements.

7.3 Blinding

Participants, investigators, the Trial management team and everyone involved in trial conduct will remain blinded with regard to the 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.

The IMP and placebo will be shipped by Genentech to the Hospital Pharmacy. Genentech will be responsible for QP release and the trial drug will arrive unblinded, pre-labelled with the approved trial outer labels. The entire Pharmacy team are unblinded and will take receipt of the IMP and placebo in accordance with their local SOPs and complete the necessary documentation including the accountability logs which will be maintained securely in the trial Pharmacy Site File. They will provide the IMP/placebo to the unblinded trial personnel only. The Unblinded trial personnel will collect and transfer the unprepared IMP/Placebo making sure that they are not visible to anyone during transport i.e. transferred in a closed non-transparent bag.

The unblinded trial personnel are designated in the Delegation Log and will be responsible for randomisation and trial drug preparation and reconstitution, which will take place in Glenfield out of sight of blinded trial personnel or the participant with clear warning notices that unblinded

IMP is being prepared. All documentation of drug/placebo preparation (including a participant accountability log), randomisation CRF, prescription, and the enrolment log containing information about randomisation for each participant, will be kept in a folder in a sealed box and location will be unknown to blinded team. A yellow label will be added directly to the syringe containing only the participant ID, initials, a statement that it is 'either drug or placebo within', date, time of preparation, and the initials of the unblinded personnel preparing it.

This 'blinded yellow label syringe' will be given to a Blinded trial personnel to be administered to the participant on site. The IMP and placebo will be identical in physical appearance within the syringe.

The randomisation results will not be revealed until the Clinical Trial Unit perform final database lock.

A DSMC will be reviewing the trial data periodically, to assess patient safety and will have access to unblinded data if necessary as outlined and agreed in the DSMC Charter. Data presented at the DSMC will be prepared by the unblinded trial statistician and take the format of an open blinded session followed by a closed unblinded session (as appropriate) to prevent unblinding of the CI, trial manager and the rest of the trial team.

7.4 Emergency Unblinding

If it is deemed necessary by the clinical or research team to unblind the patient to the allocated treatment the CI must be contacted. Only the CI 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 username and password will be tested in advance of the first patient enrolled onto the trial. 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 SUSAR.

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

To test the validity of the blinding both the patients and researchers will be asked if they were aware of treatment allocation.

Unblinding before database lock must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and recorded on the web based randomisation system when unblinding along with the date and the initials of the person who broke the code. Reason for unblinding should also be recorded in the CRF, data collection tool, in the site file and medical notes. In the case of unblinding an individual participant for safety reasons, appropriate follow-up of safety related events is required. It will also be documented at the end of the trial in any final trial report and/or statistical report. The CI/Investigating team will notify the Sponsor and the LCTU in writing as soon as possible following the unblinding detailing the necessity.

7.5 The randomisation scheme

The 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. Each participant will be given a unique screening number on consent, and a unique participant ID when they are randomised. This combination of unique screening number and participant ID will be linked on the enrolment log with the unique participant ID number being used to identify the individual participant throughout the trial following randomisation. Neither of these numbers will be re-assigned to any other subject. Participants will be assigned to trial treatment in accordance with the randomisation schedule.

Randomisation will be stratified by frequency of exacerbation in the previous 12 months (Low [2 or 3] or High [4 or more]). Randomisation results will be printed out and signed as confirmation by the unblinded trial personnel performing the randomisation and a copy will be stored securely with the unblinded documentation and presented to pharmacy alongside the prescription.

7.5.1 Method of implementing the randomisation/allocation sequence

Once the participant has given written consent to the trial, a member of the trial team will assess the eligibility of the participant by completing a screening visit. If eligible, randomisation should occur immediately after the participant undergoes their baseline assessment where possible. The unblinded trial personnel (authorised and trained) will complete a randomisation form, enter the eligibility criteria data onto the online system and randomise the participant to a treatment allocation, this will generate a unique participant ID and a blinded randomisation code which relates either to the IMP (anti-ST2 or placebo). The linkage information between the randomisation code list(s) and the allocated treatment will be generated/held by the Sealed Envelope system and by the unblinded trial personnel.

7.6 Baseline data

See Appendix 1 for detailed visit structure and trial procedures.

7.7 Trial assessments

See Appendix 1 for detailed visit structure and trial procedures. For dosage schedules please see section 8.6. For Trial restrictions and missed windows please see Section 8.10.

7.8 Long term follow-up assessments

See Appendix 1 for detailed visit structure and trial procedures.

7.9 Qualitative assessments

There will be no qualitative assessment.

7.10 Withdrawal criteria

The only specified withdrawal criteria for this study will be for participants that miss more than one dose of the study treatment, or who delay a scheduled study visit for >4 weeks. These participants will remain in follow-up for the trial duration. If a participant wishes to completely withdraw from the study, or is withdrawn for reasons other than a missed or delayed dose, the research team will encourage them to undertake the 'withdrawal visit' procedures and assessments which will signify the end of their participation. This will include participants who withdraw via telephone. It will be at the participant's discretion whether or not they attend the withdrawal visit. Withdrawal visits should be completed as soon as possible, however the timeframe will be largely dependent on what the participants finds acceptable.

Every effort should be made by the research team to keep the participants in the trial. However, participants have the right to withdraw their consent to take part in the trial at any time without having to give a reason and this will not affect their future care. Withdrawal details and reasons (if known) should be recorded on the withdrawal/loss to follow up CRF and in the medical notes. In addition, the investigator may discontinue a participant from the trial at any time if the investigator considers it necessary. The IMP will also be discontinued in the case of an adverse event which the investigator considers sufficient to jeopardise the safety of the trial participant. Participants who want to discontinue protocolled treatment should be encouraged to remain in the trial and continue to be followed-up as per protocol or as of routine care.

Every effort should be made to keep the participant in the trial to collect important efficacy and safety data. Withdrawals from the trial should be discussed with the CI or their deputy and the Trial Manager. If a participant has withdrawn from the trial for any reason, then his/her screening and participant ID number(s) cannot be issued to another participant.

Loss to follow-up will be minimised by diligent liaison with the participant, their medical team and if required the general practitioner. If a participant fails to attend the clinic for trial visit, the research team should contact the participant and re-schedule the missed visit within a week. If the participant can't be contacted or misses his/her next appointment, the research team should make every effort to contact the participant again by phone and letter. If the participant still cannot be contacted, then he/she can be withdrawn from the trial and the reason in the notes and eCRF can be recorded as 'lost to follow-up'.

A participant will be considered to have completed the trial if:

- they continue to take trial treatment until Visit 12 (Week 44) and attend Visit 14 (Week 60)
- they continue to participate in the trial until Visit 13 (Week 48) regardless of whether they continue to take IP.

As stated in section 3.3.2, participants will undergo a non-contrast CT scan at the beginning and end of the trial. Bearing in mind the average age of participants, diagnosis of COPD and smoking history, lung nodules are a very common finding in this population. Therefore participants will remain in the trial whilst they are followed up in the virtual nodule clinic, however

at the point where a suspicious nodule has led them into the cancer pathway, they will be withdrawn from the trial.

7.11 Storage and analysis of clinical samples

See Appendix 1 and trial procedures and laboratory manual for standard operating procedures (SOPs).

The following blood samples will be processed by the University Hospitals of Leicester NHS Trust central pathology labs and will be collected at room temperature from the trial site:

- Biochemistry Profile - Full (including U&E,s LFTs)
- Full Blood Count (FBC/CBC)
- NTproBNP
- HbA1c
- Lipid profile
- Total IgE
- RAST (HDM, Cat ,dog, grass pollen)
- C-Reactive Protein

The following samples will be analysed for research purposes by the research team and processed at the Respiratory BRC laboratories. Samples will be kept on ice or stored in monitored -20C or -80C freezers prior to analysis, unless contraindicated.

- Urine sample (for inflammatory biomarkers and pregnancy)
- Sputum sample *(Sputum is collected on ice and processed at 4°C as soon as possible and within 2 hours of expectoration)*
- Nasal epithelial sample (optional)
- Nasosorption
- PK and ADA samples
- Serum Plasma (for inflammatory biomarkers)
- Pregnancy Testing (blood sample)
- DNA sample
- RNA sample

The DNA and RNA samples taken during this study will be stored in a -80C temperature monitored freezer in the Respiratory BRC, all analysis on these samples will be carried out at the end of the study. The Respiratory BRC is a registered Tissue Bank.

7.12 End of trial (ET)

The end of the trial is defined as the last participant's final visit.

However, final trial closure will be when all final sample analysis has been completed or at the discretion of the TSC acting on the recommendation of the DSMC. Participants who discontinue the trial early will be asked to return to the trial centre and will undergo withdrawal or early

termination (ET) visit procedures listed in Appendix 1 under 'withdrawal'. The withdrawal visit will include all procedures to be done at end of trial visit as well as any other laboratory assessment planned at the originally scheduled follow-up visit.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

See IB for more details. MSTT1041A (anti-ST2) 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.

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.

8.2 Regulatory status of the drug

Anti-ST2 is currently in development and has not been granted marketing approval in any country yet. The drug and placebo will be supplied by Genentech, South San Francisco, California, USA.

8.3 Product Characteristics

See Investigator's Brochure (IB).

8.4 Drug storage and supply

The Anti-ST2 and placebo will be supplied by Genentech free of charge. They will be provided as open-label product to unblinded pharmacist and trial staff. Unblinded staff will be responsible for the receipt, storage, and labelling.

Both the Anti-ST2 (MSTT1041A) and Placebo should be stored at 2°C to 8°C in a secured location, protected from light, and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product(s). The drug product(s) should not be shaken.

The Anti-ST2 and placebo contain no preservatives and are suitable for single use only. Anti-ST2 should be prepared per the instructions provided in the Pharmacy Guide or trial drug preparation instructions. Vials should be checked for cracks or damage that may have occurred. Damaged product should not be administered and should be returned to Genentech. Any temperature deviations will be recorded and reported for evaluation to Genentech, LCTU and the Sponsor. Stock that has been exposed to a temperature deviation will be quarantined at

the correct temperature pending Genentech's response on outcome and authorisation from the Sponsor to use or destroy the affected stock.

8.5 Preparation and labelling of Investigational Medicinal Product and Placebo

Anti-ST2 and the placebo will be provided by Genentech to the Pharmacy in packaged vials with unblinded outer labels. Both the IMP and placebo will be ready for use and will not need to be diluted prior to administration. Allocation of trial medication (Anti-ST2 or placebo) will be managed by Sealed Envelope (web based randomisation system). The Anti-ST2 and placebo will be prepared and a blinded yellow label applied to the syringe by unblinded trial personnel (see section 7.3-7.5 on Blinding and Randomisation). All information will be documented on an unblinded participant accountability log and the enrolment log by the unblinded trial personnel, the pharmacist will maintain their own unblinded accountability logs.

8.6 Dosage schedules

See figure 1 for dosing schedule. In animal trial and phase I human studies both, intravenous and subcutaneous (SC) routes were used, with no significant difference in safety. For ease of administration we will be using the SC route in this trial. The drug dose is fixed at 490mg every 4 weeks for 12 visits.

A window of up to 4 weeks will be allowed within which a participant will be able to delay or miss taking a scheduled dose. A delay will then be carried through to all their subsequent study visits. If the participant misses a dose it will be recorded in the notes and the next scheduled dose will be administered. Participants will be allowed to miss a single dose of the study drug (See Section 7.7) and are permitted up to a 4 week treatment delay.

8.7 Dosage modifications

There will not be any dose modification during the trial (see Section 8.10 for non IMP medication changes).

If a participant has an anaphylactic reaction to the drug or placebo, they will discontinue from protocolled treatment but remain in follow-up. If the drug was stopped due to a clinical reason such as allergic reaction, we will err on side of caution and not restart the drug in the same participant.

No information on overdose, maximum-tolerated dose, or dose-limiting toxicities has been established at this time.

8.8 Known drug reactions and interaction with other therapies

There are no known drug reactions and interactions with other therapies. See Section 13.6.1 Possible Side Effects of the Trial Medication and the Placebo.

8.9 Concomitant medication

There are no restrictions on concomitant use of other medications.

8.10 Trial restrictions

There is no scope in this study for dose reduction of the IMP, however participants are permitted to miss a single dose. The dose for the patients' standard of care therapy(s) for COPD will be maintained where possible, however this will be left up to the clinician's discretion. The clinician will also have discretion to alter any concomitant medication(s) that are unrelated to their COPD as required.

Participants are required to complete the scheduled clinic visits within the time windows allowed in the protocol. As the administration of trial medication is only at the clinic, and the need to maintain the required intervals between dosing, it is very important to adhere to the time windows for each visit.

All study visits have been given a window of +/- 7days to allow for flexibility, apart from visit 14 which will have a window of +/- 14 days. Any visits completed outside of this window will be logged as protocol deviations. Participants will be permitted where required, up to a 4 week treatment delay of a scheduled dosing visit, to allow for adverse events, holidays or other unexpected events. The participant can miss a dose and receive their next dose at the scheduled visit, or they can receive a delayed dose when available and their subsequent visit schedule would be altered accordingly to incorporate the delay (see Section 8.6). Depending on the nature of the AE/SAE it will be left to the clinician's discretion to determine if the patient should be withdrawn from the study. Participants that are delayed more than 4 weeks (more than a single dose) will be withdrawn.

Persistent deviations would indicate potential non-compliance and will have to be discussed with the Chief Investigator and the Sponsor regarding possible withdrawal. Those participants who are planning to take more than a 4 week consecutive holiday would not be included in the study, this will be asked at screening.

Participants should be compliant in taking their daily COPD medications during the course of the trial. Dose and regimen of routine medications should not be changed during the course of the trial (screening, treatment, and follow-up periods) except for treatment of an exacerbation or unless absolutely medically necessary. Baseline treatment should be maintained at the same dose and regimen at it was at the time of entry to the trial.

If changes are absolutely necessary for reasons other than to treat the participant for COPD exacerbation, this should be discussed with the Local Clinical Monitor, and documented in the participant source data including the medical rationale for the change from the treating physician. The follow-up period is also an important part of the study to assess therapeutic efficacy and changes following the last dose of anti-ST2 should be avoided. After the participant completes the final clinic visit at week-48, investigator may adjust the dose or change the COPD medications without consequence to the trial objectives.

8.11 Assessment of compliance with treatment

All doses of the trial treatment will be administered SC at the investigational 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 must be recorded in the CRF. Infusion start date/time and infusion end date/time should be documented in the patient's CRF.

Drug dispensing/accountability logs will be maintained by a designated unblinded member of the site staff and by the Pharmacy team.

9 PHARMACOVIGILANCE

9.1 Operational definitions for (S)AEs

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.

9.2 Safety Assessments

All Adverse events (AEs) will be recorded throughout the study whether serious or not. Members of the research team will ask the participants about AEs at each study time point (see Appendix 1) and will complete the participant AE form, which will be a continuous log so as to capture end dates, and the study serious adverse event (SAE) log. This will be evaluated and classed according to the definitions in sections 9.1.

9.2.1 Reference Safety Information and Expectedness

For the purposes of this trial the Reference Safety Information for determining expectedness of any SAR will be Table 12 (section 6.4.1) of the Investigator's Brochure.

All fatal SAEs will be considered unexpected. No SADRs have been identified for Anti-ST2 as of March 2017 and updated in March 2018. Therefore there are no serious expected Adverse Drug Reactions (ADRs). Any treatment-emergent SAE deemed related to Anti-ST2 treatment during this study will be reported as a SUSAR. There are also a number of expected Serious Adverse Events associated with this disease population, these would be reported as SAEs, but may also be captured as part of the outcome measures exacerbations.

- Administration of MSTT1041A, a protein therapeutic, may lead to the development of anti-MSTT1041A antibodies which could lead to adverse events and/or decreased exposure.

- Hypersensitivity reactions and anaphylaxis have been described with SC administration of mAbs (Corominas et al. 2014). Signs and symptoms may include acute onset (minutes to several hours) of one or more of the following: respiratory compromise, reduced blood

pressure, skin-mucosal involvement, or gastrointestinal symptoms (Sampson et al. 2006). The potential for hypersensitivity to MSTT1041A in humans is unknown. However, as with any large-molecule, therapeutic administration of MSTT1041A may result in systemic reactions.

- Systemic reactions to large-molecule therapeutics can be IgE or non-IgE mediated or due to the release of cytokines and are generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea, vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can be severe or life threatening. Effects typically occur during or within several hours after drug administration, but they may be delayed.

- Injection-site reactions have been described with SC administration of mAbs (Corominas et al. 2014). Signs and symptoms may include pain, itching, erythema, and swelling at the injection site. The reaction may be immediate, although it usually appears within 24-48 hours with variable incidence according to the drug administered.

- Patients with a history of anaphylaxis, hypersensitivities, or drug allergies are excluded from studies with MSTT1041A.

- The intended mechanism of action of MSTT1041A suggests inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of a decrease in the protective response to infection, particularly helminthic infections (Molofsky et al. 2015). All trial participants will be monitored for signs and symptoms suggestive of infection by collection of vital signs, clinical laboratory tests, and AEs.

- Evidence has shown that the sST2 receptor is a prognostic biomarker of cardiovascular disease outcome (Sabatine et al. 2008; Shah et al. 2009; Weir et al. 2010). Although published findings suggest a possible risk of exacerbation of existing cardiovascular disease in humans, there are no identified cardiovascular risks associated with inhibiting the IL-33/ST2 axis in humans. Patients with active or unstable recent cardiovascular disease are excluded from the trial. Cardiac safety is 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 are monitored to observe for indication of possible atherogenic and metabolic effects of MSTT1041A exposure. In populations at high risk for pre-existing cardiovascular disease, such as patients with severe COPD, additional monitoring strategies including echocardiography and cardiac biomarkers (e.g., NTproBNP) may also be used.

9.3 Recording and reporting of SAEs, AESIs, SARs AND SUSARs

All **SAEs / SUSARs** occurring from the **point of randomisation** until the final trial visit following follow-up (or 100 days post cessation of trial treatment (if discontinued early), must be recorded on the SAE Form and sent to the Sponsor and the Leicester Clinical Trials Unit (LCTU) **within 24 hours** of the research staff becoming aware of the event.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

Accidental overdoses or medication errors must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug.

Adverse events of special interest (AESIs) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

Once all resulting queries have been resolved, the Sponsor will send an acknowledgement of the closure of the SAE, all correspondence and signed SAE forms will be retained by the site, within the Trial Master File and electronically on the Sponsor SAE database.

For each **SAEs / SUSARs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the CI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days.

9.4 Responsibilities

Principal Investigator (PI):

1. Checking for AEs and ARs when participants attend for treatment / follow-up.
2. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.

3. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
4. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
5. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor: (NB: where relevant, these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting [For double blind trials only].
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing any safety issues highlighted by the DSMC and acting upon them appropriately.

Data Safety Monitoring Committee (DSMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

All deaths will be reported to the Sponsor in accordance with the SAE reporting timeline described previously and within 24hours of the investigator becoming aware of it.

9.6 Reporting of Adverse Events to Genentech

For all Safety Reporting information please refer to the authorised Safety Data Exchange Agreement (referred to as "SDEA") which describes the procedures and time frames and defines the responsibilities between the University of Leicester and Genentech to ensure compliance with the applicable laws and regulations pertaining to safety reporting and its related activities, as well as related activities for the trial. The Funder (Genentech) who is remaining blinded, and an Independent Data Monitoring Committee (IDMC), who is unblinded, share the responsibility for regularly monitoring the overall safety of patients in the trial.

Adverse events related to the Genentech drug MSTT1041A (Anti-ST2) might potentially disclose important safety information. The investigator should copy Genentech into all communications when expediting SARs or SUSARs to the Sponsor, health and regulatory authorities in accordance with Sponsor Safety Reporting SOPs and should report all SARs related to Genentech's product to the local affiliate safety department within the time-frame as agreed upon in the SDEA.

- Serious AE reports that are related to the product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date, except for life-threatening or fatal SADRs which shall be transmitted to Genentech within seven (7) calendar days of the awareness date.
- All deaths in which causality is unrelated to product shall be transmitted to Genentech within (15) calendar days of the awareness date.
- Serious AE reports that are unrelated to the product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. This would include pregnancy reports where the foetus may have been exposed to the trial drug, and follow up until the outcome of the pregnancy is known, whenever possible based upon due diligence taken to obtain the follow-up information.

- Adverse Events of Special Interest (AESI) (serious or non-serious) are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the Funder's product or program, for which ongoing monitoring and expedited reporting to Genentech are required. Separate reporting forms have been provided by Genentech to capture these which will also be captured on the trial database. AESIs for this trial, which will include Major Adverse Cardiac Events (MACE) and Anaphylaxis (related or possibly related to Genentech product), shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Genentech product) shall be sent within thirty (30) calendar days. For further information please refer to the SDEA agreement.

- In addition, the following Special Situations Reports should be collected (using the Sponsor SAE reporting from) even in the absence of an AE:
    - Data related to the product usage during pregnancy or breastfeeding, data related to overdose, abuse, misuse or medication error
    - Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP).

Safety Reporting to Genentech will be done according to the current SDEA.

9.7 Pregnancy and pregnancy reporting

The effects of Anti-ST2 on embryo-foetal development have not yet been studied. Based on current scientific knowledge, embryo-foetal exposure to mAbs (Anti-ST2 type) during organogenesis is understood to be low in humans. It is not known whether Anti-ST2 can cross the placenta or cause harm to the foetus when administered to pregnant women or whether it affects reproductive capacity. As such participants will not be eligible to continue in this trial if they are pregnant, breastfeeding or intent to become pregnant. Two separate contraceptive methods must be declared.

- A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Women of child-bearing potential must have a negative blood serum pregnancy test performed at the screening visit and must agree to use two methods of birth control, (one of which must be a barrier method. However given this disease population and the average

age range, this will not be a significant proportion. Additional testing will also occur at any time during the trial if a menstrual period is missed or as required by local law.

Participants of child bearing potential both male and female will be given clear instructions regarding contraception throughout the trial which will be captured in the CRF. Adequate contraceptive measures have been defined as sterilisation, intra-uterine device, oral contraceptives, consistent use of barrier methods, male sterilisation or true abstinence (when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) should be reported to the Chief Investigator, the LCTU and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child in accordance with Sponsor and local reporting requirements and timelines.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the trial and considered by the investigator as possibly related to the trial treatment, must be promptly reported to sponsor in accordance with Sponsor and local reporting requirements and timelines.

Genentech reporting requirements are such that whilst pregnancy reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, any reports of pregnancy (including pregnancy occurring in the partner of a male trial subject), where the foetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

9.7 Overdose

The dose of anti-ST2 considered to be an overdose has not been defined. There are no known antidotes. The investigator should use clinical judgement in treating the symptoms of a suspected overdose.

9.8 Urgent safety measures

The Sponsor and Investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The measures must be taken immediately; Sponsor, MHRA, REC, HRA and R&D approval is not required before implementation.

Reporting of Urgent Safety Measures should adhere to Sponsor SOPs. Sponsor and the regulatory authorities, Genentech and the LCTU must be informed in writing of the measures taken and the circumstances giving rise to those measures, in the form of a substantial amendment within three days. The process for submitting amendments as a result of Urgent Safety Measures is covered in the Sponsor SOPs.

9.9 The type and duration of the follow-up of participants after adverse reactions.

Following an adverse drug reaction (ADR) the participants will be followed-up for an appropriate length of time as dictated by the nature of ADR and their clinical needs. ADR will continue to be recorded and reported for up to 3 months after the last dose of IMP has been administered. Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

9.10 Development safety update reports

Within 90 days following the anniversary of the authorisation date for the trial, a Development Safety Update Reports (DSURs) will be sent by the Chief Investigator to the MHRA and the Main Research Ethics Committee. A copy of the report will also be sent to Genentech (as the trial funder/drug supplier), the University of Leicester (as the trial Sponsor), and all host organisations. The LCTU will prepare the DSUR report on behalf of the CI and submit to the Sponsor who is responsible for reporting to the Competent Authority (MHRA) within the specified time frame.

The LCTU on behalf of the Trial Sponsor (University of Leicester) will also forward quarterly listings of non-serious AEs originating from the Trial to Genentech.

10 STATISTICS AND DATA ANALYSIS

See full statistical analysis plan for further details.

10.1 Sample size calculation

Recruitment of 80 participants with a drop-out rate of 10% will be sufficient to give 80% power at the 5% level assuming either an annualised 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.

10.2 Planned recruitment rate

Based on our experience of recruitment, we anticipate a recruitment rate of approximately 3 participants per week. We expect a screen failure rate of 30%.

10.3 Statistical analysis plan

A separate Statistical Analysis Plan (SAP) will contain full details of all statistical analyses and will be prepared early in the trial and finalised prior to database lock.

Reporting of results will be based on the CONSORT statement. A Trial Steering Committee and Data Monitoring Committee will be established, with appropriate charters which will specify their remit.

A total of 80 participants will be randomised in a 1:1 ratio to receive anti-ST2 or placebo. For safety and tolerability, AEs, SAEs, vital signs, physical examinations, ECGs, and clinical laboratory assessments at specific time points will be evaluated. All safety data will be summarised descriptively. Number and percentage of AEs will be presented for each treatment by Preferred Term and System Organ Class of the current Medical Dictionary for Regulatory Authorities (MedDRA) dictionary. Individual listings of all SAEs and AEs leading to investigational product (IP) discontinuation will be summarised using the current MedDRA dictionary. Similar analyses will be performed for potentially significant and clinically important AEs. Number of COPD exacerbations will be summarised using frequency count and percentage.

Summaries and listings of vital signs, physical examination, ECG, and laboratory test results will be presented.

10.4 Summary of baseline data and flow of participants

A diagram of participants flow through the trial has been produced (Appendix 3).

Baseline demographics and measurements will be summarised using number and percentage for categorical data; while continuous variables will be summarised using mean and standard deviation where data follows normality assumptions or median and interquartile range where normality assumptions are not meet. No statistical tests are planned to assess the difference in baseline variables between arms.

The baseline variables that will be summarised include the following:

- Age
- Gender
- Ethnicity
- Frequency of moderate-to-severe exacerbations in the last 12 months
- GOLD COPD stage
- Smoking pack years
- Diagnosed with diabetes mellitus
- History of hypertension
- Previous heart failure (HF)

10.5 Primary outcome analysis

The primary outcome will fit a negative binomial model for the outcome of number of COPD exacerbations in 48 week treatment period* with explanatory variables of treatment arm and number of exacerbation in the 12 months prior to the trial (stratification factor). The primary analysis will be based on an intention-to-treat population.

*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

10.6 Secondary outcome analysis

Secondary outcomes will be analysed using estimates with confidence intervals and not have hypothesis tests carried out unless otherwise stated in the statistical analysis plan.

10.7 Exploratory outcomes analysis

The accumulation of the exploratory outcome data will take several months following completion of the week 60 follow-up period. Therefore the exploratory outcome analysis 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.

10.8 Subgroup analyses

The Statistical analysis plan will include a planned sub-group analysis based on baseline blood eosinophil count as described in section 3.4.

10.9 Adjusted analysis

The analysis of the primary outcome measure (frequency of exacerbations) will take account of the frequency of exacerbation in the previous 12 months, which is used as a stratification factor at randomisation. Analyses for other outcomes will be unadjusted in the main analyses and will only be adjusted in sensitivity analyses if specified by the statistical analysis plan.

10.10 Interim analysis and criteria for the premature termination of the trial

There will be no interim analysis or formal criteria for the premature termination of the trial.

The DSMC will receive reports on the safety and other outcomes every 3-6 months (as defined in the charter), with their main focus being to ensure the safety of the trial. DSMC report will

report AEs, SAEs, demographics and efficacy outcomes. The open session of the DSMC will only report data overall, not split by arm. Outcome data will be restricted to the closed report.

There will not be any formal test or criteria for early stopping of the trial. The DSMC will advise on stopping the trial only if the acquired data provides proof that would alter current clinical management, in the light of the observed data and any other published literature.

10.11 Participant population

The primary analysis for each efficacy outcome will be by 'intention to treat' analysis; all the participants randomised in to the trial (regardless of whether they received trial drug) will be analysed in their allocated group, outcome data obtained from all participants will be included in the data analysis. The analysis of safety outcomes will be analysed using the safety population. The safety population will be compromised of the all individuals that received at least one injection of either the active dose or the placebo, with individuals that received any injections of the active dose being in the Anti-ST2 arm. Secondary analysis will be carried out on important outcomes using a per protocol population.

10.12 Procedure(s) to account for missing or spurious data

The primary analyses will consider any missing data to be missing at random (MAR). However, if comparison of patterns of missingness and descriptive differences between treatment arms indicate this assumption is not valid additionally sensitivity analyses may be carried out and will be specified in the statistical analysis plan.

10.13 Other statistical considerations

Any changes to the original statistical analysis plan will be detailed along with the reason(s) for their change in subsequent statistical analysis plans.

10.14 Economic evaluation

N/A

11 DATA MANAGEMENT

LCTU will be responsible for data management within the trial and will include validation as part of the database specification, undertake database queries and data reviews throughout the trial in line with SOPs.

11.1 Data collection tools and source document identification

Source Data is defined as the first place data is recorded, this will include:

- Medical Records
- Paper CRFs
- Laboratory Reports

- Printouts from equipment (i.e. ECG, Scales)
- Participant reported outcome questionnaires/diaries

Data collection tools will comprise of:

- Macro Database (transcribed from CRFs) and direct source data entry
- Participant reported outcome questionnaires/diaries

The research team will seek consent from participants to re-contact them based on their results, phenotype, genotype, and response to treatment following the completion of the trial. This will incur further analysis and/or additional tests on those who have responded to the treatment. In future, we may use the same cohort of patients and their data from the trial to investigate the link between their disease progression and the environmental pollution in the area in which they live. The research team will seek permission to use participants' postcodes for future studies that will link the outcomes with environmental pollution.

The research team will also request the ability to extract primary and secondary care patient data. The reason for this data linkage is many-fold; without it we cannot corroborate previous exacerbation history, often having a sporadic medical and drug history. If people are admitted during the study we can then explore the severity of the event e.g. respiratory failure. The primary care records will also have serial spirometry and in the very rare event of pregnancy we could then look at the obstetric care. We will only look at data that will be linked to understanding outcomes and mechanisms of the intervention and the people looking at these data will only be the study team.

11.2 CRF/Data Collection Sheet Management

Paper Case Report Forms (CRF) and trial questionnaires are the primary data collection instruments and treated as source data. All data requested in the CRF will be recorded. All missing data will be followed up and resolved where possible. If the item is not applicable to the individual case, N/A will be written. All entries will be printed legibly in black ink, following ICH guidelines for Good Clinical Practice.

The research team may contact the participants' GP to obtain additional information/clarification related to medical history, COPD exacerbations and medications if required.

Data captured in the paper CRFs will then be entered into a validated database under the management of the LCTU. A copy of the patient consent form and information sheet will be placed in the hospital notes of all participants and in the Investigator Site File. A sticker will be placed on the cover of the notes (or inside cover) detailing the trial title, contact details of the PI and the fact that the notes should not be destroyed for 25 years from the end of the trial. All trial visits summaries and AEs will be recorded in the hospital notes.

All CRFs will be stored in a secure area. Each enrolled participant will be allocated a unique trial ID so that the CRFs and electronic database remains anonymous.

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor and LCTU's duly authorised personnel, the Ethics Committee, and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

11.3 Documentation storage, access, security

All study documentation containing identifiable patient data will be managed in accordance with ICH GCP, the UK Policy Framework for Health and Social Care, the Data Protection Act and the EU General Data Protection Regulation (GDPR).

Information will only be obtained from the patient if necessary for the trial. The trial team will use the participants name, NHS number and contact details, to contact them about participating in the study and to make sure that relevant information about the study is recorded, to ensure patient care and for quality assurance purposes. Individuals from the Sponsor, the LCTU and regulatory organisations may look at participants medical and research records to check the accuracy of the research study. The trial team will pass these details to the Sponsor and the LCTU, along with the information collected from the participant and their medical records. The only people in the Sponsor organisation who will have access to identifiable information will be those requiring it for trial purposes or for audit of the data collection process. Those trial team members only involved in analysis will not have access to identifiable information.

The trial team will keep identifiable information for 6-12 months after the study has finished. Consent forms and details of record linkage (i.e., participant ID numbers/pseudonyms) will be kept for 25 years as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data.

Explicit consent will be obtained to store or share identifiable patient data, which will clearly outline how individual data will be used.

All electronic data will be stored on secure network drives, to which only the relevant trial staff have access, which is granted by the IT services or the research team. This drive is backed up daily by the University of Leicester Information Management & Technology (IM&T).

Direct access will be granted to authorised representatives from the Sponsor, host institution, the Leicester Clinical Trials unit, the Funder and the regulatory authorities to permit trial-related monitoring, audits and inspections, where applicable and in line with participant consent.

For the purposes of this clinical trial the Data Controller will be the Chief Investigator.

11.4 Database management

Paper CRF data will be entered by trained member(s) of the research team at site into a commercially available web based CDMS provided by the LCTU. On-entry validation checks will be applied where required and data entered will be checked for completeness, accuracy and timeliness by the trial team/trial manager/data manager, with queries managed using the data clarification functionality within the CDMS system.

The contacts database (which contains participant contact details) will be held separately from the trial database. This will be password protected and managed at site by the research team following their usual clinical practice.

A Data Management Plan will be created with specific details on data handing and record keeping.

11.5 Archiving

Personal identifiable data generated by the trial will be retained for the minimum time determined by the regulatory authorities following the notification of the end of the trial before being destroyed in a confidential manner.

Following completion of the trial data analysis, data and essential trial records, including the final trial report, will be archived in a secure location, for at least 25 years after the completion of the trial, in accordance with EU regulations. No trial-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

12 MONITORING, AUDIT & INSPECTION

The University of Leicester, as Sponsor, operates a risk-based monitoring and audit programme, to which this trial will be subject. The LCTU operates a risk-based Quality Management System which will apply to this trial with Quality Checks and Quality Assurance Audits performed as required.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

As part of the quality management process, the trial will be subject to a risk assessment and a monitoring plan will be developed by the Sponsor in accordance with the level of risk identified to participant safety, integrity of the trial and trial data validity. All trial monitoring will be conducted in accordance with the monitoring plan and will be undertaken by the trial Sponsor. All monitoring will be performed by staff who are ICH/GCP trained and are competent in monitoring to all applicable regulatory guidelines. A documented monitoring log and audit trail will be maintained throughout the lifetime of the trial. The trial may also be subject to audit by the Sponsor delegate.

The trial manager will also undertake quality checks and assurance audits to ensure compliance with protocol, ICH GCP and regulatory requirements.

All source data, trial documents, and participant notes will be made available for monitoring, audits and inspections by the Sponsor (or their delegate), NHS Host Organisation and the regulatory authorities.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements. Any substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File and an annual progress report (APR) will be submitted to the REC by CI within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will also be responsible for informing the REC of the end of trial. After completion of the trial, CI will submit a final report with the results to the REC.

13.2 Peer review

The trial has been reviewed by the Genentech Respiratory Group including clinicians and senior scientists. This review team have had the protocol reviewed by their internal senior management and approved for support.

13.3 Public and Patient Involvement

Through the NIHR BRC the trial design has been discussed by our patient involvement team within the BRC Respiratory Theme and across the wider BRC PPI group. This group will also be sent copies of the participant documentation for review. We will also invite several members of this group to act as lay committee members on the Trial Steering Committee, for which we will provide expense payments.

13.4 Regulatory Compliance

The trial will not commence until Clinical Trial Authorisation (CTA) is obtained from MHRA and REC and Sponsor Green Light has been issued. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. As the participants may have a non-contrast CT scan and Chest X-Ray at the start and end of trial, the procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research (2017) and the Medicines for Human Use (Clinical Trials) Regulations, 2004. The

Sponsor responsible for checking research governance arrangements will be the University of Leicester.

13.5 Known and Potential Benefits to Participants

For those participants that will be randomised to receive Anti-ST2 they may experience a reduction in exacerbations and an overall improvement in COPD. Those participants receiving the placebo may also experience the placebo effect in which the expectation of receiving treatment can result in health improvements.

For all participants participation in this trial will help by making a significant contribution to research into COPD and will improve management of patients in the future. During the trial all participants will receive close monitoring of their COPD and attention to ensure that they are receiving the optimal medical treatment. Any exacerbations would also be investigated and followed up by the trial team. Any abnormal findings arising from the trial procedures that are considered clinically significant by the trial team will be reported to the GP for further investigation.

Participants will be reimbursed for the inconvenience and burden of the trial visit schedule and due to the moderately higher than standard care risk of participation (see section 7.1.3)

13.6 Known and Potential Risk to Participants

The trial is as low risk as the Investigators can make it. Although some of the appointments with the full testing maybe fairly long (~half day), therefore participants will be offered a break and refreshments provided.

There is a possibility that a temporary halt or change to medications may cause worsening of symptoms. These will be adjusted at clinical review and revised where necessary.

Both the placebo and trial drug can potentially cause local reactions (e.g. rash, inflammation). Anti-ST2 may reduce exacerbation risk and symptoms and therefore might offer beneficial effects. The safety profile for this drug is considered good with a slightly higher risk than the patient would receive from standard care, based on the previous asthma studies that have been conducted at this time.

The effects and discomforts of each individual test are detailed in the Patient Information Leaflet (PIL) and described briefly below:

- **Non Contrast CT Scan (Chest)** – This is a painless procedure. The CT scan exposes patients to ionising radiation, which has theoretical risks to health. However the dose received (~7 mSv) is comparable to natural background radiation for 2 years, and therefore the risks are not considered clinically relevant.
- **Chest X-Ray (CXR)** - This is a painless procedure. The Chest X-ray exposes patients to ionising radiation, which has theoretical risks to health. However the dose received (~0.1 mSv) is comparable to natural background radiation for 10 days, and therefore the risks are not considered clinically relevant.

- **Echocardiogram (Echo)** - This is a safe test utilising ultrasound that some participants will have had before. Patients may notice some mild discomfort when the probe is pressed on their chest but there are no known long term side effects known (takes ~20min).
- **Electrocardiogram (ECG)** - The ECG is a simple painless test, with 10 electrodes used to record 12 different views of the heart's electrical activity. An electrode is attached to each ankle and wrist with sticky pads and six more are attached to the chest. The patient lies almost flat with the head and chest raised a little. Relaxing for a few minutes before the recording is made. Very rarely someone may have a slight skin reaction to the electrodes, but normally there are no after effects.
- **Blood sample** - Blood testing may cause some mild discomfort and occasionally some bruising. All samples will be taken by a doctor or fully trained health professional. Each donation of blood will be a 100ml (about 7 tablespoons) maximum per visit.
- **Sputum Collection** – involves inhaling a salty solution for three 5-minute periods. This can cause some chest tightness, wheezing and/or cough. These can all readily be reversed by inhaling a bronchodilator (ventolin). In order to monitor this, lung function testing will be performed before and during this test
  Breathing tests – Spirometry, PEX (Particle Exhaled) Machine and other breathing tests may cause some temporary light headedness, and coughing. The blowing tests during this procedure may cause airway irritation which will be reversed with Salbutamol if required.
- **Nasal Epithelial Sampling** - A small brush or scoop is inserted and gently rubbed inside the nostril (a few seconds) or a small volume of sterile salt solution will be inserted into each nostril, then allowed to run out into a collection pot (several minutes). There may be a little discomfort that induces sneezing, coughing and, rarely, minor bleeding for a short period of time. This sample will be optional.
- **Nasosorption**: A small piece of paper will be inserted into the nostril to collect nasal fluid.

13.6.1 Possible Side Effects of the Trial Medication and the Placebo

Anti-ST2 (MSTT1041A) is being developed by Genentech for the treatment of uncontrolled severe asthma and COPD. Due to its mechanism of action, Anti-ST2 has the ability to block inflammation, prevent exacerbations, and improve lung function and quality of life in both patient populations.

Anti-ST2 is in early clinical development, and the safety profile in humans is not fully known. Anti-ST2 is contraindicated in subjects with known hypersensitivity to the active substance or any of the excipients. Other exclusion criteria are listed in Section 6.2.

Three Phase I studies of Anti-ST2 to provide PK, PD, and safety information over a broad dose range have completed dosing and safety follow-up in all subjects. These include a SAD study (AMG Study 20110235), a MAD study (AMG Study 20110236), and a single-dose PK study in subjects of Japanese heritage (AMG Study 20130177). In the three completed AMG Phase I

studies there were no serious adverse events (SAEs) or adverse events (AEs) that led to treatment discontinuation in healthy subjects from the three completed AMG Phase I studies, who received single SC doses of Anti-ST2 ranging from 2.1-560 mg and IV doses ranging from 210-700 mg.

In the Phase I studies there were no clinically relevant trends in any of the following safety parameters:

- Laboratory abnormalities
- Percent change in vital signs measurements: systolic and diastolic blood pressure, pulse rate, temperature, or respiratory rate
- QTcF interval

Based on preliminary data from these studies, a Phase IIb study was initiated to study patients with uncontrolled severe asthma who are receiving standard asthma therapy. This study is currently ongoing (EudraCT 2016-001549-13, NCT 02918019).

Our trial will be the first looking at Anti-ST2 in COPD. As Anti-ST2 is in early clinical development the full safety profile in humans is not yet known. Please refer to the associated current Investigator's Brochure (IB) which lists the potential known risks and side effects for both the IMP and the placebo.

13.7 Protocol compliance

The trial team will monitor and review protocol compliance, deviations from the protocol will be captured both within the source data and the LCTU Quality Management System. Drug accountability will be monitored throughout the trial period. Where deviations frequently reoccur this may meet the criteria for a Serious Breach of GCP and will be reported in line with Section 13.6.

13.8 Notification of Serious Breaches to GCP and/or the protocol

Any serious breach (a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the participants of the trial; or the scientific value of the trial) will be reported to Sponsor immediately.

13.9 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of relevant legislation with regards to the collection, storage, processing and disclosure of personal information for the University of Leicester, the Leicester Clinical Trials Unit and the local NHS Trusts.

The personal information that is collected will be kept secure and maintained by:

- The creation of a unique participant ID number, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters

- Secure maintenance of the data, in both electronic and paper forms and the linking code in separate locations
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis
- Paper based anonymised trial records will be stored in locked filing cabinets within a locked office. Electronic records will be stored on secure University of Leicester IM&T server systems.
- The database will be password protected and only researchers collecting data will have access. All data collected during the trial will be stored anonymously.
- Participant's contact details will be held separate to the trial visit data and used to arrange data collection visits by the research team or direct care team.
- Any data transmitted will be done securely in approved University of Leicester methods (i.e. encrypted file transfer, internal email system) in accordance with LCTU SOPs.
-

13.10 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

All real and perceived conflicts will be recorded and reported to the TSC. Members of the TSC and DSMC Committees will be required to sign a declaration of conflicts of interest forms which will be retained in the TMF.

13.11 Indemnity

Sponsorship and insurance for the trial will be provided by the University of Leicester.

If a participant is harmed due to negligence, this would be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a trial participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them, the contact details for which are in the participant information sheet.

13.12 Amendments

Amendments will be submitted by the PI after approval by the Sponsor and will be implemented following all required ethical, competent authority and Sponsor approvals.

13.13 Post trial care

After the completion of trial participants will be discharged back to the care of their GP and won't be followed up, unless they have had an adverse reaction to IMP.

13.14 Access to the final trial dataset

CI and his appointed deputies will have access to trial dataset.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

A publication plan will be written by the TMG during the trial with the sponsor and funder approvals. It is envisaged that the results of the trial will be published in the relevant peer-reviewed journals. Acknowledgement of any supporting organisations, including funders, University of Leicester and the LCTU, will be included.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be determined in line with the International Committee of Medical Journal Editors.

15. REFERENCES

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16. APPENDICES

Appendix 1: Schedule of Procedures

Appendix 2: Amendment History

Appendix 3: Participant Trial Flow Chart

16.1 Appendix 1 – Schedule of Procedures

Trial assessment	Screen	Randomised treatment (visit window +/- 7 days)												Efficacy end point	3 month post-trial follow-up	Withdrawal	Unscheduled visit (e.g. exacerbation)
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V13 +/-7 days	V14 +/-14 days		
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk36	Wk40	Wk44	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	3 month post-trial follow-up	Withdrawal	Unscheduled visit (e.g. exacerbation)
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V13 +/-7 days	V14 +/-14 days		
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk36	Wk40	Wk44	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_1c	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	3 month post-trial follow-up	Withdrawal	Unscheduled visit
	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V13 +/-7 days	V14 +/-14 days		(e.g. exacerbation)
		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk36	Wk40	Wk44	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.

16.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA05	7.0	11/09/2020	Niamh Quann Prof Chris Brightling Seid Mohammed	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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA04	6.0	08/07/2020	Niamh Quann Prof Chris Brightling Dr Ahmed Yousuf Seid Mohammed Cassey Brookes	• 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. • Update to Sponsor's email address. • 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. • 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. • 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. • Addition of full BEAT-COPD study name for clarification purposes. • 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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA03	5.0	27/05/2020	Niamh Quann Prof Chris Brightling Dr Ahmed Yousuf	• Week 60 washout (visit 14) reinstated following MHRA non-acceptance of its removal on medical grounds (Notice of Non-Acceptance dated 01/05/2020). • Original schematic of trial design and participant trial flow chart reinstated in accordance with the above. • 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). • 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. **Note:** As this amendment was to cover an Urgent Safety Measure and was COVID-related, all other changes proposed but not implemented as part of SA02 will be submitted as a separate substantial amendment (SA04) at a later date.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA02	4.0	**Not issued due to MHRA non-acceptance of amendment.**	Niamh Quann Prof Chris Brightling Dr Ahmed Yousuf Seid Mohammed Cassey Brookes	• Update to Sponsor's email address. • 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. • 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). • Update to Schematic of Trial Design for anti-ST2, schedule of procedures and participant trial flow chart to reflect removal of week 60. • 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). • Clarification of subgroup objectives and analyses. • Addition of full BEAT-COPD study name for clarification purposes. • 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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA02	3.2	10/12/2019	Niamh Quann	1. Administrative corrections to appendix 1- schedule of procedures: • Visit 13 (end of efficacy endpoint): addition of visit window +/- 7 days. • Visit 14 (3 month post trial follow-up): addition of visit window +/- 14 days. 2. Administrative correction to appendix 3- participant trial flow chart: • Re-arrangement of wording to ensure clear visit window for visit 13. • Change in visit 14 window from +/- 7 days to +/- 14 days. The visit windows were omitted in error from the schedule of procedures and ambiguous in the flow chart. As a result, this incurred a large number of protocol deviations due to staffing and participant availability. Therefore it has been amended to avoid unnecessary deviations, as well as to allow flexibility for participants. The text has been amended under section 8.10 to reflect +/-14 day window for visit 14.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA01	3.1	01/10/2019	Niamh Quann	Administrative corrections to Appendix 1- Schedule of Procedures: 1. Heading of visit 13 and visit 14 updated for clarification purposes. 2. Pre and post BD spirometry moved from visit 14 to visit 13. 3. Body box added to visit 13- originally only included at baseline and omitted from visit 13 in error. 4. Lipid profile moved from visit 14 to visit 13. 5. ECG moved from visit 14 to visit 13. 6. Non-contrast CT chest moved from visit 14 to visit 13. These all form part of the secondary outcomes and thus must be completed at visit 13 (i.e. the efficacy endpoint). **NB:** As agreed with East Midlands Leicester South REC via email communication on 11/09/2019, the PIS will not be updated as all participants have been recruited and have consented to undergo the trial procedures which are documented accurately within the main text. Instead a file note will be completed to explain the discrepancy.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	3.0	28/05/2019	Niamh Quann Cassey Brookes Seid Mohammed Dr Ahmed Yousuf	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 a 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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A- part of initial submission	2.0	09/07/2018	Prof Chris Brightling Dr Ahmed Yousuf Niamh Quann	1. Rationale included to support both the dose and the duration of treatment. 2. Clarification that both the IMP and placebo will be ready for use and will not need to be diluted prior to administration. 3. Duration of follow-up, including recording and reporting of AEs/SAEs changed to 100 days after last IMP administration. 4. Clarification that the IMP will be discontinued in case of an adverse event which the investigator considers sufficient to jeopardise the safety of the trial participant. 5. Clarification that COPD exacerbation, progression, signs and symptoms do not meet the definition of an adverse event unless they are considered related to the study drug by the investigator and then they constitute a reaction. 6. Section 7.4- Emergency Unblinding: To test the validity of the blinding both the patients and anaesthetists will be asked if they were aware of treatment allocation. Anaesthetists has been changed to researchers as this was a typo. 7. Section 11.1- Data collection: The CI would like to re-call patients based on response to treatment, phenotype and genotype, extract primary and secondary care patient data, and link participants' postcodes with environmental pollution. This was raised at the REC meeting. This has been included in the protocol, consent form and PIS. 8. Appendix 1- Schedule of procedures: The mMRC was omitted from visit 0 (screening) in error. It is part of the eligibility criteria and the schedule of procedures has been updated to reflect this. LFT blood test is to be done at visit 0 (screening) so that we have baseline result. The schedule of procedures has been updated to reflect this.

16.3 APPENDIX 3 – Participant Trial Flow Chart