Study Protocol

TH**E** **M**ICROBIAL EFFECT OF INHALED STEROIDS IN SEVERE CO**P**D PATI**E**NTS WITH A**S**SOCIATED BRONCHIEC**TAS**IS

TEMPESTAS

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	Glaxo SmithKline
Funding Reference Number	213680
Chief Investigator	Dr Gourab Choudhury
Sponsor Reference	AC21046
EudraCT Number	2022-000524-38
REC Number	22/NW/0079
ISRCTN Number/ClinicalTrials.gov Reference	15449782
Version Number and Date	Version 5.0 02 May 2024

KEY TRIAL CONTACTS (* **Protocol Authors** this information must be included for insurance purposes)

Chief Investigator	
Name:	Dr Gourab Choudhury
Address:	Royal Infirmary of Edinburgh EH16 4TJ
Telephone:	0044 7837915130
Email:	g.choudhury@ed.ac.uk

Lead Co-Sponsor Representative	
Name:	Tiago Santos
Address:	University of Edinburgh, QMRI, 47 Little France Crescent Edinburgh EH16 4TJ
Telephone:	0131 242 9261
Email:	tiago.santos@ed.ac.uk

Trial Manager	
Name:	Lorna Dewar
Address:	Edinburgh Clinical Trials Unit, Usher Building, University of Edinburgh, BioQuarter, Little France Road, Edinburgh, EH16 4UX
Telephone:	0131 651 7895
Email:	Lorna.dewar@ed.ac.uk

Trial Statistician	
Name:	Ms Catriona Graham
Address:	Edinburgh Clinical Research Facility, University of Edinburgh, Western General Road, Crewe Road South, Edinburgh, EH4 2XU
Telephone:	0131 537 3350
Email:	c.graham@ed.ac.uk

PROTOCOL APPROVAL SIGNATURE PAGE

TH**E** **M**ICROBIAL EFFECT OF INHALED STEROIDS IN SEVERE CO**P**D PATI**E**NTS WITH A**S**SOCIATED BRONCHIEC**TAS**IS

TEMPESTAS

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Dr Gourab Choudhury	Gourab Choudhury Gourab Choudhury (Jul 9, 2024 14:24 GMT+1)	Jul 9, 2024
Chief Investigator	**Signature**	**Date**
Catriona Graham	C.Graham C.Graham (Jul 10, 2024 10:24 GMT+1)	Jul 10, 2024
Trial Statistician	**Signature**	**Date**
Tiago Santos	Tiago Santos Tiago Santos (Jul 9, 2024 13:57 GMT+1)	Jul 9, 2024
Lead Co-Sponsor Representative	**Signature**	**Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name				
Principal Investigator	**Signature**		**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
CAT	COPD Assessment Tool
CI	Chief Investigator
CRF	Case Report Form
CRP	C Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
EudraCT	European Clinical Trials Database
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung disease
GMP	Good Manufacturing Practice
GSK	Glaxo SmithKline
HRCT	High-resolution computed tomography
ICF	Informed consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IMP	Investigational Medicinal Product

ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IVRS	Interactive Voice Response System
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LTOT	Long Term oxygen therapy
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	THE MICROBIAL EFFECT OF INHALED STEROIDS IN SEVERE COPD PATIENTS WITH ASSOCIATED BRONCHIECTASIS
Study Acronym	**TEMPESTAS**
Clinical Phase	Phase 2b
Trial Design	Open Label Randomised Control Trial
Trial Participants	COPD patients with coexistent diagnoses of Bronchiectasis
Planned Number of Participants	80
Planned Number of Sites	3 – 6
Countries Anticipated to be Involved in Trial	UK
Treatment Duration	12 months
Follow up Duration	1 year
Total Planned Trial Duration	30 months
Primary Objective	To investigate the microbiological impact of inhaled corticosteroids over 1 year in patients with GOLD Stage D COPD and a co-diagnosis of bronchiectasis.
Secondary Objectives	Look at the effect of dual vs. triple therapies for all the endpoints mentioned.
Primary Endpoint	Baseline to 1-year change (expressed in log units) in colony forming units per ml between treatment arms (LABA-LAMA plus corticosteroid versus LABA-LAMA only)
Secondary Endpoint	Sputum colour, Sputum microbiota, Sputum bacterial load (>10^6 CFU/ml), Spirometry, Patient symptoms, serum and sputum inflammation, exacerbations and mortality rate.
IMP(s)	Delivered via standard inhalers used routinely in COPD patients: dual bronchodilators (Umeclidinium and Vilanterol 55/22 mcg) vs. triple therapy (Fluticasone furoate, umeclidinium and vilanterol 92/55/22 mcg) both once a day
IMP Route of Administration	Inhaled products
NIMP(s)	Rescue Medication - Salbutamol 5mg/2.5 ml Nebuliser Solution

Lay Summary of Trial	A key treatment for patients with advanced Chronic Obstructive Pulmonary Disease (COPD) is to optimise the airways using medicines to open the airways. In patients with recurrent flare-ups, the addition of inhaled corticosteroids to reduce inflammation in the airways is recommended by national and international guidelines. Recent published studies raised some concern that inhaled corticosteroids can promote chest infections including pneumonia. However, this is controversial, and the risks are uncertain. We plan to perform a randomised controlled trial involving a high-risk group of severe COPD patients that have recurrent flare-ups due to bronchiectasis (associated widened and damaged airways) in 80 patients from between 3 and 6 NHS hospital sites. This patient group needs special attention as association of bronchiectasis in COPD can make them more prone to these exacerbations and can increase the mortality rate by up to 20-30%. We aim to assess whether inhaled steroids along with other type of inhalers that open the airways can affect the amount and type of bacteria in the airways. This is a good patient group to test whether inhaled corticosteroids and other inhalers that open up the airways are safe and will improve patient symptoms and improve the burden of bacteria in lungs or not. 40 patients from each group will receive the dual inhaler ANORO ELLIPTA or the triple inhaler TRELEGY ELLIPTA (which includes the inhaled steroid) to determine the effect of the inhaled steroid over a variety of tests including a sputum test, breathing tests, amongst others. We will follow-up all participants for 12 months.

1. INTRODUCTION

1.1 BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality internationally. There is increasing recognition that patients with advanced COPD with co-existing bronchiectasis have increased respiratory tract infections and increased mortality[1]. Martínez-García et al reported on a series of 91 Spanish patients with well-characterized, clinically stable, moderate to severe COPD2 and found that 58% of these patients had bronchiectasis on CT scanning of the chest. Other recent studies in patients with COPD across all GOLD stages of disease showed bronchiectasis rates of 27% in 75 UK patients. Bronchiectasis was also reported as an associated pathology in 2,164 subjects in the multinational Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort[3].

A systematic review and meta-analysis in 2016 have shown that the association with bronchiectasis is an independent risk factor for exacerbation, severity of airway obstruction and mortality in COPD patients[4]. Studies have also shown that association of bronchiectasis on HRCT is common in COPD and is linked with more severe COPD exacerbations, lower airway bacterial colonization, and increased sputum inflammatory markers[5].

Most guidelines recommend a stepwise approach to inhaler therapy in COPD patients with a long-acting beta 2-agonist (LABA) plus an inhaled corticosteroid (ICS) or a long-acting muscarinic antagonist (LAMA) and LABA combination inhalers, as the first-choice treatment that have a high risk of exacerbations, and then considering escalation to triple therapy with all three class of drugs[6].

Recently the landmark IMPACT trial showed superiority of triple therapy to both LABA-LAMA and LABA-ICS therapy on the primary endpoint of reduction in the annual rate of on-treatment moderate/severe exacerbations ($p<0.001$) and a range of other clinically important outcomes, including spirometry and health-related quality of life. This is in keeping with current guidelines of prescribing triple therapy in frequent exacerbators of COPD[7].

The FLAME trial, on the other hand undertook a randomised, double-blind non-inferiority trial[8]. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA plus the LAMA once daily or the LABA plus the inhaled glucocorticoid fluticasone twice daily. The trial showed that the LABA-LAMA group was more effective in preventing exacerbations than the LABA-ICS group ($p <0.001$) and was associated with lower incidence of community-acquired pneumonia ($p= 0.02$). This reaffirms that LABA-LAMA could be a safe alternative if triple therapy is not deemed suitable for some reason in COPD patients with frequent exacerbations.

The main reported risk of ICS in COPD is that of increase risk of pneumonia and hence should be used in accordance to available protocols of COPD management. Despite this data drawn from the Adelphi Respiratory Disease Specific Program, a large multinational (France, Germany, Italy, Spain, UK, USA) cross-sectional survey generating real-world data based on actual clinical practice, showed there is still overuse of inhaled corticosteroids in all groups of disease severity in COPD (33% in Stage A, 38% in Stage B, 54% in Stage C and 51% in Stage D)[9]. Even in bronchiectasis patients, the UK National Audits 2010 (n=1460) and 2011 (n=2404) revealed that ICS are used in 78–81% with a mean dose of 1094–1252 µg/day[10], despite BTS National Guidelines recommending not for routine use.

Recent study by Contoli et al assessing the effect of LABA-ICS vs. just a LABA on bacterial and viral loads in patients with moderate COPD showed an increase in bacterial load for

patients treated with ICS. However post hoc analysis indicated that this change was driven in patients with eosinophil counts of ≤ 2% in peripheral blood[11].

This study therefore has selected this subgroup of severe COPD (GOLD 2017 classification Stage D) with a co-diagnosis of bronchiectasis as a cohort with the highest risk of infection. The aim is to explore the impact of inhaled corticosteroids in this high-risk group. No similar study has been conducted to date from a PubMed search on the 17th of September 2020.

1.2 RATIONALE FOR STUDY

Inhaled corticosteroids are routinely prescribed for patients with advanced COPD with recurrent exacerbations by international guidelines but their deleterious effect regarding risk of infection and pneumonia remain controversial and uncertain.

This is a proof-of-concept study to assess the effects of inhaled corticosteroid therapy in patients with severe Chronic Obstructive Pulmonary Disease (COPD), Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage D and a co-diagnosis of bronchiectasis and compare it with other classes of inhalers.

The trial essentially wants to review the judiciousness of inhaled corticosteroids (ICS) in this group of COPD patients with coexistent bronchiectasis. One of the known side effects of ICS is risk of pneumonia and hence is all the more important to address and answer this question in this cohort of patents. We will however be closely monitoring these patients with the symptom diaries, good worsening advice and follow up as necessary. The FLAME trial as mentioned in the protocol also showed superiority of dual bronchodilator over triple therapy, so we are reassured those patients will manage to keep their symptom burden under control (if they are in the dual bronchodilator arm of the study) with careful monitoring as planned by the research team.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

In patients with severe COPD and bronchiectasis, does the addition of inhaled corticosteroids:

- Alter the microbial load of pathogens?
    - ICS beneficial effect would lead to an expected reduction in microbial load, with less significant bacterial loads (10 colony forming units/ml or more).
    - ICS detrimental effect, would lead to an expected increased microbial load, with significant bacterial loads (10 colony forming units/ml or more)[12].

      This would be assessed between the two groups (LABA-LAMA-ICS and LABA-LAMA arms).

2.1.2 Secondary Objectives (between two arms of the study) to assess if ICS:

1. Are beneficial, patients will have a broadened microbial diversity in sputum microbiata and if detrimental there would be loss of this diversity[13-15].
2. Alter sputum colour, airways and systemic inflammation. The mechanism of inhaled corticosteroids is anti-inflammatory, and the hypothesis is that inhaled

corticosteroids might improve sputum colour and reduce sputum and serum inflammation[12].

3. Impact on microbial and mycobial community composition as explained in endpoints section 2.
4. Impact on spirometry (forced expired volume in 1 second, forced vital capacity, its ratio and mid expiratory flows FEF25-75).
5. Impact on health status using well-validated quality of life questionnaires in bronchiectasis (COPD Assessment Tool[16] and St George's Respiratory Questionnaire[17]).
6. Moderate/ severe exacerbation rate and time to first moderate/ severe exacerbation.
7. Investigate if addition of inhaled corticosteroid has an overall beneficial/detrimental effect to the mortality rate and whether that correlates with the microbial diversity that we are also assessing in these 2 groups.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

A Baseline to 1-year change (expressed in log units) in colony forming units per ml between treatment arms (LABA-LAMA plus corticosteroid versus LABA-LAMA only) [11-12]

2.2.2 Secondary Endpoints

1. Change in sputum microbial diversity and microbial biomass (see analyses below for details) [13-15] between the two arms.
2. **Sputum colour** as assessed by a standardised colour chart- patients are graded as mucoid (clear or grey phlegm, muco-purulent (light yellow or green) and purulent (dark yellow or green) [18].
3. **a) Microbial community composition** (gram negative/positive ratio, abundance of potential pathogens etc.)[14]

   b) Fungal microbiome: between the two groups to see if ICS can influence the heterogeneity of the fungal community in terms of absolute and relative abundance.[20-21]
4. **Spirometry**: forced expired volume in 1 second, forced vital capacity and its ratio and mid expiratory flows (FEF25-75) (attenuation of decline in lung function would be of long-term benefit to patients if found).
5. **Quality of Life**: quality of life assessed by the COPD Assessment Tool (CAT) [16] and St. George's Respiratory Questionnaire[17]. Breathlessness is included as part of this questionnaire.
6. **Sputum inflammation**: we will assess sputum myeloperoxidase as a measure of neutrophil burden and free elastase activity[12].
7. **Serum inflammation**: we will measure white cell count and differential, C Reactive Protein (CRP) and intercellular adhesion molecule 1 (ICAM-1)[11] Previous research has shown that at high bacterial loads there is increased ICAM-1[12]
8. **Exacerbations**: These would be categorised as

   *****time to the ***first moderate or severe exacerbation*** requiring treatment with antibiotics and/steroids, ****number of exacerbations*** (needing antibiotics and/steroids) over 12 months including hospitalisations

   *****number of participants with radiologically confirmed ***pneumonia*** over this period.

9. **Mortality rate** between the 2 arms of the study groups. Considering the group's overall but also separately broken down by microbe and microbial diversity.
10. **Safety endpoints:** The incidence of all AE and SAE across both treatment arms would be described as well as a safety endpoint. To assess and investigate safety and benefits of a trial design like this, we will also document parameters such as respiratory failure), hospitalised exacerbations (along with other exacerbation data as specified above), and trial dropout due to worsening COPD symptoms as safety endpoints. This would be documented between both the arms of the study.

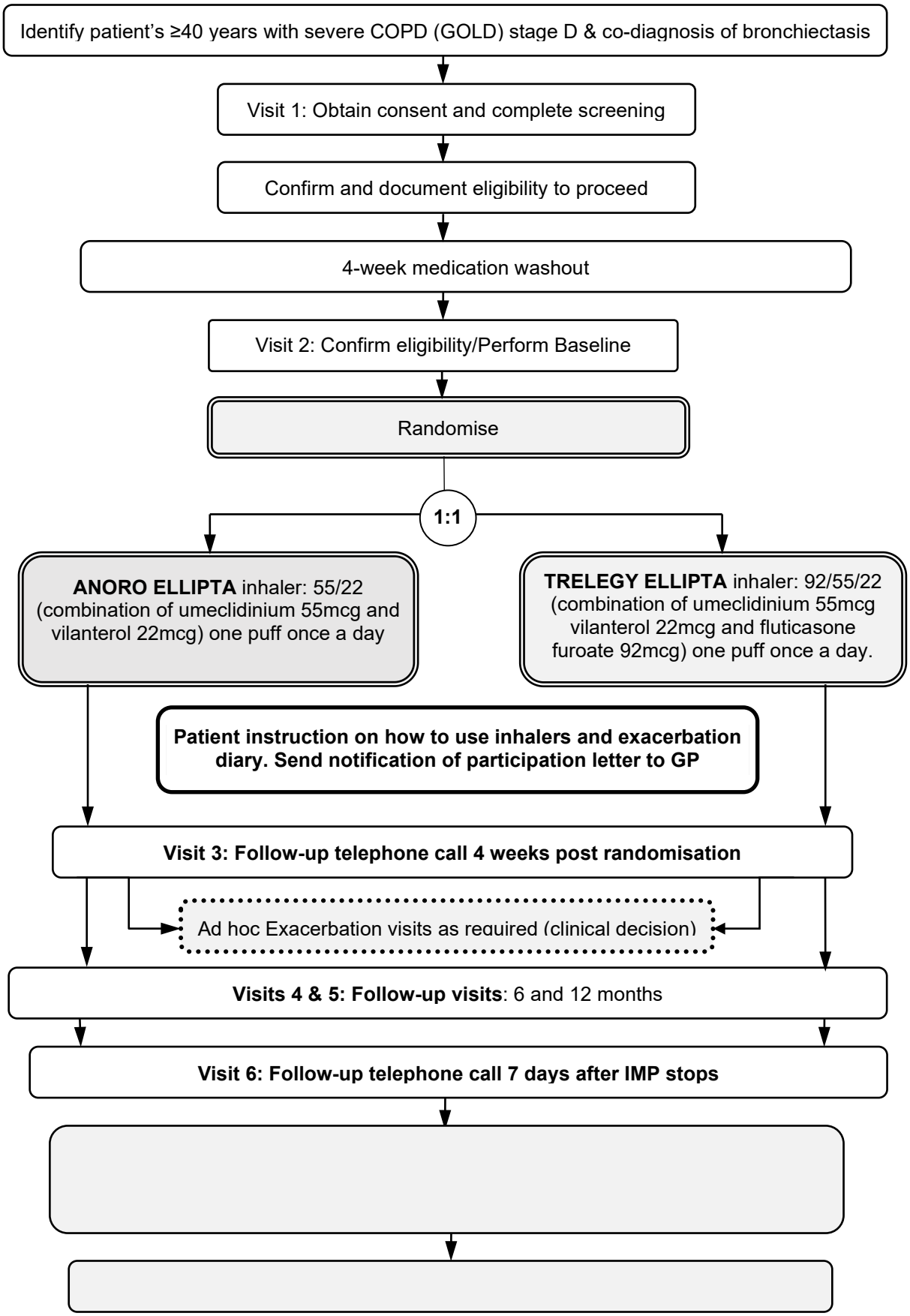
3. STUDY DESIGN

TEMPESTAS is a multi-centred, open label, parallel group randomised study across between 3 - 6 sites. We plan to recruit 80 patients.

To optimise the airflow limitation, we are treating all patients with a combined LAMA and LABA for a washout period of 4 weeks ANORO ELLIPTA 1 puff once daily (combination of umeclidinium 55mcg and vilanterol 22mcg once a day) and the study drugs selected are first line on all our formulary.

These patients will then be randomised in a 1:1 ratio to LABA-LAMA or LABA-LAMA plus additional inhaled corticosteroids (Trelegy Ellipta 92/55/22 I puff once a day). All treatment durations then would last for a year.

3.1 Trial Flow



3.2 Stopping criteria

The IMPs used in the study are routine treatments for the cohort. Safety endpoints will be reviewed by the DMC throughout the study and will determine if there is reason to stop the trial on safety grounds. Any interim decision to stop the IMP on any particular participant would be a clinical decision taken by the PI or the CI.

3.3 NUMBER OF PARTICIPANTS

We aim to recruit 80 patients with moderate-severe COPD with coexistent diagnoses of radiological proven bronchiectasis. Patients will be followed up for 12 months after randomisation.

3.4 INCLUSION CRITERIA

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed Consent:** A signed and dated written informed consent prior to study participation.
2. **Type of subject:** Outpatient.
3. **Age:** Subjects 40 years of age or older at screening visit
4. **Gender:** Male or female subjects
5. **COPD Diagnosis:** An established clinical history of COPD as documented in medical notes in accordance with the definition by the American Thoracic Society/European Respiratory Society.

   COPD-Bronchiectasis definition:

   We will include patients with:

   COPD-Bronchiectasis coexistence: smoking history of greater than 10 pack year, with a post bronchodilator FEV1/FVC ratio <0.7 with coexistent bronchiectasis on a high-resolution CT Chest (increased broncho-arterial ratio in two or more lobes of the lung). CT scans would have been done prior to recruitment as a part of usual clinical pathway.

   - Two or more exacerbations in the last 1-year (requiring antibiotics and/steroids) or one or more hospitalisation in accordance with GOLD D (2017) classification (high risk more symptom COPD patients) but clinically stable during screening period.

   - Clinically stable is defined as not requiring antibiotics and or steroid 4 weeks prior to study entry. This will be checked during the randomisation visit from patient history and documented by the research nurses.

6. **Smoking History:** Current or former cigarette smokers (cigarettes or rolled tobacco) with a history of cigarette smoking of >10 pack-years at screening (visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Note: Pipe and/or cigar use cannot be used to calculate pack-year history.

3.5 EXCLUSION CRITERIA

Subjects meeting any of the following criteria **must not** be enrolled in the study:

1. **Pregnancy**: Women who are pregnant or breast feeding or are planning on becoming pregnant during the study.

2. **Asthma:** Subjects with a current/ concurrent primary diagnosis of asthma.
3. **α1-antitrypsin deficiency**: Subjects with known α1-antitrypsin deficiency as the underlying cause of COPD.
4. **Other respiratory disorders**: Subjects with active tuberculosis, active lung cancer, primary diagnosis of sarcoidosis, primary diagnosis of lung fibrosis, primary pulmonary hypertension, or other interstitial lung diseases (ILD) as primary respiratory condition. Subjects diagnosed with mild ILD may be included in the trial, as long as ILD is not the predominant respiratory condition.
5. **Lung resection**: Subjects with lung volume reduction surgery within the 12 months prior to Screening.
6. **Risk Factors for Pneumonia**: immune suppression (e.g., HIV, Lupus) or other risk factors for pneumonia, when patients are on long standing immunosuppressive drugs or have neuromuscular conditions affecting control of the upper airway, such as Parkinson's disease, Motor Neuron Disease or Myasthenia Gravis.
7. **Pneumonia and/or moderate or severe COPD** exacerbation that has not resolved at least 30 days prior to Screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable). In addition, any subject that experiences pneumonia and/or moderate or severe COPD exacerbation during the washout period will be excluded.
8. **Other Respiratory tract infections** that have not resolved at least 7 days prior to screening including COVID19 infections (would be assessed and decided by the PI corroborated by patient history and medical notes if deemed necessary).
9. **Other diseases/abnormalities:** Subjects with historical or current evidence of any of the following clinically significant abnormalities that are uncontrolled:
    - cardiovascular
    - neurological
    - psychiatric (including documented psychiatric reactions or hypersensitivity to oral steroids)
    - renal
    - hepatic
    - immunological
    - gastrointestinal
    - urogenital (e.g., significant prostatic hyperplasia in men or bladder outflow obstruction that precludes use of a LAMA)
    - nervous system
    - musculoskeletal (including known significant osteoporosis)
    - skin
    - sensory
    - endocrine (including uncontrolled Type 1 or 2 diabetes or thyroid disease)
    - ocular (e.g., significant narrow angle glaucoma that precludes patients from getting a LAMA)
    - haematological

    Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

10. **Unstable liver disease** as defined by the presence of ascites, encephalopathy, coagulopathy, oesophageal or gastric varices or persistent jaundice.
11. **Unstable or life-threatening cardiac disease**: subjects with any of the following at Screening (Visit 1) would be excluded:

    *Type 1 Myocardial infarction or unstable angina in the last 6 months

    *Type 2 Myocardial infarction (more common in severe COPD patients) in last 3 months.

*Unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months

* NYHA Class IV Heart failure

12. **Abnormal and clinically significant 12-Lead ECG finding**: The PI will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial.

    An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

    *AF with rapid ventricular rate >120 BPM;

    *sustained or non-sustained VT;

    *Second degree heart block Mobitz type II and third-degree heart block (unless pacemaker or defibrillator had been inserted)

    * QTcF ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥ 120 msec

13. **Other Contraindications**: A history of allergy or hypersensitivity to any oral steroid or corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, uncontrolled symptomatic prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator contraindicates study participation.
14. **Cancer:** Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma in situ of the cervix, prostrate carcinoma, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5year waiting period if the subject has been considered cured by treatment.
15. **Oxygen therapy**: Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min (Oxygen use up to 3L/min flow is not exclusionary.)
16. **Medication prior to spirometry**: Subjects who are medically unable to withhold their salbutamol for the 4-hour period required prior to spirometry testing at each study visit. This will be gathered from the patient history during the study visit.
17. **Pulmonary rehabilitation**: Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 2 weeks prior to Screening or subjects who plan to enter the acute phase of a Pulmonary Rehabilitation Program during the study. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation Program are not excluded.
18. **Drug/alcohol abuse**: Subjects with a documented known or suspected history of alcohol or drug abuse within the last 1 year.
19. **Non-compliance**: Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits. Non-compliance with requirement for adherence to at least 50% compliance with washout medication, verified at visit 2. Non-compliance with requirement for adherence to at least 50% compliance with trial medication, verified at visit 5.
20. **Inability to read or write English**: In the opinion of the Investigator, any subject who is unable to read or write and/or would not be able to complete study related materials in English**.**
21. **Medication prior to screening**: Use of the following medications within the following time intervals prior to Screening (Visit 1) or during the study:

Systemic, Oral, parenteral Corticosteroids	30 days (Except during the study oral/systemic corticosteroids may be used to treat COPD exacerbations/pneumonia. Intra-articular injections are allowed.
Any other investigational drug	30 days

22. **Suspected atypical infection** like Tuberculosis or fungal infections.
23. **Already enrolled in any other clinical trial of an Investigational Medicinal Product or device**.

3.6 CO-ENROLMENT

Participants cannot take part in any other clinical trial of an Investigation Medicinal Product or device whilst taking part in TEMPESTAS until their treatment and follow-up has completed.

Participation in the interventional phase of a non-CTIMP trial while taking part in TEMPESTAS is permissible in accordance with the Sponsor's co-enrolment policy ACCORD POL008.

Contact the trial office if a potential participant is already enrolled in another interventional non-CTIMP.

Co-enrolment with a non-interventional study (sample and/or questionnaire only) is allowed without formal documentation from the Sponsor.

PARTICIPANT SELECTION AND ENROLMENT

3.7 IDENTIFYING PARTICIPANTS

Research staff who may identify potential participants for TEMPESTAS should be part of the clinical team responsible for the patient's care. We have a large COPD and bronchiectasis service in NHS Lothian with over 2,500 patients seen annually. The investigators have a strong record of accomplishment in translational research. Collaborators will be approached from other NHS sites on the basis that they have an equally good repertoire of conducting translational studies with similar set ups.

Research staff who are also part of patient's clinical care team are based at these NHS hospital sites where local resources would facilitate patient identification and eligibility assessment.

Potentially eligible patients would be identified from the NHS clinics or the NHS clinical databases.

3.8 CONSENTING PARTICIPANTS

Patients who consent to be screened will be recorded on the Consent and Subject Status log. The Principal Investigator, Sub Investigator or experienced research nurse will take face-to-face written consent at the screening visit.

Written informed consent must be conducted and obtained before any screening and study procedures are conducted. Patients must receive adequate oral and written information. Sufficient time will be given for the patient to read the Patient Information Sheet (PIS) and

Informed Consent Form (ICF) ask for more information if necessary and clarify any points they don't understand. The patient will be told that they may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The process of obtaining informed consent should be documented in the patients' medical record.

As part of the consent discussion, potential participants will be informed that signing the informed consent form does not guarantee their enrolment into the trial. The Screening phase will determine their eligibility.

The participant should receive a copy of their PIS and ICF and a copy should be filed in the patient's medical records. The original PIS and ICF should be filed in the investigator site file (ISF) along with the version of the PIL used.

3.9 SCREENING FOR ELIGIBILITY & WASHOUT

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Confirmation of eligibility will be recorded within the participants' medical records. The research team will maintain a pre-screening log. Data from this log will be uploaded onto the database.

3.9.1 Screening Logs

The local research team will maintain a pre-screening log.

3.9.2 Screening

All potentially eligible patients will undergo screening to determine whether they are eligible in accordance with the criteria described in Section 4 (exclusion/inclusion).

The screening process begins when the first contact is made by the study team to the patient or the patient contacts the study team using a register of patients who have previously agreed to be contacted for future research. For patients not in the register but deemed appropriate for the study, would be contacted by the PI or the CI (as part of their clinical ongoing care provider responsibility) to obtain a verbal consent prior to intimation by the research team. This contact may be via telephone or face-to face. If the first contact is made via telephone, a copy of the PIS and ICF will be posted to the *patient* and a follow-up call made at least 7 days after where possible to establish whether the patient would like to be screened for participating. If so, a face-to-face screening visit will be arranged. Any further queries would be answered on the day of the face-to-face screening visit.

3.9.3 Washout

Patients must satisfy the study inclusion and exclusion criteria, as possible at this stage during the screening visit to be eligible to receive the washout medication. Eligible patients will be asked to stop their regular inhaler therapy and will receive Anoro Ellipta 55/22 mcg one puff once a day (Long-acting beta agonist/long acting antimuscarinic) for 4 weeks.

Only participants who are eligible for and agree to the 4-week washout will be entered into the eCRF and allocated a trial number.

Patients who do not adhere to the washout treatment regime or do not tolerate the washout medication will be ineligible to be randomised and their participation in the study discontinued.

3.10 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Patients who are ineligible or not recruited will not be included in TEMPESTAS however they will remain within the clinical service as a part of their standard care of treatment. Their reason(s) for ineligibility will be explained to participants and any questions they have will be answered recorded. They will be thanked for their participation in screening and any relevant clinical information from this visit will be added to their hospital notes and communicated to their GP and consultant where the patient consents for this to happen.

For participants who fail screening this may be repeated and all data will be re-collected.

3.11 RANDOMISATION

3.11.1 Randomisation Procedures

Following successful completion of the 4-week washout phase, verbal reaffirmation will be sought from the patient and recorded in the medical records to collect the baseline data necessary to complete the randomisation and the exclusion criterion would be rechecked.

If still eligible, the participant would be randomised to one of the two arms of the study triple (inhaled corticosteroids/Long-acting beta agonist/long acting antimuscarinic arm) or dual bronchodilator (Long-acting beta agonist/long acting antimuscarinic arm) therapy. Allocation will be made in a 1:1 ratio of study triple: dual bronchodilator using a minimisation algorithm stratified on the following variables: prior ICS (yes/no) and prior long-term macrolides (yes, no). In order to maintain a random allocation, participants will be allocated to the group which minimises the imbalance with a pre-defined probability.

The Investigator will enter the participants data via a 24-hour secure centrally controlled web based GCP compliant central randomisation system, run by the UKCRC registered Edinburgh Clinical Trials Unit (ECTU) using a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation.

The randomisation system will provide details of the treatment allocation and a confirmatory email will be sent to the PI, RN and local Clinical Trials Pharmacy. The Trial Manager and CI will receive confirmatory treatment allocation emails for all participants at all sites.

3.11.2 Treatment Allocation

Patients would be randomised to one of the two arms of the study triple (inhaled corticosteroids/Long-acting beta agonist/long acting antimuscarinic arm) or dual bronchodilator (Long-acting beta agonist/long acting antimuscarinic arm) therapy, which is standard treatment for this group of patients.

As the study is not blinded, patients will be aware as to which treatment group they have been allocated.

3.12 WITHDRAWAL OF STUDY PARTICIPANTS

3.12.1 Study Withdrawal

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented

in the participant's eCRF, if specified by the patient. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data. The final Assessment Visit should be brought forward and they will receive the final follow-up contact.

(ii) all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected. Any patient who withdraws from all aspects of the study will be invited to return to the clinic to have a Final Assessment Visit.

Data will be kept on the CRF/database.

3.12.2 Lost to follow up

If a subject fails to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and confirm whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary, a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. If the subject continues to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF. Every effort should be made to collect survival status (whether the subject is still alive).

3.12.3 Reason for study withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. When a subject withdraws consent, the Investigator should document the reason if known to the investigator team (if reason specified by the subject) in the eCRF.

The primary reason for study withdrawal will be categorised as:

- Adverse event as decided clinically by the PI team or after discussion with the CI.
- Study closed/terminated
- Lost to follow-up
- Pregnancy
- Withdrew consent
    - subject relocated
    - frequency of visits
    - burden of procedures
    - adverse event
    - other (specify)

3.12.4 Follow-up contact

A safety follow-up contact will be made 7 days (-1/+4) following the completion of the randomised treatment period at 12 months or following the Final Assessment Visit (whichever comes first).

The follow-up contact can be made by phone call or by site visit. The following procedures will be performed:

- Adverse event assessment
- Concurrent medication assessment
- COPD exacerbation assessment

Subjects who have successfully completed all on-treatment randomised visits will be discharged from the study upon completion of the safety follow-up contact.

4. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

4.1 STUDY DRUG

4.1.1 Study Drug Identification

Pre randomisation Washout Phase for all patients – 4 weeks
ANORO ELLIPTA inhaler: 55/22 (combination of umeclidinium 55mcg and vilanterol 22mcg) one puff once a day.

Post randomisation IMP Treatment Phase – 12 months	
Arm 1	**Arm 2**
ANORO ELLIPTA inhaler: 55/22 (combination of umeclidinium 55mcg and vilanterol 22mcg) one puff once a day	**TRELEGY ELLIPTA** inhaler: 92/55/22 (combination of umeclidinium 55mcg vilanterol 22mcg and fluticasone furoate 92mcg) one puff once a day.

Both treatments will be delivered by ELLIPTA™ dry powder inhaler (DPI). The inhaler is not under investigation and will be used according to its indication. Each DPI will contain 30 doses of IMP. Subjects will be instructed to administer medication once daily in the morning for the duration of the treatment period. Subjects will self-administer their first dose of IMP the day after their randomisation visit. On the morning of each subsequent clinic study visit, subjects will be instructed to refrain from taking their morning dose of IMP until instructed to do so by clinic personnel. Subjects will take their last dose of IMP in the clinic during the 12-month visit (or Final Assessment Visit). A safety follow-up will be conducted either by phone call or clinic visit 7 days (-1/+4) after successfully completing that.

4.1.2 Study Drug Manufacturer

Glaxo Smithkline plc

4.1.3 Marketing Authorisation Holder

Glaxo SmithKline plc
980 Great West Road
Brentford
Middlesex

TW8 9GS
United Kingdom.

MA Numbers:
Trelegy Ellipta: PLGB 19494/0287
Anoro Ellipta: PLGB 19494/0268

4.1.4 Labelling and Packaging

The IMP will be provided by GSK and sent to the Investigational Supplies Group (ISG) in Edinburgh.

Receipt, over labelling, packaging, QP, storage of supplies and despatch (via courier) to the clinical sites will be carried out by the Investigational Supplies Group (ISG) supported by Edinburgh University, in conjunction with the Lothian Hospital Pharmacy Services.

Two shipments of IMP are planned for each site or as required. The initial shipment will be dispatched following QA check via an approved courier to each site by ISF triggered on receipt of a dispatch request from the Trial coordinating Centre.

This will be followed by a triggered resupply request from the Trial Co-ordinating Centre to ISG and resupply to sites 6 months post activation or as required

4.1.4.1 Preparation and Labelling of IMP

Over labelling is required. Prior to dispensing the study medication, the core text of the label will include:

- Sponsor name, address and telephone number
- Pharmaceutical dosage form, route of administration, quantity of dose, units, product name and strength
- Name of Investigator
- Directions for use
- "For clinical trial use only" or similar wording
- Storage conditions
- Period of use (MM/YYYY format)
- "Keep out of reach and sight of children"

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

4.1.5 Storage of Study Drug

Study medication will be stored at each Site Pharmacy Study medications will be stored securely, at a temperature not to exceed 30^{o}C, away from direct sunlight and monitored and recorded daily. Once dispensed patients will be advised to store their inhalers in accordance with the storage instructions in the participant information leaflet. Regulatory Release to Site and despatch

Following, receipt, relabelling and being QP certified by ISG, and the Sponsor will provide permission to release the IMP to the study. Shipment of IMP to sites will not take place until approval for release has been received.

First shipment requests will be sent following, confirmation that all regulatory requirements have been met and all start-up procedures have been completed. Sites will be activated once the drug has been receipted and the Sponsor given the green light.

ISG will arrange the despatches to sites in accordance with the agreed ISG SOP.

4.1.6 Management and Accountability of IMP at site

Study medication must be confirmed as received at site prior to patients being recruited.

Pharmacy staff will be responsible for dispensing. All study clinical supplies are to be dispensed on receipt of a signed trial specific prescription.

Pharmacy staff will maintain an accurate record of the receipt and dispensing of the IMP in a drug accountability log.

Patients will be asked to return all unused and used inhalers and packaging at:

- End of 4-week washout
- 6-month follow-up visit
- 12-month follow-up visit or at the time of discontinuation of treatment.

On return of the medicines, the Pharmacy staff will perform a check of returns and this will be recorded on the drug accountability log, according to the pharmacy manual. Compliance information will available to the study team. Unused treatment will be disposed of by the Pharmacy as per local SOP following Sponsor Authorisation.

4.1.7 Prescribing and Dispensing of IMP

Washout: Following screening and eligibility checks a trial specific prescription for the washout medication will be generated, printed and signed by the PI or delegated sub-investigator prior to being sent to Site pharmacy for dispensing.

Post Randomisation: Following randomisation, a trial specific prescription for the allocated study medication will be generated, printed and signed by the PI or sub-investigator prior to being sent to Site pharmacy. The database will generate a randomisation email indicating the randomisation allocation, this will be printed and attached to the signed study specific prescription. To allow for contingency in visit schedule, the site pharmacist will dispense the first 7 months supply (seven inhalers).

6-month follow-up: At the 6-month follow-up visit an additional 6 months' supply will be prescribed and dispensed. A resupply will be manually triggered by pharmacy when residual stock reaches 30% (minimum) and/or as necessary.

Resupply: In the event a resupply is needed (e.g., lost inhaler) to complete the study treatment period, a resupply of the patient's allocated treatment can be requested on provision of an additional prescription.

4.1.8 Destruction of Trial Drug

Any used or unused inhalers returned will be documented in the drug accountability log and destroyed locally in accordance with local policy following Sponsor authorisation.

Any IMP destroyed will be recorded on the Certificate of Destruction and retained within the pharmacy file). A copy of the Certificate of destruction will be sent to the co-ordinating centre.

4.2 DOSING REGIME

Inhalers for both arms will be prescribed once a day for 12 months of the study period.

Arm 1: ANORO ELLIPTA inhaler: 55/22 (combination of umeclidinium 55mcg and vilanterol 22mcg) one puff once a day

Arm 2: TRELEGY ELLIPTA inhaler: 92/55/22 (combination of umeclidinium 55mcg vilanterol 22mcg and fluticasone furoate 92mcg) one puff once a day.

4.3 DOSE CHANGES

No changes to dosage or regimen should be made during the course of the study.

4.4 PARTICIPANT COMPLIANCE

Study drug compliance will be assessed and recorded by trial personnel at the randomisation, six month and twelve-month (end of study) visits. The Investigator or delegate will collect used and unused medication and packaging from the patient.

Study drug compliance will be assessed by checking the dose indicator on the inhalers. Adherence to COPD treatment in this patient population overall is good. However, if a patient failed to meet a minimum 50% compliance with study medication during the washout period (i.e., they did not take the medication for at least 14/28 days with no exceptional circumstances to justify this), they will not be eligible to continue to be randomised. A 50% threshold for compliance will apply for compliance for the duration of the study.

4.5 OVERDOSE

Vilanterol: An overdose would likely lead to effects that are typical for β2 adrenoceptor agonists: tremor, headache, and palpitations. Supportive and symptomatic treatment may be indicated.

Fluticasone: Acute inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days.

Umeclidinium: Acute over dosage is not expected to be a clinical problem. Warning would however be issued around usual side effects like visual disturbances, dry mouth, constipation, micturition difficulties and tachycardia. Treatment is usually observation and symptomatic management.

Other side effects to watch out for: of study drugs are likely to be minor and expected. Candidiasis is the main side effect and withdrawal from study treatment will occur if it is marked as persistent and does not respond to symptomatic treatment. Patients should receive treatment with Nystatin 100,000 units four times daily for up to 7 days if candidiasis requires symptomatic treatment. Requirement for another or additional treatment should lead to study withdrawal as alternative treatments may impact the primary outcome.

Paroxysmal bronchospasm is a rare side effect (≥1/10 000 to <1/1000) any patients experiencing this would be withdrawn from treatment, the patient will be assessed, and an alternative therapy instituted, if necessary.

If patients withdraw from the study at some during the trial and do not wish to return for study visits, contact with them will be maintained by the PI, trial manager, research nurse or research assistant to ensure resolution of adverse event(s) and their GP notified. If withdrawal is due to an AE, it will be logged as such on the Adverse Event Log.

The following table summarises the strategy to mitigate some possible side effects from the proposed IMPs.

Potential Risk of Clinical Significance		**Mitigation Strategy**
Pneumonia in patients with COPD	Pneumonia is a class concern for any ICS-containing product for the treatment of COPD. In two replicate 12-month studies, in the FF/VI clinical program, in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the FF (at strengths of 50, 100, and 200 µg)/VI 25 µg combination than in those receiving VI 25 µg alone (3%). In some instances, these pneumonia events were fatal (including one fatality on FF/VI 100/25 µg dose). Risk factors for pneumonia observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m2 and patients with an FEV1<50% predicted. These factors should be taken into consideration when using an ICS in patients with COPD with coexistent bronchiectasis. Pneumonia risk will be important in the benefit-risk assessment for FF/UMEC/VI in COPD patients, hence a robust risk mitigation strategy is being proposed.	• Exclusion criteria as specified in the protocol (section 3.5) • Collection of information on previous history of pneumonia in past 12 months, including hospitalisation at baseline • Use of pneumonia electronic Case Report Form (eCRF) • All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable) • CXR read required whenever a patient has suspected pneumonia
Systemic effects of corticosteroids: bone disorders, bone mineral density decrease and associated fractures	A decrease in bone mineral density and the risk of fractures is a class concern for any ICS-containing product for the treatment of COPD. This is however a very small risk as has been shown in previous studies.	• Evaluation of the potential for bone systemic corticosteroid effects will be conducted through assessment of reported bone adverse events (Review AE/SAE reports)

Systemic effects of corticosteroids: Cortisol suppression	Although all steroids are likely to have some impact on the hypothalamic pituitary axis (HPA axis), the proposed dose of inhaled FF in this study is unlikely to lead to any clinically significant changes. No studies have shown a clinically relevant effect of FF/VI on HPA axis. This includes a formal HPA study in asthma subjects, which assessed the effects of FF/VI 100/25 and 200/25 doses on serum cortisol and 24 hours urinary cortisol excretion, and multiple studies with COPD subjects which monitored 24-hour urinary cortisol. During clinical development of FF & FF/VI, no events of Adrenal Suppression was reported.	• Review AE/SAE reports
Systemic ocular effects of corticosteroids: glaucoma, cataract, raised intra-ocular pressure	Systemic ocular effects (e.g., cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhaled corticosteroids compared with oral corticosteroids. During studies with FF and FF/VI in asthma subjects, and with FF/VI and UMEC/VI in COPD subjects, no associated effect on ocular disorders was observed. In addition, no effects on lens opacification were observed on formal ophthalmic assessments in a study with FF/VI, FF and FP in subjects with asthma.	• Patients with known narrow-angle glaucoma that, in the opinion of the Investigator contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in this study. • Review AE/SAE reports

Cardiovascular effects of UMEC and VI	**UMEC** Cardiovascular effects are a potential class effect associated with antimuscarinic therapies. In the UMEC/VI clinical development program in COPD patients, UMEC/VI was generally well tolerated. Overall, a low number of atrial arrhythmias were reported based on 12-lead ECGs, Holter ECGs, or AEs, of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as SAEs and none were fatal. In a narrow* Major Adverse Cardiac Event (MACE) analysis, the incidence of non-fatal myocardial infarction (MedDRA PTs of myocardial infarction and acute myocardial infarction) was low (<1%) across all treatment groups, although small imbalances in exposure adjusted frequency were observed between UMEC- and VI containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers. During clinical studies in COPD (62.5 and 125 µg daily dose of UMEC) and in Healthy Volunteers (in the Thorough QT study, UMEC 500 µg daily dose), no effect was observed on heart rate, blood pressure or QT. **VI** In the FF/VI clinical development program in patients with COPD, the cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. VI at doses up to 100 µg in healthy subjects and subjects with asthma or COPD was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. Data from Thorough QT (TQT) studies with FF, FF/VI and UMEC/VI suggest that, at the doses to be used in phase III studies, the closed triple (FF/UMEC/VI) is unlikely to cause clinically relevant effects on QTc. No difference in QTcF was observed between UMEC/VI 125/25mcg or UMEC 500mcg and placebo. UMEC/VI 500/100mcg increased QTcF on average by 8.2msec (90% CI: 6.2, 10.2) at 30 min only. A lack of effect was demonstrated for QTcF with FF/VI 200/25 mcg (for 7 days). At a supratherapeutic dose of FF/VI (800/100 mcg for 7 days), the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0) at 30 min only.	• Exclusion criteria as specified in the protocol (section 3.5). • Collection of cardiovascular risk factors and medical history at baseline o ECGs as per protocol o Vital sign assessments (heart rate and blood pressure) as per protocol • Review AE/SAE reports

Anticholinergic effects (including constipation, nausea, dry mouth, dysgeusia, glaucoma, raised intraocular pressure and blurred vision, urinary retention, eye pain)	In clinical studies in COPD, few anticholinergic effects were associated with UMEC; those observed included dry mouth, constipation and cough. ICS has a similar class risk of glaucoma and elevated IOP; however, these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.	• Patients with known significant narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that in the opinion of the Investigator contraindicates study participation will be excluded from participating in the study (see exclusion criterion in section 3.5). • Review AE/SAE reports
Hypersensitivity	Although not associated with FF/VI during the clinical studies, isolated cases of hypersensitivity reactions have been observed, post marketing, with the licensed intranasal spray, AVAMYS. In addition, the FF inhaled formulation has had some reports of hypersensitivity-type reactions. FF/VI formulation contains lactose. There have been reports of serious allergic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose.	• As per exclusion criterion in section 3.5 • Review AE/SAE reports

Radiation risk: we envisage no extra radiation risk to these patients (other than performing chest x-rays as part of clinical care for suspected pneumonias). CT scans would have happened prior to enrolment to this study as a part of their usual pathway of clinical delivery pathways.

4.6 Summary of Product Characteristics

The Summary of Product Characteristics (SmPC) for the IMP inhalers and the NIMP rescue medication (salbutamol sulfate 5mg/2.5ml Nebuliser solution) medication used in the study are provided for TEMPESTAS investigators in a separate signed and verified SmPC Booklet document. This will be kept in the Investigator Site File (ISF) for reference and updates to this booklet emailed to sites in the event of any changes to the Reference Safety Information.

The SmPC's will be reviewed at least annually. Any changes to section 4.8 of the Reference Safety Information of each SmPC which may impact on the trial the protocol will be reviewed and any amendments required will be submitted for regulatory approval.

4.7 OTHER MEDICATIONS

4.7.1 Non-Investigational

An inhaled and nebulised short acting beta agonist salbutamol sulfate 5mg/2.5ml Nebuliser solution) can be administered if required to manage an episode of bronchospasm following sputum induction. This is only if necessary following sputum induction and would be prescribed through a drug Kardex by the PI or sub investigator within the Clinical Research facility.

A complete list of the expected adverse reactions and reference safety information (section 4.8.) of the NIMP, can be found in the current TEMPESTAS SmPC booklet.

4.7.1.1 NIMP Identification

Short acting beta agonist
Salbutamol sulfate 5mg/2.5 ml nebuliser solution – as required in accordance with SmPC

4.7.1.2 NIMP manufacturer

No specific manufacturer will be used. Participants will receive the formulations available on their physicians' local formularies or at their hospital/community pharmacies.

4.7.1.3 NIMP Marketing Authorisation

Not applicable

4.7.1.4 NIMP labelling and packaging

No specific labelling or packaging will be required

4.7.1.5 NIMP Storage requirements

No specific storage instructions will be given in addition to what is advised in the SmPC

4.7.2 Permitted Medications

Permitted medications would be any drug as part of their routine treatment as well as drugs as part of their COPD management excluding single drug preparations of ICS, nasal corticosteroids, LABAs and LAMAs.

Following treatment, patients will continue in the study if they are willing to do so, but this will be noted for future analyses.

- Patient's own short acting beta agonist inhaler or Nebules (must be withheld for at least 4 hours prior to spirometry testing)
- Oral or injectable corticosteroids (short course ≤14 days) only for the short-term treatment of COPD exacerbations and/or pneumonia
- Antibiotics (short course ≤14 days) for the short-term treatment of COPD exacerbations and/or pneumonia
- Mucolytics such as acetylcysteine
- Long term oxygen therapy. (To be eligible to enter the study subjects who are on LTOT must be using at a flow rate of ≤3 litres/minute at rest. However, oxygen therapy may be adjusted as deemed medically necessary at any time during the study.) Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for patients who exhibit oxyhaemoglobin desaturation with rest or exertion (e.g.SaO2 ≤88%)
- Maintenance phase of pulmonary rehabilitation treatment (subjects are not allowed to initiate treatment during the study)
- Any COPD medication deemed medically necessary for the short-term treatment (≤14days) of a moderate/severe COPD exacerbation or pneumonia

The following non-COPD medications are permitted during the study:

- Medications for rhinitis (e.g., antihistamines, cromolyn, nedocromil, nasal decongestants)
- Topical and ophthalmic corticosteroids
- Localized corticosteroid injections (e.g., intra-articular and epidural)

- Vaccinations (Influenza vaccine, COVID vaccine if ready during the period of study recruitment, Pneumonia vaccine, Shingles vaccine, etc.) (Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Current influenza vaccines and pneumonia vaccines will be captured on the concomitant medication pages of the eCRF)
- Allergy immunotherapy
- Antibiotics for short-term treatment (≤14 days) of acute infections. (Long term treatment with antibiotics is not allowed)
- Systemic and ophthalmic beta-blockers. (Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists, and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardio selective beta-blockers should be considered, although they also should be administered with caution).
- Smoking cessation treatments
- Cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs).
- (Administer with extreme caution as they may potentiate the effects of beta agonists on the cardiovascular system, including QTc prolongation.)
- Diuretics. (Caution is advised in the co-administration of beta-agonists with
- non-potassium sparing diuretics as this may result in ECG changes and/or hypokalaemia.)
- Use of positive airway pressure for sleep apnoea
- Oral muscarinic antagonists for the treatment of overactive bladder are permitted but should be used with caution as they may exacerbate medical conditions that are contraindicated for anticholinergics (e.g., narrow angle glaucoma and bladder outflow obstruction).
- COVID-19 vaccines

4.7.3 Restricted Medications

Restricted medications are those that, in the opinion of the Investigators, could result in changes to the airway and lung bacteriology and microbiome that are not the result of the investigational treatment. Patients receiving local or systemic antibiotic treatments, or local corticosteroids e.g., nasal corticosteroids at baseline would exclude participation in the study.

Patients having an exacerbation requiring antibiotics or corticosteroids during the study period (after randomisation) will attend for an unscheduled visit if deemed necessary by the investigator team. Participants with a potential exacerbation of COPD or wishing to withdraw for any other reason during the washout phase will be offered a visit for clinical assessment by the study team.

Restricted medications therefore would be

- Nasal corticosteroid spray
- Antibiotics of any sort unless being administered for a COPD exacerbation

If restricted medications are commenced for clinical reasons the patient may continue in the study and continue to take IMP, but the trial manager should be notified that a restricted medication has been commenced, and this should be recorded in the CRF.

4.7.4 Prohibited Medications

Corticosteroids	Inhaled corticosteroids of any class should not be commenced during the study other than those provided as part of the study Systemic corticosteroids should not be commenced for the treatment of stable COPD during the study, unless in the "oral prednisolone' arm of the study at the end. If systemic corticosteroids are commenced for the treatment of acute exacerbation of COPD, this should be recorded and the patient should attend for an exacerbation visit.
Systemic antibiotics: **Penicillin** **Tetracycline** **Other antibiotics**	Patients should not commence long-term antibiotic therapy for COPD during the study period. Only exception is if they have been on long-term macrolides for more than 3 months; this will be allowed to continue. Antibiotics may be administered for the treatment of an acute exacerbation, but this should be recorded, and the patient should attend for an exacerbation visit.
Roflumilast ritonavir, itraconazole, telithromycin, or ketoconazole.	These are anti-inflammatory medications that could theoretically affect the airway microbiome by modulating the immune system.

5. STUDY ASSESSMENTS

5.1 SAFETY ASSESSMENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions of all adverse events (such as pneumonia rate and all other safety endpoints as mentioned in section 2.1.2).

All data will be collected throughout the study period as delineated in table one and appendix one table (through pre randomisation and treatment phase).

All safety assessments (e.g., pregnancy tests, 12 Lead ECG, vital parameters) will be carried out as part of eligibility screening as well as during ongoing assessments in the subsequent visits.

Patients raising concerns would be reassessed by the PI team to consider suitability to continue in the trial. All clinical assessments will be reviewed intermittently by the PI and if needed reported as AEs and acted on appropriately and discussed in the DMC.

The following laboratory variables will be measured at Baseline, 6 and 12 months:

Laboratory Safety Variables Haematology (whole blood- EDTA)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P- Urea
	S/P- C reactive protein
	Citrated sample: Fibrinogen
S/P-Alanine transaminase (ALT	
S/P-Albumin	
S/P-Potassium	
S/P-Sodium	

5.2 Follow-up Contact

A safety follow-up contact will be made

- 1 month post randomisation
- 7 days (-1/+4) following the completion of the randomised treatment period or following the Final Assessment Visit.

The follow-up contact can be made by phone call or by site visit. The following procedures will be performed:

- Adverse event assessment
- Concurrent medication assessment
- COPD exacerbation assessment
- Compliance

Subjects who have successfully completed all on-treatment randomised visits will be discharged from the study upon completion of the safety follow-up contact.

5.3 STUDY ASSESSMENTS

Investigations (All Patients)		Screening and Consenting Visit	Medication Washout Period 4 weeks	Baseline/Randomisation	Telephone Follow-up contact	Month 6 +/- 2 Weeks	Month 12 or Final Assessment +/- 3 Weeks			Exacerbation Visit (Face to face or telephone visits)
Visit Number		Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 *	Visit 7	As necessary
Time relative to randomisation		- 4w	-4w	0	1m ± 2d	6m	12m	1 to 12m	12m + 7d	1 to 12
Time window for evaluation		N/A	N/A	4 weeks ±2 days from screening		± 2 weeks from randomisation	± 3 weeks	±2d	+3d	-
Written Informed Consent		✓								
LMP, Pregnancy Test & Contraception review (where applicable)		✓		✓		✓	✓		✓	
Physical Examination (including height and weight)		✓								✓
Current COPD Medications?		✓		✓	✓	✓	✓	✓	✓	✓
Concomitant Medications		✓								
Past Medical History?		✓								
Demographics		✓								
Stratification				✓						
Lifestyle		✓								
Eligibility review		✓		✓						
Reaffirm Consent				✓		✓	✓		✓	✓
Medication Washout & Accountability				✓						
Randomisation				✓						
Spontaneous Sputum	Sputum Colour			✓		✓	✓		✓	
Sputum	Qualitative and Quantitative Microbiology			✓		✓	✓		✓	
	16S RNA Pyrosequencing									
Sputum inflammatory assays	Myeloperoxidase (MPO)			✓		✓	✓		✓	
	Free elastase activity									

Routine Bloods tests	FBC including eosinophil count, CRP, ICAM-1 U&E's, LFT's Fibrinogen			✓		✓	✓		✓	
Spirometry	FEV1 + FVC; FEV1/FVC; mid expiratory flows (FEF25-75)	✓		✓		✓	✓		✓	
Questionnaires	COPD Assessment Tool			✓		✓	✓		✓	✓
	St George's Respiratory SGRQ-C									
Modified MRC breathlessness score		✓		✓		✓	✓		✓	
12 Lead ECG		✓				✓	✓		✓	
Vital signs (Pulse, respiratory rate, blood pressure, oxygen saturations on room air and body temperature)		✓		✓		✓	✓		✓	✓
Exacerbations (Number of and time to 1st moderate/severe exacerbation)				✓	✓	✓	✓	✓	✓	
Collection of all AE and SAE data (as in section 11)				✓	✓	✓	✓	✓	✓	✓
Dispense randomised study Medication?				✓		✓				
Study Medication Adherence (& Accountability check if face to face)					✓	✓	✓		✓	✓
							✓			
							✓			
									✓	✓

Table 1 of assessments

5.3.1 Physical Examination

A detailed physical examination (including height and weight) will be performed at the screening visit to exclude patients with co-morbidities or other clinical disorders that would constitute an exclusion from the study. This will include the following systems:

- Respiratory
- Cardiovascular
- Abdominal
- Dermatological

5.3.2 ECG

A 12 Lead ECG will be performed at screening as part of the evaluation to ensure that patients are not enrolled when they have an unstable cardiovascular co-morbidity.

This will be repeated at 6 and 12 months to assess cardiovascular stability.

5.3.3 Vital Signs

The following will be performed routinely at all study visits and recorded in the medical notes: Pulse, respiratory rate, blood pressure, oxygen saturations on room air and body temperature.

5.3.4 Symptoms and quality of Life

These will be evaluated at each visit using the St. George's Respiratory Questionnaire and the COPD assessment test. Both are validated tools in COPD. Breathlessness symptoms will be quantified with the modified MRC dyspnoea scale.

5.3.5 Spirometry and sputum induction

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) will be measured at each visit. Spirometry will be performed pre- and post-bronchodilator as per local practice (as on long-acting bronchodilators). Spirometry testing will be done using ERS standards.

Sputum induction will be done using 0.9% saline and if needed move to hypertonic saline (3% and 4%), and safety spirometry performed 15 minutes after sputum induction to assess the presence of bronchospasm. If sputum cannot be obtained at a visit, the visit may be repeated within 7 days – it is not necessary to repeat all procedures, only to perform sputum induction. Spontaneous early morning sputum is also acceptable in the event of failed induction. This includes the screening visit. This will be elucidated in a laboratory procedures manual.

5.4 COMPLIANCE ASSESSMENTS

See section 4.1.6 and 4.4

5.5 LONG TERM FOLLOW UP ASSESSMENTS

Patents will be followed for the 12 months treatment phase following recruitment. After the end of the study, if deemed necessary patients would be followed up in the COPD clinics locally for ongoing clinical management.

5.6 COLLECTION, STORAGE, TRANSFER AND ANALYSIS OF SAMPLES

Blood and sputum samples will be collected as a part of this study (see Table 1 Schedule (Appendix 1).

Routine Safety bloods will be taken and tested at local NHS sites and results reported on the eCRF according to standard procedures.

Standard ICAM-1 blood samples will be collected locally for DNA analysis. These samples will be collected, frozen and stored locally at all sites in accordance with the TEMPESTAS ICAM-1 instruction document and sent in batches to the Queen's Medical Research Institute (QMRI) at the Centre for Inflammation Research, University of Edinburgh for analysis, reporting and storage.

Sputum samples will be collected locally, fixed with glycerol and stored locally at -70 degree Celsius in accordance with the TEMPESTAS Sputum instruction document. They will be sent in batches to QMRI labs at the Centre for Inflammation Research, University of Edinburgh for analysis and reporting and storage.

This information is specified in the patient information PIS and the ICF. The ICF will also specify if patients are happy for samples to be stored for 15 years and used for future research studies.

Microbiology analyses

All qualitative and quantitative microbiology assessments would be done centrally in Edinburgh having initially fixed the sputum samples with glycerol (and stored at -70 degree Celsius) and then transported the sputum samples from the other sites.

Samples will be received with an identifier code. The laboratory team will be blinded to the clinical information and treatment allocation for both arms of the study.

For microbiome analysis, induced sputum samples will be stored at -80°C. For 16S-based microbiota studies (low biomass samples), we will use a modified protocol using mechanical lysis in combination with the Agowa mag Mini DNA isolation kit which will be used to guarantee extraction of bacterial and fungal DNA from all phyla. Sequencing will be executed following amplification of the hypervariable V4 region of the 16S ribosomal subunit by universal primers.

Sequencing results will be processed through DADA2 and taxonomic annotations will be performed using the RDP naive Bayesian classifier based on the Silva database.

In addition, we will analyse the fungal community (i.e., mycobiome) by ITS amplification, including a combination of ITS1F/ITS2 regions to ensure maximum coverage of species present. Sequencing results will again be processed through DADA2 and taxonomic annotations will be performed using the UNITE dynamic database.

Standard bacterial culture: Part of the sputum samples will be processed and plated for quantitative bacterial culture with results expressed as colony forming units (cfu)/ml. The rest of the sputum sample would then be used for molecular studies. These procedures will be conducted at the central lab in Edinburgh. The other half of the sample would be stored for the microbiome analyses. Any remaining sputum will be stored within the QMRI with patient consent for up to 15 years for use in future research.

Airway inflammatory markers

Bacterial colonization drives neutrophilic airway inflammation, which is a feature of COPD; therefore, airway inflammation will be characterized throughout the study

This will be done by measurement of airway inflammatory markers using commercially available ELISA assays (for sputum MPO and free elastase). Any remaining sputum sol will be stored with patient consent for up to 15 years for use in future research. This will be specified in the patient ICF. This will be conducted in the same laboratory setting as the microbiology analyses.

Systemic inflammation

Systemic inflammation will be measured using established markers in blood including serum C-reactive protein and serum Fibrinogen and ICAM-1. White blood cell total and differential cell counts for neutrophils and eosinophils will be performed. Peripheral blood eosinophilia in particular has been shown to predict sputum eosinophilia and response to ICS and will be documented.

Symptoms and quality of life

These will be evaluated using the St. George's Respiratory Questionnaire and the COPD assessment test. Both are validated tools in COPD. Breathlessness symptoms will be quantified with the modified MRC dyspnoea scale.

6. DATA COLLECTION

The PI, co-investigators and local researcher staff at each site will collect the local data listed in the Visit Schedule in Table 1. Research staff in the TCC will collect the central data.

Data will be collected by a delegated member of the research team at each hospital site using electronic case report forms (eCRF) via the secure web interface to the trial database. The data that will be collected by each eCRF are listed below at each time point.

Identifiable data will not be recorded on the eCRF until after consent has been obtained.

6.1 Visit 1 – Screening & Washout

Pre-screening will be undertaken by a member of the clinical team where applicable using the patient's medical records. If the patient is potentially eligible, their name and date of birth and contact details will be collected for the purposes of making an appointment.

The screening process begins when a member of the clinical team makes contact with or is contacted directly by the potential study participant. An initial assessment will include a verbal assessment of the patient's medical history, including history of their COPD and current medications. If the initial contact was by telephone, a face-to-face visit will be arranged and the PIS and ICF sent to the participant in preparation for the screening visit.

All women of child-bearing potential must have a confirmed menstrual period and a negative highly sensitive pregnancy test 7 days or fewer before starting washout medication and must use a highly effective method of contraception throughout their participation in the study. Effective contraceptive methods may include: hormonal contraception (oral, intravaginal, transdermal, injectable, implantable) or intrauterine device. Exceptions to use include: bilateral tubal occlusion, vasectomised partner or true sexual abstinence (i.e., within line of the person's preferred and usual lifestyle).

Collection and documentation of sputum and blood samples would then be carried out as per protocol.

Screening/Washout:

After eligibility has been established and consent procedures completed, local research staff will complete the eCRF to confirm

- Who confirmed eligibility
- Demographic details
- What the patient has consented to (including their consent to data being kept and used for other research)
- Who obtained consent
- When consent was obtained
- Version and date of PIS and ICF used

Baseline data will be collected from the patients, medical records and reports. This data including

- Pre and post bronchodilator spirometry assessments (post bronchodilator spirometry will be used to calculate GOLD COPD stage)*.
- Current COPD medication
- Co-morbidities
- Pregnancy test and contraception review
- ECG
- Concomitant medication
- COPD Assessment
- Lifestyle information
- Anthropometrics (height, weight)
- Vital signs (Pulse, respiratory rate, blood pressure, oxygen saturations on room air and body temperature)

*Spirometry assessment is performed at each visit and completed according to British Thoracic Society Guidelines. Lung function assessment is measured by pre- and post-bronchodilator spirometry (only if on long-acting bronchodilator therapy) (Forced expired volume in 1 second, forced vital capacity (Forced expired volume in 6 seconds-FEV6 will be used as the surrogate of FVC) and mid- expiratory flows (FEF 25-75).

Entry of these data will generate a unique ID number for the consented participant and a prescription for the washout medication to be printed.

Research staff will record the participant's trial number and treatment allocation in the participant's medical records.

Those who are ineligible to continue to randomisation will be given the reason and with their consent, their GP will be notified of any abnormal findings.

6.2 Visit 2 - Baseline and Randomisation

The following assessments are expected to be conducted in clinic at the baseline visit and must be reported in the eCRF:

- Participant status (continuing or discontinuing participation)
- Any exacerbations of COPD
- Any changes in concomitant medications
- Pregnancy and contraceptive review (if there is concern of pregnancy, another pregnancy test will be administered)
- Vital signs
- Lab assessments (Biochemistry)
- ICAM-1 collection
- Sputum collection
- Washout medication returns and accountability
- Adherence to washout medication (at least 50% adherence)
- Spirometry
- Demographics, socioeconomic status, stratification (prior ICS and prior long-term macrolides
- Modified MRC breathless score
- Collection of AE's and SAE's

The participant will be asked to complete the following validated questionnaires recording:

- St. George's Respiratory Questionnaire C (SGRQ-C) to measure health status (quality of life).
- COPD Assessment Test (CAT) to measure the impact of COPD on wellbeing and daily life.

If patient fulfils the criteria for randomisation the randomisation can be initiated. A Randomisation ID for the patient will be generated and a treatment allocation provided. Treatment for the first 7 months to be dispensed in-person

6.3 Visit 4 - 6m ± 14 d

The following assessments are expected to be conducted in clinical and must be recorded in the eCRF:

- Participant status (continuing or discontinuing participation)
- Adverse Events
- Any exacerbations of COPD
- Any changes in concomitant medications
- Pregnancy and contraceptive review (if there is concern of pregnancy, another pregnancy test will be administered)
- Vital signs
- Blood analysis (Biochemistry)
- ICAM-1 collection
- Sputum collection
- ECG
- Spirometry
- SGRQ-C assessments
- COPD Assessment Tool (CAT) Modified MRC breathless score•
- Return of unused study medication and accountability
- Study medication adherence and accountability
- Study Prescription to be generated for printing and signing for dispensing 6 months study medication.
- 6 months study medication dispensed
- Participants should be reminded to re-initiate their standard repeat prescription (if appropriate) to ensure continuity of clinical care after they have stopped the study drug (i.e., after 12-month appointment)

6.4 Visit 5 – 12 months/Final Assessment

A final Assessment Visit will be completed for all participants at completion of the study or earlier if required.

The following assessments are expected to be conducted in clinic and must be recorded in the CRF:

- Adverse Events
- Any exacerbations of COPD
- Any changes in concomitant medications
- Pregnancy and contraceptive review (if there is concern of pregnancy, another pregnancy test will be administered)
- Vital signs
- Blood analysis (Biochemistry)
- Sputum collection
- ECG
- ICAM-1 collection
- Adherence to study treatment
- Spirometry
- SGRQ-C assessments
- COPD Assessment Tool (CAT)
- Modified MRC breathless score

- Return of unused study medication and accountability
- Study medication adherence and accountability

6.5 Exacerbation visits

All reported moderate and severe COPD exacerbations that occur from washout until the study medication has stopped and the final safety assessment call completed should be recorded in the database. The data required includes

- Symptom start Date
- Symptom resolution date;
- increase in sputum
- change in colour of sputum
- worsening cough
- worsening breathlessness
- antibiotics or oral steroids prescribed.
- Watch out for signs of pneumonia: e.g., crepitations/bronchial breathing on auscultation and if so then proceed to do perform a chest x-ray to confirm or refuse radiological presence or absence of pneumonia.

Any medications prescribed should be recorded in the exacerbation medication log.

Patients commencing washout will be given an Exacerbation Diary and asked to record and report to the local study team any exacerbations that occur throughout the duration of the study period. They will be asked to record details of each episode, including what treatments were received (in the exacerbation medication log) and any change in symptoms for a period of 2 weeks (or until they report they are well again). They will be advised to bring this with them to each follow-up visit. These will be checked against any other reported exacerbations.

Patients will be advised to contact a member of the study team to inform them if they develop worsening symptoms of their COPD. A clinical decision will be made whether the patient needs to attend for a visit for further investigation to rule out pneumonia.

Reports of exacerbations may come from a variety of sources patients; GP'S, clinic visits, hospital admissions.

6.6 Visits 3 and 6* - Safety Follow-up Telephone Calls

A member of the research team will telephone the participant and document:

- 1 month post randomisation to review their adherence to the study medications: check for any exacerbations (as specified in secondary endpoints in section 2.2) and ask about any AEs/SAEs

- 7 days (+3d) from end of all study medication to check for any SAE's or exacerbations. This will be recorded on the eCRF.

6.7 CASE REPORT FORMS

Data will be collected using electronic case report forms (eCRF) via the secure web interface to the trial database.). The data that will be collected by each eCRF are listed below at each time point.

Identifiable data will not be recorded on the eCRF until after consent has been obtained.

All consented participants will be entered into the eCRF.

Those who do not satisfy the washout period compliance (taken at least 50% of washout medication) will be logged as a screen fail in the eCRF.

6.8 SOURCE DATA COLLECTION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first

The Investigator will maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information relevant to a participant's general medical history on CRFs must be traceable to these source documents in the patient's case notes. The CRF will be used as source data unless otherwise detailed in the source data plan.

Source data for each critical data point will be documented in a site level source data plan.

6.9 TRIAL DATABASE

A secure trial database will be provided using REDCap and maintained by the Edinburgh clinical Trials Unit. A bespoke randomisation system will be built to manage the randomisation and allocation of IMP. Medication will be automatically assigned once randomised through the randomisation system. This will be linked to REDCap via the REDCap Application Programming Interface (API). Access to the database is role based and site users are restricted to access their own site data only. Trained and delegated members of the study team will be given password-protected logins to the database to complete data entry. All users will require training before access is granted.

The TM and ECTU will provide support for users during working hours. The database will have a secure audit trail and back-up procedures to minimise potential data loss.

Local research staff delegated to do so on the delegation log will enter all trial data into the trial database using eCRF's. Data entry errors will be minimised by using range, completeness and consistency validation checks. REDCap provides the facility for sites to download and print PDFs of the participant's entered data.

The unblinded trial statistician will be given 'read only' access to the database.

Data will be stored on secure servers hosted by the University of Edinburgh that require user authentication, archived after the end of the trial, and made available in de-identified format to satisfy data sharing requirements at the end of the trial.

7. DATA MANAGEMENT

7.1 Personal Data

Demographic, clinical, and personal data will be collected as part of the research, as described

Personal data will be stored by the local research study team on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All local paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only.

7.2 Transfer of Data

Participants are informed about the need for the trial to share data to the following sources, which involves transfer of their personal data to ensure that they are identified correctly: sources such as the participant's general practitioner; hospitals involved in TEMPESTAS.

Participants consent to the use of information about them to support other research in the future, and that the information may be shared anonymously with other researchers, whatever happens to the participant.

Data Transfer will be in accordance with General Data Protection Regulations, ICH GCP and SOPs that cascade from the practices defined by the Academic and Clinical Central Office for Research and Development (ACCORD) SOPs.

Delegated research staff will enter the data required by the protocol into the eCRF following training in the definitions and methods used in completing the eCRF.

On completion of data collection, the Investigator must certify that the data entered into the eCRF is complete and accurate.

Data verification and cleaning will be performed as per ECTU local procedures and detailed in the Data Management Plan.

General laboratory data methods will be documented in laboratory notebooks and then analysed and written up for publication and dissemination to the scientific community. This lab data will act as the source data. All electronic data will be stored on secure personal computers and with rolling off-Site backup – the University of Edinburgh's central provision for this process (through ECTU). All data will be retained for 5 years in accordance with sponsor policy.

7.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g., the site)

The Investigator will maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information relevant to a participant's general medical history on CRFs must be traceable to these source documents in the patient's case notes. The CRF will be used as source data for other information.

A data management system will be provided by ECTU. The study system will be based on the protocol and the CRF for the study and individual requirements of the Investigators. Development and validation of the study database and QC and extraction of data will be done according to ECTU procedures. Extracts for analysis will be based on the dummy data tables provided by the study team. Core laboratory data will be inputted directly from the individual sites into the ECTU built database.

The eCRF will not collect more information than is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The CRF will be used as source data but data relevant to a participant's general medical history will be recorded also in the electronic case notes.

7.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

8. STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

With a sample size of 36 per group we would be able to detect a difference of 0.76 log unit in the change in bacterial load between treatment arms assuming a common standard deviation of 0.98 log units based on a two-sided, two-sample test with 5% level of significance and 90% power[19]. A 10% drop out rate increases this to 80 patients (40 per group).

8.2 PROPOSED ANALYSES

Analysis

Full details of the statistical analysis will be detailed in a separate Statistical Analysis Plan developed prior to examination of any accumulated trial data. A summary of the planned analysis is given below.

Results will be presented broken by treatment allocation. Where data is categorical number and percent will be presented however where data is continuous descriptive statistics including mean, standard deviation (sd), median, q1, q3, min, max will be presented. As this is a proof-of-concept study we will present descriptive statistics for markers of interest by treatment arm at each time point as well the baseline to 1-year change. No covariates are planned to be adjusted for these analyses.

Where responses are continuous for example the level of change in cfu, comparison between groups will be made using a two-sample t-test and results of this will be presented accompanied by the mean and 95% for the difference between groups. We will present the time to first exacerbation using a Kaplan-Meier survival curve stratified by treatment allocation and present this will the accompanying log-rank statistic.

Where responses are binary i.e., presence of clinically significant change in cfu, comparisons between groups will be made using a binomial test for the comparison of proportions and accompanying this we will present the difference in proportion and 95% CI for the difference.

The number of participants experiencing adverse events and serious adverse events will be reported as well as the number of events per participant. Comparison will be made between treatment arms.

As information on AE/SAE will be captured during the washout phase prior to any dosing with study drug we will present this information separately for AE/SAE occurring prior to the first dosing and AE/SAE occurring after the first dosing.

Dropouts during the study will be reported and where available a reason for dropout will be captured. The dropout rate will be compared across both treatment arms

16S and ITS data: we will summarise and visualise microbial and fungal community compositions using ordination techniques/PERMANOVA-tests, allowing for global comparisons between groups. To compare alpha diversity between samples, we will look at the richness, as well as the Shannon diversity index. Beta diversity, which represent the between sample diversity, will be investigated using the Bray-Curtis dissimilarity. In addition, using a data-driven, unsupervised clustering approach we will discern profiles that will subsequently be linked to host phenotypes, enabling us to identify microbial structures associated with host infection susceptibility. Depending on the distribution of data, we will use either classical regression (MetagenomeSeq) or a machine learning technique (randomForest) to identify microbes driving differences between patient groups.[14-1]

Metagenomic sequencing: Microbial DNA will be isolated and processed as previously described.[17] For bacterial community profiling, the V4 hypervariable region of the 16S-rRNA gene was amplified using barcoded primer pair 533F/806R.[17] To profile the fungal community, we will target the ITS1 region using a two-step protocol as described by Illumina (Fungal sequencing and classification with the ITS Metagenomics Protocol) with some modifications. Amplicons will be quantified using PicoGreen (Thermo Fisher Scientific, Invitrogen, Eugene, OR, USA) and pooled in equimolar amounts. Amplicon pools of samples and controls are sequenced using the Illumina MiSeq platform (San Diego, CA, USA).

***Bioinformatic processing*:** Bioinformatic processing of 16S reads will be performed as previously described[19] and included quality filtering/trimming, error correction, read assembly and binning reads in OTUs of 97% similarity. Bacterial sequence variants will be annotated using the Silva database (version 119).[20] Taxonomic assignment of fungal sequence variants will be annotated using the UNITE QIIME release database version 01.12.2017 and the RDP classifier in QIIME version 1.9.[21]

***Quality control*:** To control for contaminating DNA we will process DNA isolation and PCR controls, and use mock communities as positive controls. Following, the *decontam* R-package[22] will be used to identify contaminating sequence variants for 16S- and ITS-based data separately.

***Quantifying biomass*:** We will quantify the fungal DNA concentration using Picogreen. For bacteria, we will use qPCR.

Statistical/data analysis: All analyses will be performed in SAS v9.4 or later (SAS Institute Inc., Cary, NC, USA.) or R version 3.6.3 within R studio version 1.2.5033 (Boston, MA) or a later version

We will use the packages vegan, phyloseq[23], microbiome[24], and ggplot2[25] for our microbial community structure (microbiota) analyses.

For both datasets, the relative abundances will be calculated by dividing the sequencing reads assigned to different taxa by the total number of reads per sample.

Benjamini-Hochberg (BH) adjusted P values (q values) will be used where appropriate. A P value and a q value of 0.05 will be considered significant.

All patient samples will be subjected to a similarity-based, unsupervised hierarchical clustering approach based on absolute abundances to identify community state types/clusters.

For comparisons of group differences, a one-way analysis of variance, Wilcoxon rank-sum test, Kruskal-Wallis test, or chi-square test will be used where appropriate depending on the variable(s) tested.

Group differences in diversity will be calculated using Wilcoxon tests and linear mixed-effect models. Associations between group and overall microbiota composition will be analysed using the adonis2 function (vegan package[69]), based on permutational multivariate analysis of variance (PERMANOVA)-tests. Differences between groups on the lowest taxonomic annotated level (OTU) will be tested using the metagenomeseq package in R studio or the machine learning method Random Forest, depending on the distribution of data in our cohort.

9. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until the final follow-up assessment must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

9.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant; is life threatening*
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;

- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria and will be reviewed by the local PI and if needed by the CI. This is because this is a high-risk exacerbator group that is being dealt with and would naturally be prone to exacerbations and hospital admissions.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

9.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g., laboratories.

9.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g., hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

9.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e., existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

9.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

9.3.3 Adverse Events to be reported on eCRF

For a complete list of the expected adverse reactions and reference safety information of the TEMPESTAS study medication, refer to section 4.8 of each SmPC in the current TEMPESTAS SmPC booklet. To better assess the events that are of special interest to the trial, the following adverse events will also be reported in the eCRF from Baseline until the Final assessment regardless of severity and seriousness:

- Any community respiratory exacerbations of COPD
- Community diagnosed pneumonias
- Any oral infection
- New respiratory conditions detected or diagnosed after study treatment administration
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication any cardiovascular or cerebrovascular events

Laboratory, Spirometry and Vital Signs assessments
Deterioration as compared to baseline in CSP-mandated laboratory values, spirometry values and vital signs should only be reported as AEs if:

- They fulfil any of the SAE criteria, or
- Are the reason for discontinuation of treatment with the study intervention, or
- Are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or study intervention interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

Events not listed in this section will be recorded in the patient medical notes.

9.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

9.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

9.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

9.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet.

Unexpected: the AR is not consistent with the toxicity in the SPC Booklet.

ARs known to be attributable to the IMP's are described in the SmPCs.

Fatal and life-threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SmPC that the IMP causes fatal SARs.

9.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

9.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

9.6 REPORTING OF SAEs/SARs/SUSARs OUTCOMES IN TEMPESTAS

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance ***within 24 hours****. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

9.7 REPORTING CLINICAL SAFETY DATA TO GSK

SAE's: ACCORD shall report only SAEs arising during the Study for which the Investigator/designee considers there to be a reasonable possibility of causal association with the GSK IMP(s) (as specified by the Protocol), regardless of expectedness, to GSK (as specified below) within twenty-four (24) hours of first becoming aware of the event, regardless of ACCORD expectedness assessments against GSK IMP(s).

GSK Medical Devices: The Chief Investigator shall report medical device incidents arising during the Study, that meet the criteria for MHRA notification via the Yellow Card scheme, to GSK using the documentation provided by the MHRA Yellow Card scheme and within twenty-four (24) hours of first becoming aware of the event. The Chief Investigator will not assess the expectedness or relatedness of medical device incidents and will not affect or alter the original content of the Yellow Card reports provided by sites.

Pregnancy Reports: ACCORD will report pregnancy information on any female participant who becomes pregnant while taking part in the Study, and following exposure to a GSK IMP, to GSK within two (2) weeks of first becoming aware of the pregnancy. Follow-up reports which include the outcome of the pregnancy (including any premature termination of the pregnancy) and the status of the mother and child will be forwarded to GSK. Follow-up will be requested by GSK no longer than six (6) to eight (8) weeks following the estimated delivery date.

Reporting Period: Any SAEs, medical device incidents, events for targeted monitoring and pregnancy reports that are subject to the above reporting provisions are those that occur following the first dose of the GSK IMP(s) and/or GSK medical device(s) through to twenty-eight (28) days, or after discontinuation of the GSK IMP(s).

9.8 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

9.9 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

9.10 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy or any pregnancy of a female partner of a male participant, who became pregnant while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and pregnant partners of male participants will be followed up until the outcome of the pregnancy.

Female participants, if become pregnant during the study will be discontinued from the study, as a safety measure.

10. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders (Chief Investigator and the Edinburgh Clinical Trial Unit in Edinburgh), the ECTU Trial Manager, the Trial Statistician (Catriona Graham) and a coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the site Investigator or delegated member of the trial team.

The TMG will meet regularly to ensure that all aspects of the study are trial is progressing well. A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

10.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) coordinated by ECTU will be established to oversee the conduct and progress of the study in accordance with the Terms of Reference agreed in a TSC Charter.

We do not envision any major challenges in running the study as the investigational products are very much standard of care first line inhaler therapy for this group of patients.

10.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the study. The terms of reference of the Data Monitoring Committee, the outline of the DMC report, and the names and contact details will be detailed in the DMC Charter. The DMC Charter will be agreed and signed by the appropriate individuals prior to the study commencing.

10.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

10.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits as necessary.

11. GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

11.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

11.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Form's will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Informed Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed ICF and a copy will be filed in the participant's medical notes.

11.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

11.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local

Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

11.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

11.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information. Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

12. STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

12.2 PROTOCOL NON-COMPLIANCE

12.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

12.2.2 Protocol Waivers

Prospective protocol deviations, i.e., protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

12.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

12.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

12.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

12.5 STUDY RECORD RETENTION

Chief Investigators and Local Principal Investigators are responsible for the secure archiving of the trial site documents and database as per their trust policy.

All paper and electronic trial records will be retained following the end of the trial for 5 years after completion of the trial as per CTIMP record retention protocol. Archiving will be authorised by the Sponsor following submission of the end of study report. Other essential documents, including source data, consent forms, and regulatory documents, will be archived by or for the Investigator in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection. The trial database will be held by ECTU for a minimum of 5 years from the defined end of study point.

When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the Sponsor.

When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.6 END OF STUDY

The end of study is defined as the last participant's last follow-up.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT 2022-000524-38 as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

12.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

The IMP will be discontinued at the final follow-up visit and IMP inhalers returned. A treatment plan will be initiated through standard clinical follow up if deemed appropriate. Participants should be reminded to re-initiate their standard repeat prescription (if appropriate) to ensure continuity of clinical care after they have stopped the study drug (i.e., after 12-month appointment)

12.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.

- The manufacturer supplying IMP (GSK in this case) has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

13. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

13.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD and to GSK, for review and comment, prior to finalisation. The clinical study report may be used for publication and presentation at scientific meetings. Material for public dissemination will be submitted to ACCORD and GSK for review prior to submission for publication, public dissemination or review by a publication committee.

Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Patients will be given the option of receiving a summary of the results of the trial by post within 1 year of the end of the study.

Summaries of results will also be made available to Investigators and disseminated within their clinics discretion) through our Respiratory Managed Clinical Networks (MCN). The Chief Investigator (Dr Choudhury) chairs the MCN in Lothian and has strong ties with the respective chairs of involved Health Boards.

13.3 DATA SHARING

After publication, anonymised patient level data and samples from the Study may be shared with other researchers on reasonable request in writing to the Chief Investigator.

13.4 PEER REVIEW

The protocol was reviewed by GSK when submitted as a grant application. A review has also been conducted by the co-sponsors and the other investigators who have agreed to collaborate in this study.

13.5 PATIENT INVOLVEMENT

A draft of trial protocol was presented to the Lothian Bronchiectasis Patient Advocacy Group and was wholeheartedly supported by them. A member of this group will be invited to join the Trial Steering Committee as an independent member.

14. REFERENCES

1. Du Q et al. Bronchiectasis as a comorbidity of COPD: a systematic review and meta-analysis. PloS One. 2016 Mar 15;11(3): e0150532.
2. Martinez-Garcia MA et al. Prognostic value of bronchiectasis in patients with moderate-to-severe COPD. Am J Respir Crit Care Med. 2013; 18:823-831.
3. Agusti A1, Calverley PM, et al; Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010 Sep 10; 11:122. doi: 10.1186/1465-9921-11-122.
4. Du Q[1], Jin J[1], Liu X[1], Sun Y[1,2]. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. PLoS One. 2016 Mar 15;11(3):e0150532. doi: 10.1371/journal.pone.0150532. eCollection 2016.
5. Patel I. S., Vlahos I. & Wilkinson T. M. et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170, 400–407 (2004).
6. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org
7. Lipson et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018; 378:1671-1680
   DOI: 10.1056/NEJMoa171390
8. Wedzicha JA et al. Indacaterol-Glycopyrronium versus Salmeterol- Fluticasone for COPD. NEJM. 2016;374(230:2222-34.
9. Price D1, Miravitlles M2, Pavord I3, Thomas M4, Wedzicha J5, Haughney J1, Bichel K6, West D6. First maintenance therapy for COPD in the UK between 2009 and 2012: a retrospective database analysis. NPJ Prim Care Respir Med. 2016 Nov 3;26:16061. doi: 10.1038/npjpcrm.2016.61.
10. Hill AT[1], Welham S, Reid K, Bucknall CE; British Thoracic Society. British Thoracic Society national bronchiectasis audit 2010 and 2011.Thorax. 2012 Oct;67(10):928-30. Epub 2012 Jul 17.
11. Contoli M, Pauletti A, Rossi MR et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J. 2017 Oct 5;50(4). pii: 1700451. doi: 10.1183/13993003.00451-2017. Print 2017 Oct.
12. Chalmers JD, Smith MP, McHugh BJ, et al. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2012; 186:657-665
13. Tunney MM, Einarsson GG, Wei L, et al. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. Am J Respir Crit Care Med 2013; 187:1118-1126
14. Wing Ho Man, Nienke M Scheltema, Melanie Clerc, Marlies A van Houten, Elisabeth E Nibbelke, Niek B Achten, Kayleigh Arp, Elisabeth A M Sanders, Louis J Bont, Debby Bogaert. Infant Respiratory Syncytial Virus Prophylaxis and Nasopharyngeal Microbiota Until 6 Years of Life: A Subanalysis of the MAKI Randomised Controlled Trial. Lancet Respir Med. 2020 Mar 20;S2213-2600(19)30470-9. doi: 10.1016/S2213-2600(19)30470-9.
15. Wing Ho Man, Marlies A van Houten, Marieke E Mérelle, Arine M Vlieger, Mei Ling J N Chu, Nicolaas J G Jansen, Elisabeth A M Sanders, Debby Bogaert.

Bacterial and Viral Respiratory Tract Microbiota and Host Characteristics in Children With Lower Respiratory Tract Infections: A Matched Case-Control Study. Lancet Resp Med 2019 May;7(5):417-426.doi: 10.1016/S2213-2600(18)30449-1. Epub 2019 March.

16. Jones P *et al.* Eur Respir J 2009; 34: 648-654
17. Wilson CB et al. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. Am J Respir Crit Care Med 1997; 156:536-541.
18. Murray MP et al. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. Eur Respir J 2009; 34:361-364.
19. Murray MP, Govan JR, Doherty CJ, et al. A randomised controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2011; 183:491-499.
20. Ravishankar Chandrasekaran, Micheál Mac Aogáin, James D Chalmers, Stuart J Elborn, Sanjay H Chotirmall. Geographic Variation in the Aetiology, Epidemiology and Microbiology of Bronchiectasis.BMC Pulm Med. 2018 May 22;18(1):83. doi: 10.1186/s12890-018-0638-0.
21. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007; 30:782–800.
22. Linh D N Nguyen[1], Eric Viscogliosi[1], Laurence Delhaes. The Lung Mycobiome: An Emerging Field of the Human Respiratory Microbiome. Front Microbiol 2015 Feb 13;6:89 doi: 10.3389/fmicb.2015.00089. eCollection

TEMPESTAS Protocol_V5.0_02May2024

Final Audit Report 2024-07-10

Created:	2024-07-09 (British Summer Time)
By:	Lorna Dewar (lorna.dewar@ed.ac.uk)
Status:	Signed
Transaction ID:	CBJCHBCAABAAkhBDsEqXnYt8HQIxDsOd2ZSJdLwXXz5G

"TEMPESTAS Protocol_V5.0_02May2024" History

Document created by Lorna Dewar (lorna.dewar@ed.ac.uk)
2024-07-09 - 13:55:15 GMT+1- IP address: 192.41.114.224

Document emailed to gourab.choudhury@nhslothian.scot.nhs.uk for signature
2024-07-09 - 13:56:32 GMT+1

Document emailed to Tiago Santos (Tiago.Santos@ed.ac.uk) for signature
2024-07-09 - 13:56:33 GMT+1

Document emailed to c.graham@ed.ac.uk for signature
2024-07-09 - 13:56:33 GMT+1

Email viewed by Tiago Santos (Tiago.Santos@ed.ac.uk)
2024-07-09 - 13:57:34 GMT+1- IP address: 104.47.11.254

Document e-signed by Tiago Santos (Tiago.Santos@ed.ac.uk)
Signature Date: 2024-07-09 - 13:57:57 GMT+1 - Time Source: server- IP address: 77.103.18.247

Email viewed by gourab.choudhury@nhslothian.scot.nhs.uk
2024-07-09 - 14:24:26 GMT+1- IP address: 52.102.18.53

Signer gourab.choudhury@nhslothian.scot.nhs.uk entered name at signing as Gourab Choudhury
2024-07-09 - 14:24:50 GMT+1- IP address: 62.253.82.231

Document e-signed by Gourab Choudhury (gourab.choudhury@nhslothian.scot.nhs.uk)
Signature Date: 2024-07-09 - 14:24:52 GMT+1 - Time Source: server- IP address: 62.253.82.231

Email viewed by c.graham@ed.ac.uk
2024-07-10 - 10:07:33 GMT+1- IP address: 104.47.11.62

Signer c.graham@ed.ac.uk entered name at signing as C.Graham
2024-07-10 - 10:24:40 GMT+1- IP address: 129.215.23.33

Document e-signed by C.Graham (c.graham@ed.ac.uk)

Signature Date: 2024-07-10 - 10:24:42 GMT+1 - Time Source: server- IP address: 129.215.23.33

Agreement completed.

2024-07-10 - 10:24:42 GMT+1