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**

3.4 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

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.

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%.

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. **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:

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

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)